Dementia is pandemic. Almost all persons with dementia exhibit neuropsychiatric symptoms (NPS) during the course of their illness. One-third of the care expenses of home-dwelling patients are due to these symptoms. NPS such as aggression, agitation, delusions and depression increase the risk for institutionalization. Psychotropic drug use, especially use of antipsychotics, has been concerning in this vulnerable group of people. The aim of this study was to describe the use of antipsychotics and other drugs, and their associations with NPS.
Neuropsychiatric symptoms, psychotropic drug use and physical restraints in older persons
MARJA KURONEN

Neuropsychiatric symptoms, psychotropic drug use and physical restraints in older persons

Cross-sectional study in home care and residential care

To be presented, by permission of the Faculty of Health Sciences, University of Eastern Finland, for public examination in auditorium Mikropolisali, Building M, the South Eastern Finland University of Applied Sciences, Mikkeli, on Friday, March 10th, 2017, at 12 noon

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The inquiry of restraint use was restricted to persons aged 65 years or more (NPI) in residential care. Psychotic symptoms was associated with hyperactivity and psychotic symptoms. R-cognitively impaired, 31% used antipsychotics; 38% used memantine with the drug or (54%). The use of memantine was common among persons with dementia diagnosis. Apathy was studied. NPS were collected from medical records and used only as a characteristic. The latest Mini Mental State Examination was made diagnosis of dementia found to treat hyperactivity and psychotic symptoms. The anti-dementia drug was obtained from the electronic subgroups. The prevalence and types of neurobehavioral symptoms (NPS) of NPS were compared to related factors. Patients' activities of daily living (ADL) and use of benzodiazepines were investigated. One of the aims of the study was to seek and promote pharmacological approaches for NPS in two different populations, especially in residential care. The anti-psychotic use manifested with the prevalence and types of neurobehavioral symptoms (NPS) and use of benzodiazepines. The majority of the persons used AChEIs. The use of drugs in residential care suffered from AChEIs and memantine. The prevalence and types of neurobehavioral symptoms (NPS) in regular home care was assessed AChEIs. On this basis, the higher the score, the better the functioning. Furthermore, the use of drugs in residential care and in home care was equally common. One of the aims of the study was to examine the use of psychotropic and related drugs in two different populations, especially in residential care.
Kuronen, Marja
Neuropsychiatric symptoms, psychotropic drug use and physical restraints in older persons. Cross-sectional study in home care and residential care.
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ABSTRACT

The South Savo Hospital District has one of oldest populations in Finland. The majority of the persons in residential care and many in home care suffer from cognitive impairment or dementia, which regularly manifests with non-cognitive disturbances called neuropsychiatric symptoms (NPSs). The growing concern of using antipsychotics for NPS in persons with cognitive impairment raises the need for further research to seek and promote alternative treatments for NPSs to reduce the risk of maltreatment of older persons. The aims of this study were to examine the use of psychotropic and anti-dementia drugs in two different populations, in regular home care and in long-term residential care, and the associations with NPSs and personal characteristics. The prevalence and types of physical restraints in residential care and how resident-related factors, such as NPSs, psychotropic drugs and activities of daily living (ADL), were associated with restraining were investigated. Furthermore, the use of non-pharmacological approaches for NPSs was evaluated.

Nurses collected the data on characteristics of participants in May 2011 and the study population comprised 2821 persons. Nurses assessed ADL by the Barthel Index. On this scale the higher the score, the better the functioning. The first criterion by which persons were classified as cognitively impaired was a physician-made diagnosis of dementia found in the medical records. Nurses classified patients' cognition into four categories (normal, slightly impaired, moderately impaired or severely impaired), with all persons from the last three categories subsequently classified as "cognitively impaired". The latest Mini Mental State Examination score (MMSE, scale 0-30) if carried out in 2010 or 2011 was collected from medical records and used only as a characteristic. Current use of regularly administered drugs was obtained from the electronic medical records of each patient. The prevalence of NPSs and associations between drug use and Neuropsychiatric Inventory (NPI) -defined NPSs were studied. NPSs were categorized as hyperactivity, psychosis, or mood symptoms and apathy subgroups.

Patients' mean age was 81 years and 68% were female. Dementia had been diagnosed in 31% of home care patients and in 56% of residential care patients. Anti-dementia drugs were used by 69% of patients with dementia diagnosis. One-third of the persons in residential care suffered from hyperactivity symptoms, whereas mood and apathy symptoms were more prevalent in home care (54%). The anti-dementia drug use was equally common in both care settings. Any anti-dementia drug or combinations of acetylcholinesterase inhibitors (AChEIs) and memantine were associated with the mood and apathy subgroup. The hyperactivity subgroup was associated with combination use of memantine and AChEI. Cognitive impairment was found in 1909 persons (68%), and 1188 of whom lived in residential care.

Antipsychotics were used by 28% of persons of the entire study population. Among the cognitively impaired, 31% used antipsychotics; 38% in residential care and 16% in home care. The use was associated with hyperactivity and psychotic symptoms. Results suggest that antipsychotics are commonly used to treat hyperactivity and psychotic symptoms, especially in residential care.

The inquiry of restraint use was restricted to residential care; 52% of these patients were restrained during the preceding 24 hours. Psychotic symptoms and use of benzodiazepines and related drugs (BZRDs) were associated with restraint use, whereas no such association was found for antipsychotic
or antidepressant drug use. Concomitant use of at least two restraints was associated with high prevalence of hyperactivity NPSs. Psychotic symptoms and BZRD use increased the risk of restraint use. Persons who were most dependent on others were the most frequently restrained.

NPSs occur frequently in persons in residential and home care facilities. Antidementia drugs and antipsychotics were abundantly used in both care settings. More than half of the patients in residential care were restrained recently; restraint use was associated with low ADL score. Various non-pharmacological approaches were used and the findings are summarized here.

National Library of Medicine Classification: QV 77.2, WM 35, WT 150, WT 155, WT 166
Medical Subject Headings: Mental Disorders/therapy; Behavioral Symptoms; Psychomotor Agitation; Psychotic Disorders; Mood Disorders; Apathy; Dementia; Cognition; Cognitive Dysfunction; Activities of Daily Living; Home Care Services; Residential Facilities; Long-Term Care; Psychotropic Drugs; Antipsychotic Agents; Cholinesterase Inhibitors; Memantine; Restraint, Physical; Aged; Aged, 80 and over; Cross-Sectional Studies; Finland

Psykoosilääkkeiden epäasianmukaisesta ja virallisten käyttöaiheiden vastaisesta käytöstä vanhuksilla on paljon tutkimustietoa. Yleisesti käytetyt fyysiset rajoitteet voivat myös lisätä kaltoinkohtelun riskiä. Tutkimuksen tarkoituksena oli selvittää muistisairauslääkkeiden ja psykosenlääkkeistä erityisesti psykoosilääkkeiden käyttöä sekä yhteyskiä näiden lääkkeiden käytön ja käytösoireiden välillä. Tavoitteena oli myös selvittää fyysisten rajoitteiden käyttöä laitoksissa ja tutkin niiden liittymistä käytösoireisiin, psykosenlääkkeiden käyttöön ja päivitytä mistä toimintoista selvitymiseen. Tutkimuksessa kartoitettiin myös käytösoireiden yleisimpiä lääkkeittömiä hoitomuotoja laitoshoidossa.


Fyysisiä rajoitteita tutkittiin vain laitoshoidossa, missä 52 % potilaista käytti niitä edeltävän vuorokauden aikana. Samanaikainen useamman rajoitteen käyttö oli yleisintä yliaktiivisuus-alaryhmän oireista kärsivillä. Psykoottiset oireet ja bentsodiatsepiinien käyttö olivat yhteydessä

Luokitus: QV 77.2, WM 35, WT 150, WT 155, WT 166
Yleinen suomalainen asiasanasto: mielenterveyshäiriöt; käyttäytymishäiriöt; hyperaktiivisuus; psykoosit; mieliala; apatia; dementia; kognitio; toimintakyky; kotihoito; laitoshoito; pitkäaikaishoito; lääkeroito; psykyenlääkkeet; lääkkeetön hoito; ikääntyneet; vanhukset; poikittaistutkimus; Suomi
rajoitteiden käyttöön, mutta hyvä toimintakyky ja psykoosilääkkeiden käytön välillä oli negatiivinen yhteys.

Lääkkömistä hoitokeinoista käytettiin eniten sanallista rauhoittamista ja ajan ja huomion antamista käytösoireiden lievittämiseksi. Ne uropsykiatristen oireiden esiintyminen sekä muistisairauksien ja psykoosilääkkeiden käyttö olivat yleistä sekä laitossa että kotihoidossa.

Yli puolelle laitospotilaista käytettiin fyysisiä rajoitteita ja suurimmassa riskissä olivat kaikkein huonokuntoisimmat.

Luokitus: QV 77.2, WM 35, WT 150, WT 155, WT 166

Yleinen suomalainen asiasanasto: mielenterveyshäiriöt; käyttäytymishäiriöt; hyperaktiivisuus; psykoosit; mieliala; apatia; dementia; kognitio; toimintakyky; kotihoito; laitoshoito; pitkäaikaishoito; lääkehoito; psyykenlääkkeet; lääkkeetön hoito; ikääntyneet; vanhukset; poikittaistutkimus; Suomi

Small and fragile
hold of a person
It's the same feeling as touching the wind
Small and fragile hold
- that's all

Dave Lindholm

Dedicated to my mother and the loving memory of my father
Acknowledgements

Docent Pertti Karppi, after founding a geriatric unit in Mikkeli Central Hospital in 2009, suggested to me a research topic concerning older persons' health issues in the South Savo Hospital District. The research was put in hold because of the renewal of the psychiatric services of the South Savo Hospital District in 2010. The data for this study were then gathered in May 2011. I am grateful to everyone who facilitated carrying out this study and who contributed in various ways.

My sincere and warm gratitude is particularly owed to my supervisor, Professor Sirpa Hartikainen, for her determined and continuous guidance in research and geriatrics and her willingness to give her valuable time over the years.

Professor Hannu Koponen, my co-supervisor, has always encouraged me to continue the study, even inch by inch, and has supported me not only in the research, but also in the clinical work since the 1990s. His comments have helped me to develop my thinking.

Docent Pertti Karppi has believed in the study, although the beginning was not easy. His patience and encouragement have carried me through many frustrating moments. His gift for languages has also been most helpful.

To cooperate with Statistician Hannu Kautiainen and Irma Nykänen, PhD, has been interesting, and I am very grateful for their valuable advice and help. Carol Ann Pelli has corrected the language of the manuscript.

I highly appreciate all my colleagues in psychiatric clinic who from time to time took care of my patients, and Auvo Mahlanen, MD, and Jussi Seppälä, MD, PhD, for enabling me from time to time to concentrate on the study.

I thank Inspector Marja Kuhmonen from the Regional State Administrative Agencies, for her supportive attitude towards the study.

Tuija Kärkkäinen and Päivi Heikura deserve my warm thanks, Tuija organized the data collection and Päivi prepared the data into a computerized form. I sincerely thank the nurses for collecting data, and the doctors and supervising nurses for enabling study on the field.

I am very grateful to former chief physician of the South Savo Hospital District Matti Suistomaa, MD, PhD, for his supportive attitude both as a clinician and as a researcher, and to my mentor, Professor Jouko Lönnqvist, for his warm attitude in sharing new perspectives.

I thank the official reviewers, Professor Esa Leinonen and Professor Kaisu Pitkälä, for valuable comments on this thesis. I also warmly thank Professor Jaakko Valvanne for accepting the invitation to act as opponent in the defense of my doctoral dissertation.

I owe a heartfelt thanks to my mother Anneli and my late father Olli, and admiringly acknowledge my mother's resilience in taking care of my father during his course of AD. My parents-in-law always kindly offered their home when in Kuopio, for which I am most grateful. My deepest gratitude is owed to my husband Jarmo and children Paula, Sini and Jaakko. Thank you for sharing your life, music and faith with me! New family members have brought joy, too.

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Mikkeli, February 2017

Marja Kuronen
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Mikkeli, February 2017

Marja Kuronen
List of original publications

This dissertation is based on the following original publications, referred to in the text by their Roman numerals:

I

II

III

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APPENDICES:

Questionnaire in home care
Questionnaire in residential care
ORIGINAL PUBLICATIONS (Studies I-III)
Abbreviations

ACHeI  Acetylcholinesterase Inhibitor
ADL   Activities of Daily Living
AD    Alzheimer’s Disease
APA   American Psychiatric Association
ATC   Anatomical Therapeutic Chemical
BI    Barthel Index
BPSD  Behavioural and Psychological Symptoms of Dementia
BZD   Benzodiazepine
BZRD  Benzodiazepines and Related Drugs
CDR   Clinical Dementia Rating scale
CGI   Clinical Global Impression
CI    Confidence Interval
CMAI  Cohen-Mansfield Agitation Inventory
CNS   Central Nervous System
CSF   Cerebrospinal Fluid
CT    Computed Tomography
FDA   (United States) Food and Drug Administration
IADL  Instrumental Activities of Daily Living
LTC   Long-Term Care
MAO   Monoamine Oxidase Inhibitor
MCI   Mild Cognitive Impairment
MMSE  Mini Mental State Examination
MRI   Magnetic Resonance Imaging
MSS   Multisensory Stimulation
MT    Music Therapy
NCD   Neurocognitive Disorder
NH    Nursing Home
NICE  National Institute for Health and Clinical Excellence
NMDA  N-methyl-D-aspartate
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<th>Abbreviation</th>
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<tr>
<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
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<td>NPI-NH</td>
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<td>NPI-Q</td>
<td>Neuropsychiatric Inventory Questionnaire</td>
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<tr>
<td>NPS</td>
<td>Neuropsychiatric Symptom</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>RAI</td>
<td>Resident Assessment Instrument</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SNRI</td>
<td>Serotonin and Noradrenalin Reuptake Inhibitor</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
</tr>
<tr>
<td>STATA</td>
<td>Data Analysis and Statistical Software</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic Antidepressant</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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1 Introduction

The proportion of aged people of the world population is increasing. In Finland, the average age of the population is at the European level, but some areas, such as South Savo, are especially aged, with 28% being 65 years or more (The Regional Council of South Savo 2016). This area is now as aged as Finland overall is estimated to be in the next 10-15 years. The same pattern of ageing is to continue over the next decade, and Finland will lead the way for other countries (McQuinn and Whelan 2015). The health care facilities in Finland and in Europe will face vast challenges due to ageing in the near future. The proportion of persons receiving residential care in the age group of 75 years or more was 3.1% in the South Savo Hospital area, and the proportion receiving regular home care was 14.8% (Sotkanet 2011).

As the number of aged persons increases, those with cognitive problems and dementia will be more numerous. Currently, in Finland, there are approximately 120 000 people suffering from mild to severe dementia and an additional 120 000 persons with mild cognitive impairment (MCI) (National Institute for Health and Welfare 2016). The number of people with Alzheimer’s disease (AD) has been projected to nearly triple between 2010 and 2050 (World Alzheimer Report 2015). Over 80% of persons in residential care are estimated to suffer from impaired cognition (Gruneur et al. 2007), and in home care services the proportions have varied between 12% in nine European countries (Alanen et al. 2008a) and 42% in Norway (Wergeland et al. 2014). During the course of the illness practically all of those afflicted suffer from neuropsychiatric symptoms (NPSs), also called behavioural and psychological symptoms of dementia (BPSD) (Zuidema et al. 2007, Steinberg et al. 2008, Selbaek et al. 2013). These symptoms include agitation, aggression, apathy, depression, eating or sleeping problems and psychotic symptoms and they may be even more distressing for persons with dementia and their caregivers than the cognitive decline (Allegri et al. 2006). In long-term residential care, approximately 80% (Zuidema et al. 2007, Seitz et al. 2010) of persons with dementia exhibit NPSs at any time and about 55% in the home care setting (Wergeland et al. 2014).

An important challenge of health services is to manage these problems in a medically appropriate, humane and economically sustainable way. At the moment, the expenses related to older age form 37% of all social security expenses (Statistics Finland 2015). The growing number of cognitive disorders increases social welfare and health care expenditures, which are dependent on the stage of the disease. An estimated 85% of the costs incurred by memory disorders are caused by residential care (National Institute for Health and Welfare 2016). Society as a whole, and especially families, will face the challenges brought by the dementia pandemic. Families take care of about 75% of dementia patients in their homes (Schulz and Patterson 2004), and therefore, need special support and education to survive this task. NPSs are a major source of functional disability (Okura et al. 2010) causing caregiver stress and family disruption (Lyketsos and Olin 2002). Providing care for persons with dementia causes more stress than providing care for physically frail older adults (Pinquart and Sörensen 2003).

According to previous studies, the use of antipsychotics for older persons (Alanen et al. 2006, Alanen et al. 2008b) and psychotropics for older persons with dementia (Taipale et al. 2014b) in combination with physical restraints (Feng et al. 2009) is common in our country, which is a concern. The studies indicate that the differences between care practices are mostly organizational and less person-related (Pekkarinen et al. 2006, Feng et al. 2009). Education and promotion of good caring practices combined with new approaches to treat NPSs and restraint-free services are needed in nursing homes (NHs) and other types of residential care as well as in home care services. To improve the care practices, detailed data concerning the use of anti-
dementia drugs, psychotropics, prevalence of physical restraints and non-pharmacological approaches for NPSs must be collected.

In Finland, the municipalities are responsible for providing both medical and social services. They must decide whether a frail older person is to receive regular home care services or residential care. The care may be home-based or some level of residential care. There are several forms of long-term care, which are categorized according to the intensity and substance of care (Johansson 2010). Long-term residential care is available in NHs and in inpatient wards of health care centres. The difference between inpatient wards and long-term NH care is somewhat indeterminate. There is a new type of service between the NHs and inpatient wards called sheltered housing, which can be either ordinary sheltered housing or intensified sheltered housing, with nursing care available 24/7. In this study, the services offering 24/7 care were included in the category of long-term residential care.

The aims of the study were to investigate the use of anti-dementia and psychotropic drugs in cognitively impaired older persons in home care and in residential care and to determine any associations with drug use, NPSs and use of physical restraints in this vulnerable group of people.
2 Review of the literature

2.1 COGNITIVE IMPAIRMENT AND DEMENTIA

According to the diagnostic category in the Diagnostic and Statistical Manual for Mental Disorders 5 by the American Psychiatric Association (APA) (2013), dementia and amnestic disorder now form two diagnostic categories: major and minor neurocognitive disorders (NCDs). The NCDs include delirium, syndromes of major NCD, minor NCD and their aetiologic subtypes. The NCDs include disorders in which the primary clinical problem is acquired rather than developmental cognitive deterioration (APA 2013). According to the APA, the term dementia can still be used to refer the condition major NCD.

Since the 1990s, the concept minor neurocognitive disorder was categorized as MCI. To diagnose MCI, the following criterion should be fulfilled: 1) a concern regarding a change in cognition, from the patient, from a person who knows the patient well or from a clinician, 2) an impairment in one or more cognitive domains and 3) independence in functional abilities has preserved (Albert et al. 2011). As in MCI, in mild NCD the level of cognitive decline requires the person to use compensatory strategies in maintaining independence and perform activities of daily living, but the difficulties do not rise to the level of a major NCD (APA 2013).

As a progressive neurodegenerative disorder, dementia forms a largely irreversible clinical syndrome. In dementia, social or occupational functioning is impaired. It causes not only impairment in cognitive functions but also NPSs and difficulties in performing basic and instrumental activities of daily living (Burns and Iliffe 2009). The majority of patients, 60-80%, suffer from AD. In those with a clinical diagnosis of AD, the combination of cerebrovascular lesions and Lewy body pathologies has been common (Jellinger 2006). In a large Canadian cohort study, 34% of dementias were mixed (Feldman et al. 2003), and they are especially common in older age groups (National Institute for Health and Welfare 2016). Dementia associated with cerebrovascular disease has formed 16-24% of all dementias (Lobo et al. 2000, Brunnstöm et al. 2008), dementia with Lewy bodies 2.5% (Feldman et al. 2003), dementia due to Parkinson's disease 3.6% (Aarsland et al. 2005) and frontotemporal lobar degenerations 4-5% (Brunnström et al. 2008). Conditions like hypothyroidism and vitamin B12 deficiency can cause dementia that may be reversible. Fast progressing dementia can even be caused by, for instance chronic subdural haematoma (Velasco et al. 1995). Dementia cannot be explained by delirium, which is an acute decline in cognitive functioning (Inouye et al. 2013), or a major psychiatric disorder.

In the diagnostics history from the patient and from a relative, as well as objective cognitive assessment are needed in evaluating the patient. Radiological examinations, previously computed tomography (CT scan), nowadays magnetic resonance imaging (MRI), and investigation of cerebrospinal fluid (CSF) biomarkers might be helpful in verifying the diagnosis and making differential diagnosis. For example, reduced CSF levels of amyloid beta 42 can be found in AD (Panegyres et al. 2016). Elevated total tau and phospho-tau levels in CSF are less specific to AD, but have also been proposed as research biomarkers (APA 2013). They have not yet been validated or approved for clinical diagnostic use (Hugo and Ganguli 2014). In any case, however, the final diagnosis is based on clinical judgement.

In many countries, one-third of the dementia cases are assumed to remain undiagnosed (Lithgow et al. 2012, Kosteniuk et al. 2015). Early diagnosis of dementia is important to enable early interventions to prevent or slow the progression of the disease and to allow the use of treatments that are not effective at more severe stages of dementia. The progress from mild NCD to dementia has been 10% -15% per year (Panegyres et al. 2016). Early dementia detection requires
a comprehensive clinical evaluation, history taking, cognitive assessment, determination of functional status, brain imaging and CSF examination (Panegyres et al. 2016).

In Finland, an estimated 35 000 persons have early and 85 000 moderate or severe dementia (National Institute for Health and Welfare 2016). Approximately 47 million persons worldwide are believed to suffer from dementia, most of them living in the community (World Alzheimer Report 2015). The number will rise to 75 million in 2030 and to 132 million in 2050 (World Alzheimer Report 2015). In 2015, nearly 60% of these patients lived in low- or middle-income countries. The risk of the disease increases with age. Of those aged 65-75 years, less than 5% have the disease, but approximately 10% of those aged 75-84 years and one-third of those aged 85 years or over suffer from moderate to severe dementia. In the EU, the economic impact of dementia was estimated to be 160 billion euros per year in 2008 (Wimo et al. 2011). About one third of the costs of care for community-dwelling persons with dementia are directly caused by management of NPSs (Beeri et al. 2002). Direct medical costs form about 20% of all costs of dementia, whereas 40% of the costs of are due to social care and 40% to informal care of dementia (World Alzheimer Report 2015). The average direct and indirect treatment costs of one person suffering from dementia were 36 000 euros in Northern Europe per year in 2008 (Wimo et al. 2011). An estimated two thirds of people with dementia live in private households and one-third in care homes. For example, 70% of people with dementia in Australia continue to live in the community rather than in residential care (Australian Institute of Health and Welfare, 2012).

2.2 NEUROPSYCHIATRIC SYMPTOMS (NPSs)

2.2.1 Definitions of NPSs

NPSs are considered to refer generally to cognitive, behavioural and psychological disturbances (Halbauer et al. 2009) or more narrowly to behavioural and psychological symptoms of dementia (BPSD) (Lyketsos et al. 2001). In this study, BPSD is replaced by NPSs, which refers more to Neuropsychiatric Inventory (NPI) -defined symptoms (Cummings et al. 1994). NPSs are regarded as non-cognitive disturbances of dementia, which frequently manifest with cognitive decline. Factors contributing to the development of NPSs can be categorized as caregiver factors, environmental factors and factors related to neurobiological disease, and caregiver and environmental effects can modify a person’s behaviour alone or with neurobiological changes (Kales et al. 2015). NPSs occur during all stages of dementia, (Aalten et al. 2005, Aalten et al. 2007, Steinberg et al. 2008).

García-Alberca (2015) presented four models of precipitating factors of NPSs:
1) The unmet needs model (Cohen-Mansfield 2000), which assumes that NPSs could be the result of the patient’s difficulty in expressing emotional, physical or social needs and the caregiver’s difficulty in identifying these needs. This is supported by the conclusions of Livingston et al. (2014a), who considered agitation more a sign of unmet needs than a diagnostic entity. These unmet needs might be a need for relief from physical pain or discomfort, the need for stimulation or, emotional comfort or the need to communicate. In home care patients with dementia, high levels of pain, other NPSs, somatic comorbidities and low quality of life were associated with depressive symptomatology (Giegel et al. 2016).
2) The progressively lowered stress threshold model (Hall and Buckwalter 1997) suggests that dementia progressively lowers the threshold for tolerating stress or unpleasant stimuli, e.g. catastrophic reactions can be triggered by frustrating experiences such as inability to manage everyday tasks. As the ability of the person to process stimuli decreases, frustration potential increases and severe anxiety and agitation can develop (Volicer et al. 2007). One important cause of frustration may be aphasia, i.e. the inability to produce speech. However, no studies were found on the topic, although aphasia is a core symptom of dementia and is present regardless of age at disease onset (Cummings et al. 1985).
3) The learning model (Teri et al. 2000, Cohen-Mansfield 2001) proposes that certain environmental stimuli may initiate behaviours that patients learn to continue or repress. For example, screaming draws attention of a caregiver, whereas opposite behaviour may result in being ignored. Negative communication styles can worsen the symptoms, but good coping abilities and strategies are helpful, as is avoiding a discrepancy between caregiver expectations and the stage of illness (de Vugt et al. 2005).

4) Environmental factors such as excessively noisy or poorly lighted environment, lack of routines and intense demands may also precipitate NPSs (Lyketsos et al. 2006). Such psychosocial problems as disability, relocation, isolation, bereavement and economic poverty contribute to physiological changes and increase the risk of depression in already vulnerable persons (Alexopoulos 2005). In a European study of depressive symptoms in persons with AD, the symptoms were consistently associated with lower quality of life in both in home care and residential care, and no differences in quality of life among the settings were found (Beerens et al. 2014).

NPSs in cognitive disorders are not straightforward to evaluate or to distinguish. A consensus definition exists for agitation in cognitive disorders (Cummings et al. 2015). According to this definition for clinical and research purposes, agitation in cognitive disorders “1) occurs in persons with a cognitive impairment or dementia syndrome, 2) exhibits behaviour consistent with emotional distress, 3) manifests as excessive motor activity, verbal aggression or physical aggression and 4) evidences behaviours that cause excess disability and are not solely attributable to another disorder (psychiatric, medical or substance-related)”. There are accepted definitions for depression in AD (Lyketsos and Lee 2004) and for psychosis in AD and related dementias (Jeste and Finkel 2000). Attempts to define apathy in cognitive decline have been made by Robert et al. (2009), who described apathy as a “disorder of motivation that persists over time and meets the following requirements: 1) diminished motivation for at least four weeks, 2) at least two of the following: reduced goal-directed behaviour, goal-directed cognitive activity and emotions and 3) identifiable functional impairments attributable to the apathy”. It has been hypothesized that better characterization of NPSs, such as apathy in MCI and preclinical AD, using more nuanced clinical assessments as well as biomarkers may facilitate early diagnosis of AD (Guercio et al. 2015).

Rating scales such as the Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield et al. 1989) and the Behavioral Pathology in Alzheimer’s Disease (BEHAVE-AD) (Reisberg et al. 1987) are often used to identify patients for clinical trials of anti-agitation agents and to measure the clinical symptoms in other descriptive and intervention studies. Rating scales are means of measuring the frequency or severity of symptoms. In evaluating and measuring NPSs, the NPI is one of the most frequently used instruments (van der Linde et al. 2013). It consists of 10-12 items and is based on caregiver interview. The total score ranges from 0 to 140, and lower score indicates less symptoms. The frequency and severity of the symptoms over the past month are rated and caregiver stress is assessed separately. The items include delusions, hallucinations, agitation and physical or verbal aggression, depression or dysphoria, anxiety, apathy, disinhibition, irritability or lability, motor disturbance, euphoria or elevation of mood, problematic night-time behaviours and problems with appetite or eating (Cummings et al. 1994). A brief informant-based version of the NPI called the Neuropsychiatric Inventory Questionnaire (NPI-Q) has been shown to reliably assess NPSs and associated caregiver stress (Kauf et al. 2000, Boada et al. 2002). It has 12 yes/no questions with brief explanations, and simple scoring of severity (mild, moderate, severe) as well as a brief assessment of caregiver stress.

In a European study comparing depressive symptoms in home care and residential care, depressive symptoms were most prevalent in patients with severe dementia in home care setting (Giebel et al. 2016). Especially distressing symptoms for patients and caregivers have been agitation, aggression and psychosis, and they correlate with early transfer to long-term residential care (Allegri et al. 2006). Untreated NPSs are associated with poor quality of life (Karttunen et al. 2011), caregiver stress (Tan et al. 2005), premature placement (Chan et al. 2003),
higher health care utilization and costs (Murman et al. 2002) and more rapid disease progression (Rabins et al. 2013). NPSs have been strongly associated with depression and stress in caregivers; 23-85% of those who care for persons with dementia have been noted to suffer from depression (Adkins 1999, Clare et al. 2002, Okura et al. 2010, Brodaty et al. 2012), and NPSs reduce income and quality of life of family caregivers (Clyburn et al. 2000, Beeri et al. 2002). People who take care of dementia patients have shown higher levels of psychological distress and lower physical health, self-efficacy and feeling of well-being than those of other patient groups (Ballard et al. 2009a). The burden of spouses of patients with dementia-related NPSs was higher than that of the spouses of patients with depression (Leinonen et al. 2001). For formal care providers, caring for persons with NPSs has been associated with higher job dissatisfaction and burnout (Brodaty and Donkin 2009, Miyamoto et al. 2010).

The prevalences of NPSs in persons with dementia have varied between 58% and 97% (Brodaty et al. 2001, Lyketsos et al. 2002, Pitkälä et al. 2004, Steinberg et al. 2008). In long-term residential care, a review of 28 studies showed that 82% of persons with dementia suffered from at least one NPS (Selbaek et al. 2007), whereas the figure was lower, 55%, in home care (Wergeland et al. 2014). The most common symptoms have been apathy and depression (Lyketsos et al. 2002), followed by irritability, anxiety and agitation (Petrovic et al. 2007, Karttunen et al. 2011). A recent systematic meta-analysis of studies using the NPI as a measurement for NPSs reported that most frequent NPS was apathy (49%) followed by depression (42%), aggression (40%), anxiety (39%) and sleep disorder (39%) (Zhao et al. 2016). Less frequently detected NPSs were irritability (36%), appetite disorder (34%), aberrant motor behaviour (32%), delusion (31%), disinhibition (17%) and hallucination (16%). Euphoria was detected in 7% of patients (Zhao et al. 2016). In a systematic review of psychotic NPSs across different care settings, median prevalence of psychosis among persons with AD was 41% (range 12-74%) (Ropacki and Jeste 2005). Another review of NPSs in NHs (Selbæk et al. 2013) indicated that delusions were present in 22% (range 1-54%) of individuals and hallucinations in 14% (range 1-39%).

NPSs increase with the severity of dementia, but there were no differences in severity of NPSs between AD and vascular dementia at initial assessment (Thompson et al. 2010). Depressive symptoms and apathy have been most prevalent in persons with MCI and early AD together with such symptoms such as physical or verbal agitation, which are common during the various stages of dementia (Lyketsos et al. 2011). Aggressive and psychotic symptoms appear more commonly as the disease progresses, apathy remaining the most persistent and frequent NPS (Lyketsos et al. 2011). Psychotic symptoms and aggression present more episodically in moderate and severe stages of AD (Lyketsos et al. 2011). NPSs are an important prognostic factor in dementia. However, it is not known whether the treatment of NPSs could slow the cognitive decline (Gitlin et al. 2014).

### 2.2.2 Neurobiological background of NPSs

It is not known whether certain NPSs emerge in some persons in association with genetic factors, simultaneous medical conditions or lifestyle preferences. Some NPSs appear to involve of certain neurotransmitter systems or regional disconnection and atrophy in the anterior brain region (Lyketsos et al. 2011). NPSs exhibit universally regardless of various dementia types (Gitlin et al. 2014). However, certain dementias are associated with set behaviours; e.g. vascular dementia predisposes to mood symptoms, whereas visual hallucinations appear more often in dementia with Lewy bodies (Kales et al. 2015). Persons with frontotemporal dementia suffer frequently from executive control loss, wandering and apathy (Nyatsanza et al. 2003). Persistent psychiatric disorders such as schizophrenia or unipolar or bipolar depression and their treatments may increase NPSs in dementia patients as well as pre-existing personality disorders in patients (von Gunten et al. 2009, Kales et al. 2015). Symptoms often co-occur, increasing their impact.

Some studies indicate that certain variations in brain pathology (cerebral atrophy, changes in brain perfusion, metabolism and histopathology) are more frequently found in patients exhibiting NPSs than in dementia patients without NPSs (Robert et al. 2005). The neurobiological
factors may result in NPSs by disturbing the circuit system of the brain connected with behaviour and affect (Geda et al. 2013). Cognitive decline cannot alone explain the occurrence of NPSs, which are often seen already in the early stages of dementia. However, NPSs have been shown to increase as cognitive ability declines and they may predict the change from MCI to dementia (Edwards et al. 2009).

Depression has been found to be more prevalent in patients with than without AD (Rosenvinge and Rosenvinge 2003), and most persons with dementia suffering from apathy also had concomitant depression (Starkstein et al. 2005). In AD, the loss of adrenergic cells may lead to depressive symptoms; decreased monoaminergic neurotransmitter function and frontoparietal metabolism have been observed in depression (Nowrangi et al. 2015). In addition, reduction in glucose metabolism in certain brain areas (frontal and parietal cortex) and reduced thickness of the entorhinal cortex have been associated with depression in dementia (Nowrangi et al. 2015). Frontal and medial cerebral regions have been connected with motivation and reward mechanism linked with apathy (Guercio et al. 2015). Agitation and aggression have been associated with cortical atrophy of the frontal gyrus, cingulum and insula together with amygdala and hippocampal atrophy (Nowrangi et al. 2015). Psychotic symptoms have correlated with lower regional cerebral blood flow in the angular gyrus and occipital lobe and increased atrophy in the cingulum and neocortical, frontal and parietal areas (Nowrangi et al. 2015). Neuroimaging and investigations of CSF biomarkers have increased the understanding of which structural and biochemical changes are potentially associated with NPSs and have helped to develop better theoretical models to account for the neurobiological changes in dementia (Kales et al. 2015). Better understanding of these changes is needed to develop more targeted pharmacological and non-pharmacological treatments for NPSs and to improve caregiver coping skills (Lyketsos et al. 2011).

2.2.3 Differential diagnosis of NPSs
Undiagnosed illnesses may be important risk factors for NPSs. Among community-dwelling persons with dementia, more than one-third had undetected medical conditions associated with several NPSs such as agitation and psychotic symptoms (Hodgson et al. 2010). Pain is an important risk factor for NPSs and has been associated with aggressive (Kunik et al. 2010) and depressive symptoms (Giebel et al. 2016) in persons with dementia (Kunik et al. 2010); pain management may reduce NPSs (Husebo et al. 2011). Adverse effects of drugs or drug interactions may induce NPSs, e.g. anticholinergic drugs may induce agitation and aggression (Mintzer and Burns 2000). Unmet needs of persons with dementia are associated with NPSs and may worsen the non-cognitive symptoms (Cohen-Mansfield et al. 2015). The loss of ability to communicate verbally may lead one to express needs through various NPSs. Boredom may develop into unmet needs and NPSs (Colling and Buettner 2002).

The most common conditions in older persons causing widespread cognitive problems are dementia and delirium. The prevalence of delirium among older patients treated in internal medicine wards has been around 10-30% (Siddiqi et al. 2006). The vast majority of patients in palliative care suffer from delirium (Breitbart and Alici 2008). There is a high comorbidity between these conditions, with a symptoms overlap of 22-89% in community and hospital settings (Fick et al. 2002). A differential diagnosis between is particularly challenging as the connection between dementia and delirium is reciprocal. Dementia often predisposes the development of delirium, particularly if the person has other medical or neurological diseases (Rabins et al. 2007), but also delirium due to, for instance, cerebrovascular accidents predisposes to the development of dementia (Hölttä et al. 2011). Nevertheless, the most common predisposing factors for delirium are older age and organic brain diseases, especially progressive cognitive disorders (Inouye 1994).

Delirium negatively affects cognition, ADL and quality of life and increases the risk for institutionalization and mortality (Fick et al. 2002, Inouye et al. 2014). It can arise with certain drugs, e.g. anticholinergic drugs, and also with physical restraints. In the case of delirium, the
patient’s medication should be assessed critically; particularly anticholinergic drugs, opiates and sedatives should be discontinued or reduced whenever possible. Restricted movement is associated with poor prognosis and should be avoided; instead, early mobilization should be promoted (Piikälä et al. 2006).

The combination of confusion and agitation that emerges especially in late afternoon, evening or night-time is known as “sundowning”. Its aetiology, clear definition and interventions are under debate (Khachiyantis et al. 2011). It has proposed to affect up to two-thirds of patients with dementia and is closely related to disturbed circadian rhythms (Volicer et al. 2001). Risk factors include poor light exposure and disturbed sleep (Martin et al. 2000).

### 2.2.4 Subgrouping of NPSs

There have been efforts to define symptom groups or subgroups of NPSs not only for the purposes of taxonomy and research but also for everyday clinical practice. Subgrouping of NPSs could enhance communication between clinicians, patients and families and assist in setting goals for therapeutic efforts (van der Linde et al. 2014). As yet, there is no consensus of which NPSs should be categorized together or the number of symptom groups. The European Alzheimer Disease Consortium concluded that the clinical evidence supports the subgrouping of NPSs, and examining interventions for subgroups could be more effective than for individual NPSs (Robert et al. 2005). In addition, the United States Food Drug Administration (FDA) has stated that more specific behavioural subgroups are needed to develop better treatment goals (FDA 2005). Furthermore, the decreased number of symptoms in each subgroup may result in a greater possibility of finding associations (Aalten et al. 2003).

NPS subgroups could reflect different prevalences, disease courses, biological correlates and psychosocial determinants. Subgroups can be distinguished with many statistical techniques by exploring correlated variables. NPSs may be grouped into ‘factors’ or ‘clusters’. In cluster analysis, patients are grouped on the basis of their symptom profile, leading to non-overlapping clusters of patients, whereas in factor analysis symptoms rather than patients are grouped. An individual patient may have several factors of NPSs, and an individual symptom may appear in more than one factor. Also clinical judgement based on the occurrence of NPSs in the clinic and hypotheses regarding their aetiology can be used to group symptoms (van der Linde et al. 2014). Nowrangi et al. (2015) summarized that even though NPSs often cluster together it is challenging to formulate definite subgroups. Canevelli et al. (2013) performed a systematic review of literature of studies by using NPI-defining NPSs and clusters and found some consistent associations of specific NPSs across studies, defining potential subsyndromes in AD. Nevertheless, the studies vary regarding subgrouping of NPSs, (Table 1).

Lyketsos et al. (2001) described the following NPS profiles: 1) no symptoms or monosymptomatic; 2) affective and 3) psychotic. Aalten et al. (2003) found that delusions and hallucinations clustered together in the psychosis group; agitation/aggression, aberrant motor behaviour, disinhibition and euphoria formed the hyperactive subgroup; depression, loss of sleep and appetite and apathy formed the mood and apathy subgroup; and anxiety clustered alone. Petrovic et al. (2007) identified four NPI-based factors: psychosis, psychomotor factor, mood liability and instinctual factor, results highlighting the nature of mood and mood oscillations from depression to disinhibition. Aalten et al. (2007) found in her cross-sectional study of patients with dementia living in the community three NPS subsyndromes: mood/apathy, psychosis and hyperactivity. Anxiety was regarded as a separate symptom. Vilalta-Franch et al. (2010) investigated patients with probable AD in a cross-sectional and observational study. The NPI revealed psychosis factor, depressive factor and hypomanic factor. More recently, Cheng and colleagues (2012) used hypothetical NPS subgroups based on clinical observations to guide factor analysis, supporting a four-factor model (behavioural problems, psychosis, mood disturbance and euphoria).

Differences in factor solutions have emerged between studies, likely due to large differences in population characteristics and study design, including setting, population age, dementia
severity and dementia type. The most difficult NPS to group has been apathy, which was observed to load on any factor. Some overlap has occurred between apathy and depression, although either can occur without the other (Starkstein et al. 2005). This had been reflected in the results of van der Linde et al. (2014); apathy was included in the affective factor in nine studies, whereas it occurred independently or was associated with other symptoms, such as sleep problems and/or appetite changes in 14 studies. Because apathy is an important NPS in predicting poor outcome for people with dementia (Landes et al. 2001, Benoit et al. 2008), it should be understood in more detail.

Table 1. Overview of studies concerning NPS subgroups or clusters.

<table>
<thead>
<tr>
<th>Reference, year, country</th>
<th>Population</th>
<th>Design</th>
<th>Subgrouping</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyketsos et al. 2001</td>
<td>Age 65 or more with AD n=198</td>
<td>Population-based study (n=5092 screened for AD)</td>
<td>Groups of NPS profiles: 1) no NPS or mono-symptomatic 2) affective 3) psychotic</td>
<td>NPS divided into 3 groups</td>
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<tr>
<td>USA</td>
<td></td>
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<tr>
<td>Aalten et al. 2003</td>
<td>Patients with dementia living in the community n=199</td>
<td>Cross-sectional study</td>
<td>NPS subsyndromes: 1) mood/apathy 2) psychosis 3) hyperactivity</td>
<td>Anxiety regarded as a separate symptom</td>
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<td>Netherlands</td>
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<tr>
<td>Petrovic et al. 2007</td>
<td>Memory clinic practice n=194</td>
<td>Cross-sectional study</td>
<td>NPI-based factors: 1) psychosis 2) psychomotor 3) mood liability 4) instinctual</td>
<td>Highlights the nature of mood and mood oscillations from depression to disinhibition</td>
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<tr>
<td>USA</td>
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<tr>
<td>Aalten et al. 2007</td>
<td>12 centres from the European AD Consortium n=2354</td>
<td>Cross-sectional data:Principal component analysis used for factor analysis</td>
<td>Neuropsychiatric subsyndromes: 1) hyperactivity 2) psychosis 3) affective symptoms 4) apathy</td>
<td>Additional evidence for existence of NPS subsyndromes in AD</td>
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<tr>
<td>Several countries</td>
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<td>Vilalta-Franch et al. 2010</td>
<td>Patients with probable AD and after 12 months n=191</td>
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<td>Different physiopathogenic mechanisms may be involved in NPSs</td>
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<td>Spain</td>
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<tr>
<td>Cheng et al. 2012</td>
<td>Community-dwelling persons with mild/moderate AD n=224</td>
<td>Cross-sectional, two samples</td>
<td>4-factor model: 1) behavioural problems 2) psychosis 3) mood disturbance 4) euphoria</td>
<td>4 syndromes of NPSs corresponding to clinical observations of the disease</td>
</tr>
</tbody>
</table>

2.3 PHARMACOLOGICAL TREATMENTS FOR NPSS IN DEMENTIA

Treatments for NPS in dementia can be categorized as pharmacological, medical or non-pharmacological. Management of NPSs has included a wide range of psychotropic medications as well as non-pharmacological approaches (Nowrangi et al. 2015). Psychotropics are best used
when there are severe and complex NPSs, when the symptoms are psychotic and when psychosocial interventions did not have an effect or there are pre-existing mental health conditions (Alexopoulos et al. 2005, Burns et al. 2012). Medical treatments include e.g. pain management and treatment of infections. Of pharmacological treatments, antipsychotics have shown the strongest evidence of efficacy (Kales et al. 2015). Increased mortality and risk of stroke are associated with antipsychotic use in persons with dementia (Brodaty et al. 2003, Schneider et al. 2006, Ballard 2009b). Anti-dementia drugs have been useful in targeting mild NPSs in dementia, as they promote attention increasing activity and delay incidence of severe NPSs, thus being recommended as a first-line approaches for treating mild and moderate NPSs in AD (Finnish Medical Society Duodecim 2010, Press et al. 2017). The aim of the treatment of depression in dementia is to increase cognitive functioning (Rabins et al. 2007). However, the prolonged half-life of many psychotropic drugs in older persons can lead to their accumulation in the body, making the older persons more susceptible to adverse effects, e.g. impaired cognition or falls. Impaired cognitive function may itself lead to difficulties in walking, as mobility requires cognitive processing (Snijders et al. 2007).

2.3.1 Anti-dementia drugs
Acetylcholine esterase inhibitors (AChEIs) prevent the breakdown of acetylcholine and so maintain central nervous system (CNS) activity. Since the introduction of the AChEIs at the end of the 1990s, they have been used as the first-line pharmacotherapy for mild to moderate AD (Birks 2006). They are used not only to upgrade cognition but also to enhance ADL and to alleviate NPSs (National Institute for Health and Clinical Excellence; NICE 2013, Press et al. 2017). Early initiation of AChEIs may delay NH admission and slow down cognitive and functional impairment (Rabins et al. 2014). The AChEIs donepezil, rivastigmine and galantamine have slightly different pharmacological properties, but no differences in efficacy (Trinh et al. 2003). Memantine inhibits glutaminergic N-methyl-D-aspartate (NMDA) receptors. It is recommended in moderate to severe dementia to manage NPSs (Finnish Medical Society Duodecim 2010, NICE 2013).

The results of the studies concerning the efficacy of anti-dementia drugs on NPSs in dementia have been controversial. Most studies have been primarily designed to evaluate their effect on cognition, not on NPSs. A small improvement in NPSs in persons with dementia with AChEIs over placebo was noted in a meta-analysis during six months of treatment (Trinh et al. 2003). Studies evaluating rivastigmine found no benefit compared with placebo (Ballard et al. 2005, Holmes et al. 2007). The effect sizes on NPSs (Trinh et al. 2003) and cognition (Birks 2006) have been small. In the Cochrane review (Birks 2006), donepezil was seen as efficacious, and small benefits were noted in ADL and cognition. Furthermore, AChEI treatment was associated with a small reduction in the NPI score.

One study reported that galantamine was associated with reduced incidence of NPSs and improvement of existing symptoms in patients with mild to moderate AD, with a concomitant reduction in caregiver distress (Cummings et al. 2004) (Table 2). However, no significant difference between donepezil and placebo in the CMAI, the NPI or the Clinical Global Impression (CGI) scores in patients with AD was found (Howard et al. 2007). Another study allocated the patients randomly to memantine or placebo (Fox et al. 2012). After six weeks, no improvement was seen with memantine. A meta-analysis of the efficacy of memantine for NPSs was studied using the NPI-defined results (Maidment et al. 2008). Patients who were in various stages of AD without significant NPSs were managed primarily to enhance cognition, not behaviour. The authors questioned whether the small improvement on the NPI was clinically beneficial. Tariot et al. (2004) suggested that combination therapy of donepezil and memantine might be useful in treating NPSs in moderate or severe AD. Some RCTs of memantine in persons with moderate or severe dementia have indicated a benefit in NPSs (McShane et al. 2006, Gauthier et al. 2008, Wilcock et al. 2008). Rodda et al (2009) analysed 14 studies of AChEIs in the treatment of NPSs, with a median treatment duration of 24 weeks. Three of nine studies reported a significant
beneficial effect of donepezil, only one of three studies with galantamine showed a significant improvement in NPSs, and no studies of rivastigmine found any significant differences in NPSs relative to placebo (Rodda et al. 2009). However, the so-called floor effect, i.e. low NPI scores at baseline, hinders the interpretation of the results of many studies (Rodda et al. 2009). The study of Parsons and colleagues (2013) indicated that AChEIs and memantine act through two different but associated pathways, and thus, their combination may enhance their positive effects compared with either drug used alone.

Cummings et al. (2006) performed an RTC comparing a combination of memantine or placebo in patients with AD using donepezil. The NPI was used to assess the effects on behaviour, and a significant reduction in NPI in favour of memantine in agitation/aggression was found in the patients with moderate to severe dementia. Gauthier et al. (2008) detected that the patients treated with memantine had significantly lower NPI total scores than those with placebo. In addition, analyses of the NPI domains showed significant effects on agitation and aggression, eating problems and irritability. Memantine seemed to reduce agitation/aggression in those patients who had agitation at baseline and to delay its emergence in those who were free of this NPS at baseline (Gauthier et al. 2008). Another study suggested also that agitation was less prevalent in the treatment group than in the placebo group (Raina et al. 2008.) Persons with dementia improved their cognition, ADL and behaviour by combining memantine with donepezil, and a significantly beneficial effect was seen on agitation/aggression compared with placebo (Tariot et al. 2004).

Many types of adverse events have been reported. Nausea, vomiting and diarrhoea have been significantly more frequent in the AChEI groups than in placebo groups (Birks 2006). In one trial, 29% of patients in the donepezil group dropped out because of adverse events compared with 18% in the placebo groups (Howard et al. 2007). Patients should be regularly monitored for any potential hazardous adverse effects of AChEIs as bradycardia or atrioventricular blocks and gastric ulcer (Kim et al. 2011). If the use has no efficacy or causes adverse effects, the drugs should be discontinued. The most common adverse effects of memantine have included gastrointestinal symptoms, dizziness and headache (Raina et al. 2008).
Table 2. Efficacy of RCT studies concerning the use of anti-dementia drugs for NPSs in dementia.

<table>
<thead>
<tr>
<th>Reference, year, drug</th>
<th>Sample and setting</th>
<th>Methods</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cummings et al. 2004</td>
<td>Patients with mild to moderate AD randomly assigned to placebo or galantamine n=978</td>
<td>Changes on NPI. Data at 0 and 12 and 21 weeks after baseline</td>
<td>Patients with 16 or 24 mg/day of galantamine had better NPI subscale scores than patients receiving placebo</td>
<td>Galantamine reduced NPSs in patients with mild to moderate AD and reduced caregiver distress</td>
</tr>
<tr>
<td>Howard et al. 2007</td>
<td>Patients with AD who had clinically significant agitation n=272</td>
<td>10 mg of donepezil per day or placebo for 12 weeks. Primary outcome: a change in score on the CMAI at 12 weeks</td>
<td>No significant difference between donepezil and placebo in CMAI, NPI or CGI-C</td>
<td>Donepezil was not more effective than placebo in treating agitation in patients with AD</td>
</tr>
<tr>
<td>Gauthier et al. 2008</td>
<td>Patients with moderate–severe AD (MMSE &lt;20). n=959 with memantine and n=867 with placebo</td>
<td>NPSs on the NPI. Six 24/28-week, randomized, placebo-controlled, double-blind studies</td>
<td>Memantine 20 mg/day lowered significantly the NPI total score and single NPI items (delusions, hallucinations, agitation/aggression, irritability)</td>
<td>Memantine is effective reducing and preventing NPSs in moderate to severe AD</td>
</tr>
<tr>
<td>Fox et al. 2012</td>
<td>Persons with AD and agitation n=153</td>
<td>Several instruments, e.g. NPI, MMSE, CMAI, at 0, 6 and 12 weeks</td>
<td>No differences between memantine and placebo in primary outcome (CMAI), NPI</td>
<td>Memantine did not improve agitation in people with moderate to severe AD</td>
</tr>
<tr>
<td>Cummings et al. 2006</td>
<td>Moderate – severe AD patients with donepezil n=201 with placebo and n=202 with donepezil and memantine</td>
<td>Double-blinded, memantine (20 mg/day) compared with placebo. NPI at 0, 12 and 24 weeks</td>
<td>Significant reduction in NPI in favour of memantine in agitation/aggression, eating/appetite and irritability/lability</td>
<td>Memantine and AChEIs may offer additional benefits in AD when used together</td>
</tr>
</tbody>
</table>

AChEI = Acetylcholinesterase Inhibitor, AD = Alzheimer’s disease, CGI-C = Clinical Global Impression of Change, CMAI = Cohen-Mansfield Agitation Inventory, MMSE = Mini Mental State Examination, NH = Nursing Home, NPI = Neuropsychiatric Inventory, NPS = Neuropsychiatric Symptom, RTC = Randomized Controlled Trial

2.3.2 Psychotropics

According to the World Health Organization (WHO) psychotropic drugs are defined as chemical substances affecting mental processes (WHO 1994). They include antipsychotics, antidepressants, benzodiazepines and related drugs (BZRD) and mood stabilizers. The effectiveness of psychotropic medications in treating NPSs is considered to be limited in general (Sink et al. 2005). However, two-thirds of the persons in residential care and even more of those with dementia use psychotropics (Hosia-Randell and Pitkälä 2005, Mann et al. 2009). Atypical antipsychotics have the strongest evidence of effect (Kales et al. 2015), but only one-fifth of persons with dementia receiving any antipsychotic medication have been suggested to gain some benefit from treatment (Banerjee 2009). Psychotropics are widely used to alleviate NPSs in dementia, but they may also impair cognitive function (Hindmarch 2009). In Finland, every fourth community-dwelling person was found to take at least one psychotropic (Linjakumpu et al. 2002). Of older adults with
dementia in NHs and acute care geriatric units, 87% were taking one psychotropic drug, 66% two drugs, 36% three drugs and 11% four or more psychotropics concomitantly (Pitkälä et al. 2004). A recent study in USA showed that 41% of dementia patients were prescribed a psychotropic; 84% in NHs and 29% in the community (Maust et al. 2016).

2.3.2.1 Antipsychotics
The first conventional antipsychotic was chlorpromazine, invented in 1952. The therapeutic effect of chlorpromazine is supposed to be blocking dopamine receptors, which are widely present throughout the brain. Other conventional alternatives to treat psychosis (haloperidol, levomepromazine, perphenazine, pericyazine, zuclopenthixol, chlorprothixene) are also dopamine receptor blockers and they may cause severe extrapyramidal side effects, including initially appearing parkinsonism and later tardive dyskinesia in the later stage (Shireen 2016). With the advent of clozapine, other atypical antipsychotics followed in the 1990s, expanding the therapeutic options for psychosis. The first study indicating efficacy of risperidone in the treatment of NPSs in patients with severe dementia was performed by Katz and colleagues (1999). In their study, aggression and psychotic symptoms were reduced significantly with a 1 mg daily dose of risperidone. Also De Deyn et al. (1999) detected efficacy and good tolerability of low-dose risperidone in the treatment of NPSs, particularly in reduction of the severity and frequency of aggression. According to Street et al. (2000), low-dose (5 mg) olanzapine was more effective than placebo in treating agitation and psychotic symptoms in persons with AD. With a daily dose of 7.5 mg per day, olanzapine reduced psychotic symptoms and overall NPSs significantly in persons with AD (De Deyn et al. 2004).

In addition to treating aggression or psychotic symptoms in dementia, they also may reduce the risk of violence and patient distress, thus improving the patient’s quality of life and reducing caregiver burden. However, in clinical trials, the effect sizes of antipsychotic medications are at best small (Corbett et al. 2014, Kales et al. 2015, APA 2015). Atypical antipsychotics have the best evidence in treatment of agitation (APA 2015), and they also have lower risk of extrapyramidal side effects and slightly better overall tolerability than conventional ones (Ritsner et al. 2004). Compared with haloperidol, especially older patients with multiple illnesses had minor side effects with atypical antipsychotics (Han and Kim 2004, Boettger and Breitbart 2005).

This more favourable adverse effect profile of atypical antipsychotics expanded the use of these drugs to vulnerable dementia patient groups, which are especially prone to neurological adverse effects of conventional antipsychotics (Jeste and Finkel 2000). However, an increased mortality associated with atypical antipsychotics was detected by Schneider and colleagues (2005). They conducted a meta-analysis of 14 trials of atypical antipsychotics for persons with dementia, and found a 1.5-fold increased risk for death among antipsychotic users compared to non-users. Evidence for differential risks for individual antipsychotics or diagnosis was not found in the study. Due to this, the FDA in USA issued a boxed warning regarding the risk of atypical antipsychotics prescribed for older patients with dementia (FDA 2005). This warning was associated with a decrease in use of antipsychotics (Dorsey et al. 2010). After Gill et al. (2005, 2007), studied more than 27 000 matched pairs of persons with dementia and concluded that mortality with conventional antipsychotics may be even higher than with atypical ones, the FDA gave a corresponding warning concerning conventional antipsychotics in June 2008 (FDA 2008). The current studies also suggest increased mortality (Maust et al. 2015, Koponen et al. 2017b). There have been some differences in mortality between molecules, but the differences between antipsychotics have been subtle. However, Koponen et al. (2017b) found that haloperidol was associated with the highest risk of mortality, and the use of higher doses of haloperidol and risperidone was associated with an increased risk of mortality compared with low-dose...
risperidone use. With newly diagnosed AD, quetiapine was associated with a lower risk of death than risperidone (Gerhard et al. 2014). Widely reported adverse effect of antipsychotics are extrapyramidal symptoms, sedation, metabolic and cardiovascular problems, accelerated cognitive decline and increased risk of stroke, pneumonia and falls (Gareri et al. 2014, Rabins et al. 2014). The risk of hip fractures increased from the very first days of use of antipsychotic, remaining increased thereafter (Koponen et al. 2017a).

Despite the well-known risks of antipsychotics in long-term care (LTC) and the continuous discussion of their proper indications in dementia, the off-label use of antipsychotics is widespread. In USA and in European countries, 20-50% of persons with dementia in residential care are administered antipsychotics (Azermai et al. 2011, Chen et al. 2010, Zuidema et al. 2011). A recent figure in Europe is 32.8% (Foebel et al. 2014). The use has also been high in Scandinavia, with 25-40% of persons with dementia using antipsychotics (Selbæk et al. 2014, Gustafsson et al. 2013b, Gustafsson et al. 2013c) and even higher proportions in those with late-stage dementia (Nijk et al. 2009). Patients in LTC in Asia are frequently on antipsychotics; 27% of persons with dementia in residential care in Korea and Japan were using these drugs (Okumura et al. 2014, Lee et al. 2015). A nationwide survey in USA found that 26% of NH residents used antipsychotics, and 40% had no appropriate indication for such a use (Chen et al. 2010). In the same country, almost one-third of NH residents with dementia used antipsychotics (Kamble et al. 2009).

Community-dwelling persons with AD have been subjected less to antipsychotics, with 5-10% using them (Shah et al. 2011, Wergeland et al. 2014). However, in Finland, the corresponding figure has been 22-30% (Hartikainen et al. 2003, Laitinen et al. 2011). Older persons in the community using an atypical antipsychotic were three times more likely to develop a serious health problem, such as increased mortality during the 30-day follow-up, and in those with a typical antipsychotic the risk was nearly fourfold compared with persons not using any antipsychotic drug (Rochon et al. 2008). When the community-dwelling persons with AD were followed for seven years, more than one-third had started antipsychotic use (Koponen et al. 2015). Compared with Norway (Wergeland et al. 2014) and nine European countries, the use of antipsychotics among persons in home care in Finland is higher (11%) (Alanen et al. 2008a).

Based on the Expert Consensus Panel for using antipsychotics in older persons, use of antipsychotics is indicated in schizophrenia, delusional disorder, mania with psychosis, psychotic major depression and agitated dementia (Alexopoulos et al. 2004). Treatment with antipsychotics may be indicated for severe agitation that endangers patient safety or for psychotic symptoms causing severe distress (APA 2015). It has been widely accepted that in delirium medication should start with antipsychotics (Jackson and Lipman 2004, Lonergan et al. 2007). This has, however, been challenged by Inoye et al. (2014). The best evidence for antipsychotics reducing NPSs has emerged for risperidone, olanzapine and aripiprazole (Ballard et al. 2005, Seitz et al. 2013). Quetiapine was not effective for agitated persons with dementia in residential care, and its use was associated with a significant cognitive deterioration compared to placebo (Ballard et al. 2005).

Evidence has supported only the short-term use of antipsychotics (Ballard and Waite 2006). Sultzber et al. (2008) found that antipsychotic drugs may be effective in treating particular symptoms such as paranoid ideation and aggression. Nevertheless, the advantages of long-term treatment of aggression have been limited, and antipsychotic treatments have not seemed to ameliorate the quality of life, ADL scores or care demands (Ballard et al. 2009a). The dose of the antipsychotic should be the lowest possible and the duration of medication the shortest possible, with a regular re-evaluation of the use (Alexopoulos et al. 2004, Zuidema et al. 2015, APA 2015).

The risk of antipsychotic drug use should be considered within the context of medical need for the drugs, efficacy evidence, medical comorbidity and the efficacy and safety of alternatives. There is a lack of regulatory approval of antipsychotic use in dementia, excluding risperidone, which is approved in Canada for NPSs in severe dementia (Kales et al. 2015), and in Finland for psychosis and agitation in dementia (Finnish Medical Society Duodecim 2010). Also at the
European Union level, risperidone is officially indicated for the short-term treatment of severe aggression. In Australia, the regulatory authority allows the use of risperidone for the treatment of psychotic symptoms and aggression if non-pharmacological treatments fail. Most antipsychotics are thus used off-label (Maher et al. 2011).

Lövheim et al. (2006) studied geriatric care unit residents (n=2017) aged 65 years and over with cognitive impairment in a cross-sectional study (Table 3). NPSs were associated with lower age, imposed mental workload, male sex and living in a group dwelling. Antipsychotic drug treatment was common and determined by NPSs as well as the caregiver and caring situation. In a study by Gustafsson et al. (2013a), one-quarter of cognitively impaired persons in geriatric care units used antipsychotics, and the use was associated with NPSs and MCI. Selbaek et al. (2007) assessed NH patients with the NPI, the Clinical Dementia Rating scale (CDR) and Lawton’s ADL scale, and the drug use was obtained from medical records. Dementia was found in 81% of the patients, NPSs were present in 72% and antipsychotics were used by 26%. Wergeland et al. (2014) investigated persons with AD receiving home care, and only 5% used antipsychotics; the use was connected to delusions. In conclusion, the studies on associations between antipsychotics and NPSs are relatively scarce, especially in home care settings. Most of them have found associations between the use of antipsychotics and aggressive or agitated behaviour, hallucinations and delusions. The diagnosis, target symptoms and treatment goals should be reviewed and alternative interventions or other agents should be considered.

Table 3. Overview of cross-sectional studies on antipsychotic drug use and associations with NPSs in older persons in residential care and home care.

<table>
<thead>
<tr>
<th>Reference, year, country</th>
<th>Sample and setting</th>
<th>Measurements</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lövheim et al. 2006</td>
<td>Geriatric unit &gt;65 years with cognitive impairment n=2017</td>
<td>NPSs measured by MDDAS during the preceding week, psychotropics, ADL and cognition</td>
<td>Associations with NPSs, male sex, living in a group dwelling, ability to rise, ADL, dependency and lower age</td>
<td>Antipsychotic drug use common (26%) and associated with aggressive behaviour, verbally disruptive behaviour and wandering</td>
</tr>
<tr>
<td>Sweden</td>
<td></td>
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<tr>
<td>Gustafsson et al. 2013a</td>
<td>Cognitively impaired persons in geriatric care units n=2019</td>
<td>NPSs measured by MDDAS, psychotropics, anti-dementia drugs, ADL and cognition</td>
<td>Antipsychotics used by 25%, associated with NPSs and MCI</td>
<td>Antipsychotics were commonly used and associated with NPSs and cognition</td>
</tr>
<tr>
<td>Sweden</td>
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<tr>
<td>Selbaek et al. 2007</td>
<td>NH patients n=1163</td>
<td>NPSs assessed by NPI, the and the Lawton ADL scale</td>
<td>Antipsychotics used by 26% of persons with dementia</td>
<td>NPSs frequent in NHs and increase with progression of the dementia. Drug use associated with NPSs</td>
</tr>
<tr>
<td>Norway</td>
<td></td>
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<tr>
<td>Wergeland et al. 2014</td>
<td>Home care patients 70 years or more, random sample n=1000</td>
<td>A standardized interview, NPS measure NPI-10, MMSE, drug use</td>
<td>Antipsychotics used by 5% of persons with AD, associated with delusions</td>
<td>NPSs associated with antipsychotic drug use</td>
</tr>
<tr>
<td>Norway</td>
<td></td>
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AD = Alzheimer’s disease, ADL = Activities of Daily Living, MCI = Mild Cognitive Impairment, MDDAS = Multi-Dimensional Dementia Assessment Scale, MMSE = Mini Mental State Examination, NH = Nursing Home, NPS = Neuropsychiatric Symptom

The modest efficacy of these drugs and the risks for serious adverse effects (Schneider et al. 2005) have led to recommendations to use these only for a restricted time for severe NPSs such as psychosis, aggression and agitation (Gauthier et al. 2010). The proportion of unnecessary prescriptions for antipsychotics, if appropriate support was available, is unclear and may vary
by setting, but it may be even two-thirds of all prescriptions (Banerjee 2015). As the provision of antipsychotics has not been sufficiently addressed in consensus papers and practice guidelines, a new guideline for use in dementia patients in residential care has been proposed (Zuidema et al. 2015). There is a need for detailed instructions regarding

1) indications and thresholds to prescribe antipsychotics in agitation, aggression and psychosis,
2) risk factors to be considered before prescription,
3) circumstances in which antipsychotics should be stopped or tapered,
4) specific criteria for justifying long-term treatment and
5) involvement of the multidisciplinary team and family caregiver in the prescription decision.

Antipsychotic use should be discontinued when NPSs have at least partly resolved (Gareri et al. 2014). In case of no improvement, the dose should be increased until side effects appear, but if no improvement occurs within four weeks, the antipsychotic should be withdrawn (Ballard et al. 2009b). Discontinuation of an antipsychotic after 3–6 months of use is recommended in patients who remain relatively asymptomatic (Steinberg and Lyketsos 2012). The APA recommends an attempt to taper and withdraw an antipsychotic within four months of initiation in those who have responded to therapy and who have not earlier had relapses connected to tapering (Corbett et al. 2014, Press et al. 2017). The withdrawal ought to be performed through tapering and monitoring of any relapse of symptoms, and caregivers should always be informed. Because of the fluctuation of NPSs, antipsychotic dose can be gradually tapered and discontinued safely (Rabins et al. 2014). This is often possible without relapses of symptoms (Declercq et al. 2013), although a small proportion of people will have a return of NPSs with cessation or reduction of antipsychotics (Ballard et al. 2009b, Devanand et al. 2012). NPSs should be assessed at least once a month during the tapering of an antipsychotic medication and at least four months after its discontinuation in order to identify a recurrence of symptoms (APA 2015). As the risks of adverse effects of antipsychotics and other psychotropics remain high, with the risk being highest during the first month of use (Rochon et al. 2008), there is an urgent need for safer and effective alternatives to these drugs (Wang et al. 2005, Gill et al. 2007).

2.3.2.2 Antidepressants

Antidepressants are drugs to treat depression and anxiety. Treatment of depression may also reduce other NPSs such as aggression, apathy and psychotic symptoms (Rabins et al. 2007). Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressants, and four RCTs have suggested that they have good tolerability and provide a positive treatment response in depression associated with dementia (Bains et al. 2002). Sertraline, citalopram and escitalopram are considered to have fairly good safety profiles for older persons (Alexopoulos et al. 2001, Wiese 2011). Significant improvement over placebo was seen in older persons with and without dementia (Nyth et al. 1992). In the study of Porsteinsson et al. (2014), persons with probable AD received citalopram up to 30 mg per day and showed significant improvement compared with those who received placebo on several clinical measures, together with lower caregiver stress. Some evidence exists that sertraline and citalopram may reduce agitation better than placebo (Seitz et al. 2011).

However, Banerjee et al. (2013) found sertraline and mirtazapine to have no efficacy on depression (Cornell Scale score >8) in AD. They concluded that alternative drug therapies for depression in dementia, e.g. venlafaxine or AChEIs, should be evaluated. Nevertheless, the APA recommendations prefer SSRIs for NPSs in dementia due to the anticholinergic activity of TCIs (Press et al. 2017).

SSRIs in older persons may increase the risk of hyponatremia, seizures and gastrointestinal bleeding and may cause headache, nausea, vomiting, sleeping problems and agitation (Procyslyn et al. 2015) together with the risk of osteoporotic changes (Fernandes et al. 2016). Citalopram and escitalopram prolong the QT-interval, and the cardiac adverse effects may limit the use of citalopram at 30 mg per day (Porsteinsson et al. 2014). For persons more than 60 years old, a maximum daily dose of 20 mg is recommended (Procyslyn et al. 2015), and special
attention should be paid to individuals with cardiovascular problems (FDA 2012, Procyshyn 2015). The use of such SSRIs as fluoxetine, paroxetine and fluvoxamine may increase the risk of drug-drug interactions with other medications e.g increasing the plasma levels of antipsychotics (Procyshyn et al. 2015). Fluoxetine is not usually recommended for older persons due to its long half-life.

Serotonin and noradrenalin reuptake inhibitors (SNRIs), like venlafaxine and duloxetine, and other antidepressants, such as mirtazapine, mianserin and bupropion, may also be used in depression due to dementia and can be recommended to treat moderate depression (Rabins et al. 2007). The group of other antidepressants may be associated with an increased risk of stroke or transient ischaemic attacks, fractures and seizures (Coupland et al. 2011). They are, however, regarded as safe in terms of drug-drug interactions. The melatonin agonist agomelatine has a well-tolerated profile in antidepressive and sedative use (Kales et al. 2015).

Tricyclic antidepressants (TCAs), introduced in the 1950s and monoamine oxidase inhibitors (MAOIs) were the first antidepressants. TCAs, e.g. amitriptyline, trimipramine and doxepine, have been shown to have anticholinergic side effects, such as dry mouth, urinary retention and constipation, together with CNS problems, such as dizziness, drowsiness, confusion, delirium anxiety and cardiovascular problems, and are thus not recommended for older persons (Procyshyn et al. 2015, Press et al. 2017). Together with such side effects as orthostatic hypotension, these drugs have been largely replaced by the SSRIs, SNRIs and other newer antidepressants. Use of antidepressants is associated with falls in older adults (Hartikainen et al. 2007).

Depressive symptoms are among the most frequent NPSs, with up to half of AD patients affected by them during the course of dementia, increasing the suffering of both patients and caregivers (Lyketsos and Lee 2004). In older persons, depression affects especially those with chronic medical illnesses and cognitive impairment, worsening the outcomes of many medical illnesses and increasing NH placement, family disruption, disability and even mortality (Lyketsos and Olin 2002, Alexopoulos et al. 2005). Laitinen et al. (2015) found that the prevalence of antidepressant use was higher among persons with than without AD, 29% vs. 11%, and 90% of antidepressant users with AD were also using anti-dementia drugs.

Despite the weak efficacy of antidepressants on depression in dementia (Rabins et al. 2007) an antidepressant drug attempt is recommended to treat clinically significant depression in patients with dementia, because depression lowers ADL, impairs quality of life and increases mortality risk in this patient group (Rabins et al. 2007). Also discontinuation of antidepressant treatment in patients with NPSs and dementia has been found to increase depressive symptoms (Bergh et al. 2012). However, more severe depression and apathy were not associated with antidepressant use in NH residents with dementia (Maust et al. 2016). When choosing an antidepressant, the choice should be based on the best side effect profile and the lowest risk of interactions (NICE 2009).

According to the WHO guidelines, antidepressants should not be the first-line treatment for persons with dementia in mild to moderate depression (WHO 2015).

2.3.2.3 Benzodiazepines and related drugs (BZRD)
BZRD include benzodiazepines (BZDs), such as diazepam, oxazepam and temazepam, and BZD-related drugs, which are mostly hypnotics, e.g. zopiclone and zolpidem. BZDs are drugs with anxiolytic, sedative, anticonvulsive and muscle relaxant properties (Ashton 2005). BZD-related drugs, introduced in the 1980s, are chemically different from BZDs, although the effects are comparable. BZDs have caused some clinical improvement in NPSs compared with placebo (Stoppe et al. 1999, Kindermann et al. 2002), although good-quality RCTs are lacking, as are data
on the efficacy of BZDs after 8 weeks, or comparisons of the efficacy of various BZDs in the treatment of NPSs (Rabins et al. 2007, 2014).

BZDs have been associated with cognitive decline and falls (Hartikainen et al. 2007), and especially long-acting BZDs, such as diazepam and nitrazepam, produce prolonged sedation and risk of falls. Other adverse effects include dizziness, respiratory depression and drug dependency (Peisah et al. 2011). The risk of falling was shown to increase after a new prescription of BZDs and with long-term use (Saarelainen et al. 2016). A combination of two or more BZDs doubled the risk of hip fracture (Pierfittie et al. 2001, Saarelainen et al. 2016). BZDs with a long elimination half-life seemed to increase the risk of falling similarly to drugs with a short half-life (Landi et al. 2005).

According to Kales et al. (2015), BZDs should be used only on a short-term basis to treat acute crisis associated with AD. Nevertheless, their use is very often continued (Rikala et al. 2011). Among community-dwelling older people, the prevalence of BZD use has been approximately 10-12% (Blazer et al. 2000). In Finland, one-third (30%) of persons with AD had long-term BZRD use compared with 26% of those without AD (Taipale et al. 2015). The same study indicated that the use started to increase from 12 months before the diagnosis of AD, peaking at six months after the diagnosis had been made. The study of Alalen et al. (2015) did not support anxiolytic drug use for NPSs in persons with dementia because of substantial functional decline in users. BZDs should be avoided in dementia due to the risk of further cognitive decline, falls and paradoxical agitation (Hugo and Ganguli 2014).

2.3.2.4 Other drugs for NPSs
The use of mood stabilizers and anticonvulsants has been studied for NPSs in dementia. Use of sodium valproate is not recommended due to inconsistent results from several RTCs (Rabins et al. 2014). No differences between oxcarbazepine and placebo in dementia with hyperactive NPSs were found by Sommer et al. (2009). Gabapentin reduced aggression in some small studies (Hawkins et al. 2000, Kozman et al. 2006). Carbamazepine was found to decrease hyperactivity symptoms and anxiety (Tariot et al. 1998), but it has problematic side effects like hyponatremia and its long-standing benefits have not been verified (Kozman et al. 2006). Interactions with other drugs may be increased due to the induction of cytochrome P450 3A4.

Beta blockers have been evaluated for treating NPSs. In one study, low-dose propranolol reduced aggressive behaviour in outpatients (Shankle et al. 1995), but no controlled trials exist (Shankle et al. 1995, Kozman et al. 2006). Several other compounds are being investigated in the treatment of hyperactive symptoms in dementia without consistent evidence. They include prazosin, an α1 adrenoceptor antagonist used for hypertension and benign prostatic hypertrophy (Wang et al. 2009), dextromethorphan and quinidine (Pope et al. 2012). In addition, effective management of pain may alleviate NPSs (Husebo et al. 2011, Bradford et al. 2012).

2.4. NON-PHARMACOLOGICAL TREATMENTS FOR NPSS

2.4.1 Description of non-pharmacological treatments
Non-pharmacological treatments comprise the broad spectrum of behavioural, environmental and caregiver supportive interventions. Despite the best practice recommendations, non-pharmacological approaches have not been sufficiently transferred into clinical management and standard care, and the providers are unclear about which treatments are most effective or how they could be best utilized (Kales et al. 2015). Because dementia is pandemic (Alzheimer’s Association 2012), the demands for more effective non-pharmacological interventions to treat NPSs are growing (Gitlin and Rose 2014). However, we do not yet know which psychosocial interventions work best for various NPSs, caregiver and patient profiles and different care settings (Rabins et al. 2014).
Kales and her colleagues (2015) divided non-pharmacological interventions into approaches, which 1) target the person with dementia, 2) target the caregiver or 3) target the environment. Non-pharmacological treatments may include general approaches, e.g. offering caregiver education and training in problem solving, enhancing the activity of the person by exercise or music, stimulating communication with the patient or simplifying the physical environment or tasks. In the targeted approaches, predisposing factors of specific NPSs are identified and modified, e.g. night-time routines are changed to alleviate sleep disturbances (Gitlin et al. 2013). Non-pharmacological interventions have been also categorized as emotion-oriented, stimulation-oriented, behaviour management techniques and cognitive-oriented treatments (Rabins et al. 2007) together with other psychosocial interventions and interventions targeting specific NPSs (O’Neil et al. 2011).

General approaches, which target the person with dementia, include life history and biography work, also called reminiscence therapy, which has been important in increasing the understanding of individual needs and enabling insights into behaviour (Kales et al. 2015). Advantageous impacts of physical activity on AD have been observed (Pitkälä et al. 2013a, 2013b), and integrating physical exercise into the treatment of AD has been beneficial (Ballard et al. 2016, Chen et al. 2016). Approaches aiming to reduce specific NPSs or NPS subgroups such as hyperactivity, include use of preferred or live music (Garland et al. 2007), aromatherapy (Ballard et al. 2002, Lin et al. 2007), simulated presence or recorded conversation (Camberg et al. 1999, Garland et al. 2007) and physical exercise. Simulated presence is an emotion-oriented intervention usually accomplished by playing pre-recorded voices of the loved ones and may include discussions, anecdotes and mutual memories.

The most important non-pharmacological approaches have been general approaches, which are targeted to family caregivers in order to 1) enhance communication, 2) simplify the environment and 3) simplify tasks (Kales et al. 2015). A stepwise multicomponent intervention protocol is based on five meetings where the team members are trained in the stepwise working method of the protocol and the unmet needs of AD patients are targeted by enhanced physical and affective assessment skills (Pieper et al. 2011). Support programmes for persons with dementia and their caregivers have decreased the risk of transfer to LTC and increased the wellness of caregivers (Rabins et al. 2014). Olazarán et al. (2010) concluded that multicomponent interventions for the caregiver delay the transfer of patients with dementia to residential care.

Approaches targeting the environment include, for instance, multisensory stimulation (MSS) or “snoezelen” rooms. These are environments structured to be calming for persons with AD and other dementias and may contain bubble tubes or walls or a projector throwing pictures across the ceiling (Rosenzweig 2016). A recent study comparing snoezelen therapy to common best practice interventions for the reduction of the dementia related NPSs showed no differences between the two groups (Bauer et al. 2015).

Targeted approaches affect the precipitating conditions where specific NPSs are identified and modified. The NICE guideline (2013) recommended MSS, music therapy (MT) and dancing, animal-assisted therapy, aromatherapy and massage for agitation. Teri et al. (2003) found positive effects on mood with exercise training combined with teaching caregivers of AD patients behavioural management techniques. Agitation has been targeted by aromatherapy with lemon balm (Ballard et al. 2002). However, there has been no evidence of any effect on aromatherapy or bright light therapy for agitation (Livingston et al. 2004b).

Fossey et al. (2006) performed a cluster RCT for people with dementia (Table 4). The training intervention was delivered and support given to nursing staff. Antipsychotic use in the intervention homes was reduced from 42% to 23%, but no significant differences were seen in disruptive behaviour or agitation. Milev et al. (2008) conducted a RTC with MSS. They concluded that MSS could be useful when added to the standard care of dementia patients. Raglio et al. (2008) performed a study on MT where persons with dementia received 30 MT sessions, while
the control group received educational support or entertainment activities. NPSs according to the NPI decreased significantly in the MT treatment group (Raglio et al. 2008). NPI total scores decreased in the treatment group. Specific NPSs such as agitation, irritability, aberrant motor behaviour, delusions, anxiety, apathy and sleep disturbances improved and the positive relationship and patients’ active participation in the MT group also improved (Raglio et al. 2008). Weekly physical exercise for older persons in NHs did not improve the mood measured by the Geriatric Depression Scale in a large cluster-RCT by Underwood et al. (2013). However, exercises were largely done while seated which reduces the intensity of the treatment. Light therapy has not been improved effective in the treatment of non-cognitive symptoms of dementia (Forbes et al. 2014). Nevertheless, Riemersma-van der Lek and colleagues found light exposure having modest benefit in improving some NPSs due to dementia, e.g. depressive symptoms, aggressive behaviour and sleeping problems.

How the above-mentioned treatments relate to neuropathology remains unknown. Further studies are needed to investigate the relationships between dementia subtypes and non-pharmacological treatments (Lyketsos et al. 2011). Non-pharmacological treatment strategies should encourage health care providers to be more person-centred in dealing with severe distress due to dementia (Mitchell and Agnelli 2015).

Psychosocial interventions have been found to enhance or maintain cognitive and ADL functions as well as increase adaptive behaviour and quality of life, but no specific intervention has proven to be more effective than another (Rabins et al. 2014). In practice, their use is often sporadic, and no systematic treatment procedures exist for non-pharmacological treatments for NPSs in AD. Due to this, psychototropic drug prescription is often the first-line management for NPSs (Kales et. al. 2015).
Table 4. Examples of studies of non-pharmacological treatments for NPSs in persons with dementia or cognitive impairment.

<table>
<thead>
<tr>
<th>Reference, year country</th>
<th>Sample and setting</th>
<th>Design, intervention</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fossey et al. 2006 Great Britain</td>
<td>Residents with dementia of 12 NHs. Control homes n=168, intervention homes n=181</td>
<td>Intervention study Person-centred care</td>
<td>15% reduction in antipsychotic doses at 12 months</td>
<td>Person-centred care and good practice provides an effective alternative to antipsychotics in NPSs</td>
</tr>
<tr>
<td>Milev et al. 2008 Canada</td>
<td>Dementia patients in LTC n=330</td>
<td>24-week single-blinded RTC MSS</td>
<td>Positive outcome by DOS or CGI-I with the increase of treatment sessions per week</td>
<td>MSS may be a useful addition for patients with dementia</td>
</tr>
<tr>
<td>Raglio et al. 2008 Italy</td>
<td>Persons with AD in NHs n=59</td>
<td>RCT, 18-week intervention, 30 sessions, MT</td>
<td>NPI total score decreased</td>
<td>MT may be effective to reduce NPSs in moderate-severe dementia</td>
</tr>
<tr>
<td>Riemersma-van der Lek et al. 2008 Netherlands</td>
<td>12 group care facilities, 5-year follow-up n=189</td>
<td>Long-term, double-blind RTC Bright light therapy + melatonin 2.5 mg or placebo</td>
<td>MMSE, Cornell Scale for Depression in Dementia, CMAI</td>
<td>Depressive symptoms decreased with light therapy and aggression in combination with melatonin</td>
</tr>
<tr>
<td>Underwood et al. 2014 Great Britain</td>
<td>NH residents 65 or older, 78 NHs at randomization n=765</td>
<td>Cluster-randomized controlled trial Physical exercise, group exercise sessions</td>
<td>GDS-15 score was worse at 12 mths for the intervention group compared with the control group</td>
<td>Exercise did not reduce depressive symptoms in NHs</td>
</tr>
<tr>
<td>Pieper et al. 2016 Netherlands</td>
<td>12 NH residents with advanced dementia n=288</td>
<td>Cluster RCT intervention: Stepwise multidisciplinary training. Control: training on nursing skills</td>
<td>CMAI, NPI-NH and depression scores decreased</td>
<td>Challenging behaviour and depression decreased. Reduction of antidepressants</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease, CGI-I = Clinical Global Impression of Improvement, CMA I= Cohen-Mansfield Agitation Inventory, DOS = Daily Observation Scale, GDS-15 = Geriatric Depression Scale, LTC = Long-Term Care, MSS = Multisensory Stimulation, MT = Music Therapy, NH =nursing home, NPI-NH = Neuropsychiatric Inventory for Nursing Homes, RTC = Randomized Controlled Trial

2.4.2 Efficacy and risks of non-pharmacological treatments for NPSs
The magnitude of the effect sizes of non-pharmacological treatments has been similar to those of psychotropic drugs, i.e. mild or at the best moderate (Olazarán et al. 2010). Non-pharmacological treatments have had a reducing effect on patients’ NPSs and caregivers’ psychological morbidity (Phung et al. 2013). Non-pharmacological approaches delivered by family caregivers have reduced the frequency and severity of NPSs in dementia, equaling the effect sizes of psychotropic use (Karttunen et al. 2011, Brodaty and Arasaratnam 2012). These approaches have had an even greater effect on NPSs than antipsychotics (Schneider et al. 2006, Brodaty and Asaratnam 2012)
or AChEIs (Courtney et al. 2004). Interventions have appeared to be most efficacious when they are tailored individually (Kverno et al. 2009). Supervised person-centred care, communication skills, dementia care mapping (an observational tool to develop person-centred care and for research), sensory therapy activities and structured MTs reduced agitation in persons with dementia in NHSs (Livingstone et al. 2014). A small effect size of 0.23 produced by family caregiver interventions for overall NPSs in dementia was found in a meta-analysis (Brodaty and Arasaratnam 2012). The effect sizes of person-centred care and communication skills training to reduce agitation in care homes have been 0.2-2.2 in a 6-month follow-up (Livingston et al. 2014).

Reminiscence therapy is a biographical intervention, which includes group work where the participants’ past is discussed, or stimuli such as pictures or music are used. It may lead to overall improvements in depression and loneliness and promote psychological well-being as well as improve relationships between people with dementia and their caregivers (Chiang et al. 2010). MSS brought no improvement in NPSs relative to the control group (Baker et al. 2001, 2003).

Physical exercise and activity have been found to be beneficial in numerous trials in the general older population. Nevertheless, only a few studies have investigated their effectiveness in people with dementia. The exercise intervention significantly improved NPSs but not depression (Ballard et al. 2016). However, none of the exercise interventions had a significant impact on agitation (Ballard et al. 2016). A recent study of intensive and long-term exercise programmes for AD patients showed positive effects on physical functioning, with no increased total costs to health and social services or any significant harmful effects (Pitkälä et al. 2013a). In addition, studies have consistently demonstrated that intensive physical rehabilitation enhances mobility and, when administered over a longer period, may also improve the physical functioning of patients with dementia (Pitkälä et al. 2013b).

Pet therapy and social robots in advanced dementia have been introduced, but the results are inconsistent. The positive findings in NPI total score and in irritability in the initial phase were not replicated in the follow-up (Soler et al. 2015). Both living and interactive robotic dogs have reduced loneliness in persons in residential care, and residents become attached to robot as well as to living dogs (Banks et al. 2008). A seal robot (Paro) decreased loneliness in older persons in NHSs but did not reduce depression (Robinson et al. 2013). Jöransson et al. (2015) investigated the use of a seal robot in NHSs and found significant differences in agitation and depression in dementia patients.

A review of non-pharmacological interventions for agitation in dementia suggests that the best approaches to decrease severe agitation in residential care were person-centred care, communication skills training and adapted dementia care mapping (Livingston et al. 2014b). In addition, MT and activities such as hobby crafts and other pleasant activities decrease overall agitation, whereas light therapy and aromatherapy seem ineffective (Livingston et al. 2014a, 2014b). Evidence-based interventions such as person-centred care and communication skills training are available for residential care, but further research is needed to implement these strategies in home care (Livingston et al. 2014b). Evidence suggests that activities and MT reduce agitation in care homes, thus increasing the well-being of patients and caregivers (Livingston et al. 2014a). MT is a potential non-pharmacological treatment for NPSs in dementia. It has been used successfully to treat agitation (Svansdottir and Snaedal 2006, Raglio et al. 2008). Apathy has been targeted by live music (Holmes et al. 2006). However, the use of non-pharmacological approaches is not indicated in acute crisis, when there is a direct threat to health or safety of a person (Kales et al. 2015).

In general, non-pharmacological approaches are well tolerated do not have significant side effects (Olazáran et al. 2010), although some adverse effects have been reported. Agitation may be associated with cognitive or emotion-oriented interventions and physical aggression and agitation related to sensory approaches such as MT, touch therapies and aromatherapy have been reported (Cooke et al. 2010, O’Neil et al. 2011). Despite good tolerability and the possibility to
easily tailor the treatment, organizational or educational factors might influence the underuse of non-pharmacological approaches (Kales et al. 2015).

The benefits of non-pharmacological interventions have been increasingly recognized (Rasmussen et al. 2015), but the lack of sound methodology, small samples in most studies and concentrating on persons in LTC and with advanced dementia have raised doubts concerning their efficacy (Kales et al. 2015). They have been associated with reduction of symptoms without a significant risk of adverse effects and should therefore form a crucial component of the standard care of persons with dementia (Gitlin et al. 2013, APA 2015). In fact, they should be used as the first-line treatment for NPSs (American Geriatrics Society 2003, Kales et al. 2015). It has been suggested that reductions in antipsychotic use may not benefit people with dementia unless non-pharmacological approaches are provided simultaneously (Ballard et al. 2016). In conclusion, non-pharmacological approaches should not be seen as alternatives to psychotropics but as complementary treatments (Olazarán et al. 2010).

2.5 SUMMARY OF TREATMENTS FOR NPSS

Despite extensive documentation of the importance of NPSs in dementia, they have remained mis- or undertreated (Kales et al. 2014). The interventions for relatives and nurses providing education and support, specific problem solving skills and training in stress reduction have shown the strongest evidence of effect. Their target is to increase the activity of a person with dementia by enhancing communication and simplifying the environment and tasks (Kales et al. 2015). However, the effect sizes of all non-pharmacological treatments have been relatively small, and pharmacological management is often also needed. After initiating anti-dementia drugs, if NPSs persist or are severe, psychotropics are commonly used. Antipsychotics can be used in severe agitation and psychosis, but only for a restricted time, and withdrawal should occur within 3-4 months (Ballard et al. 2009b, APA 2015). Atypical antipsychotics have the strongest evidence of effect on NPSs, but the benefits should be weighed against the risks of adverse effects (Kales et al. 2015). Antidepressants are also widely used to treat depression and agitation in dementia, but the effect is limited. The use of BZDs for NPSs should be restricted to the period of acute crisis. Potential risks and benefits of drug use should be discussed with patients and their caregivers, and relatives should be informed when drug therapy is initiated (Kales et al 2015). Individual treatments of this kind challenge current care settings, because the established care practices do not always support time-consuming approaches (Kales et al. 2014).
2.6 RESTRAINTS FOR OLDER PERSONS IN RESIDENTIAL CARE

2.6.1 Definitions of physical and other restraints
Physical restraints, such as bedrails, binding and other restrictions in movement, are commonly used in residential care of older persons worldwide. Physical restraints are considered to be mechanical devices, materials or equipment that restrict freedom of movement or normal access to one’s body (Retas 1998). Indirect measures such as removing walking aids or alarm bells, locking the door or keeping the person undressed can also be regarded as restraining. The prevalence and indications for use of these restraints as well as instructions and associated legal aspects vary markedly between and within countries (Feng et al. 2009). Restraints are most often aimed at protecting patients from falls or other injuries, and bedrails are the most commonly used restraint. However, physical restraining increases the risks of disability, reduces performance and cognition and causes behavioural problems and falls (Castle et al. 1997, Kirkevold et al. 2004). When several restraints are used concomitantly, the negative effect is augmented (Foebel et al. 2016).

Bedrails and removing mobility aids have been considered “high-risk restraints”, whereas seclusion and leg, wrist or ankle restraints are considered “extreme restraints” (Todd et al. 1997). An “environmental restraint” means that the movement of a patient is restricted without an informed consent, as in locked units and fenced areas (Peisah and Skladzien 2014).

2.6.2 Prevalences and associations of restraint use
Globally there is wide variation in the use of physical restraints. Their use has ranged between 4% and 85% in Europe (Meyer et al. 2009, Beerens et al. 2014) and between 9% and 64% in USA (Hamers and Huizing, 2005, Feng et al. 2009). Variations may be due to different populations as well as the instruments used in detecting the restraint use, e.g. the Resident Assessment Instrument (RAI) excludes bedrails as a restraint if bedrails are used for totally bedridden persons, i.e. individuals unable to rise from bed. However, different restraints are used worldwide (Feng et al. 2009, Huang et al. 2013, Beerens et al. 2014). The prevalence of bedrails in aged care facilities ranges from 12% to 49% (Feng et al. 2009, Hamers et al. 2004). Other restraining methods have been belts for the trunk and limbs, chair-tables (Breithauer et al. 2005), locking the door, removing the patient’s walking aid and use of physical force (Saarnio and Isola, 2010). Physical restraints (bedrails excluded) may be more dangerous than the use of antipsychotics (Foebel et al. 2016). In addition, physical restraints are often used continuously, and one study found that 90% of restrained residents had been subjected to restraint use for more than three months (Pellfolk et al. 2010).

Variability in the frequency of physical restraint is abundant both between and within countries (Feng et al. 2009). In a Norwegian study, the use of restraints in one week covered 37% of patients in regular units and 45% of those in dementia units (Kirkevold and Engedal 2004) (Table 5). In a study by Retas et al. (1998), the directors of NHs in Australia completed a survey covering more than 10 000 inhabitants; the results revealed that nearly 40% of patients were restrained with bedrails and 29% with restraint belts in a one-week period. Feng et al. (2009) performed a large population-based study with the RAI (Hawes et al. 1997), and noted that the prevalence of restraint use varied from 6% in Switzerland to 28% in Finland to over 31% in Canada. Raivio et al. (2007) found that 4.7% of patients without dementia were restrained in the preceding two weeks, and the corresponding figure for patients with dementia was 12.2%. Based on cross-sectional data from long-term units in Finland, Pekkarinen et al. (2006) reported that restraints were used for 17% of patients. According to this study, enhancing nurses’ working conditions might reduce restraint use.

Meyer et al. (2009) reported physical restraint use to be associated with a reduced quality of life. Bedrails were used for up to 25% of residents, but fixed tables, belts and other restraints were more rare. Variation between the units suggested that restraint-free care is possible (Meyer et al.
Restraints were on cross prevalence of restrained with countries (Feng et al. 2009). (90% of al.
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Kirkevold et al. 2004).
Restraints do not reduce falls or fall-related injuries, nor do they control NPSs (Köpke et al. 2012,
Möhler et al. 2012, Tang et al. 2012). Restraints may in fact increase the risk of falling and lower
cognitive and ADL functions (Hofmann and Hahn 2014). Their use may impact negatively on a
person’s dignity, autonomy and personal integrity and may cause a traumatic experience
(Gallinagh et al. 2001).
The use of physical restraints is most often associated with high ADL dependency and low
cognitive status (Heinze et al. 2012, Hofmann et al. 2015). Older persons with dementia in
residential care suffer from more advanced stages of the disease and multiple medical conditions
(Schneider et al. 2006, Seitz et al. 2013). Moreover, they tend to receive lower quality of routine
and preventive care than outpatient or hospital populations (Fahey et al. 2003). The restrained
residents have also been more often disoriented, delirious or aggressive (Pellfolk et al. 2010).
Physical restraint use, especially combined with antipsychotic use, has correlated with low ADL
functioning and cognitive functioning in NH residents with dementia (Foebel et al. 2016).
Repeated verbal and physical agitation and aggression were found to be positively associated
with restraint use (Kirkevold et al. 2004). Restraint use decreased in USA after the Omnibus
Budget Reconciliation Act of 1987, a legislation that strongly discouraged NHs from using
restraints unless medically indicated (Konetzka et al. 2014). However, antipsychotic use
simultaneously increased.
In conclusion, the studies on restraint use show discrepancies in defining restraints, and
marked variation is present in prevalences of use between institutions and countries. Bedrails are
the most commonly used restraint devices in many studies.
### Table 5. Cross-sectional studies of prevalences and types of physical restraints used in residential care.

<table>
<thead>
<tr>
<th>Reference, year country</th>
<th>Sample and setting</th>
<th>Method, detection time of restraining</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retsas et al. 1998 Australia</td>
<td>272 NHs, n=10 065</td>
<td>Directors of NHs completed a 48-item survey, point prevalence at the time of completing survey</td>
<td>25.5% were restrained, most common types of restraining were bedrails (39%) and restraining belts (29%)</td>
</tr>
<tr>
<td>Kirkevold and Engedal 2004 Norway</td>
<td>Random sample from 222 NH wards n=1501</td>
<td>Structured interview with primary carers. Population-based study, past 7 days</td>
<td>37% in general units and 45% in dementia units were subjected to any restraint</td>
</tr>
<tr>
<td>Pekkarinen et al. 2006 Finland</td>
<td>23 NHs and 8 health centres, n= 2430</td>
<td>RAI, population-based, past 7 days</td>
<td>Restraints used for 17% of residents</td>
</tr>
<tr>
<td>Feng et al. 2009 Canada, Finland, China (Hong Kong), Switzerland, USA</td>
<td>LTC facilities, n=14 504</td>
<td>RAI, population-based past 7 days</td>
<td>Prevalence of restraint use: Switzerland 6%, USA 9%, Hong Kong 20%, Finland 28%, Canada 31%</td>
</tr>
<tr>
<td>Meyer et al. 2009 Germany</td>
<td>30 NHs, n=2367</td>
<td>Observational study, one day</td>
<td>26% were restrained, bedrails used for 25%, but fixed tables, belts and other restraints were rare</td>
</tr>
<tr>
<td>Heinze et al. 2012 Germany</td>
<td>76 NHs n=5521 and 15 hospitals n=2827</td>
<td>Standardized questionnaires, point prevalence at the time of the survey</td>
<td>9% of hospital patients had bedrails and/or belts and 26% in NHs</td>
</tr>
<tr>
<td>Hofmann et al. 2015 Switzerland</td>
<td>20 NHs, n=1362</td>
<td>Data from residents’ records, past 7 days</td>
<td>At least one physical restraint in 27%. Bilateral bedrails in 20%</td>
</tr>
</tbody>
</table>

NH = Nursing Home, LTC = Long-Term Care, RAI = Resident Assessment Instrument

#### 2.6.3 Ethical aspects of restraint use

Physical restraints are often meant to increase safety and prevent falls, but they may fail to achieve these goals (Kirkevold et al. 2004), even increasing falls (Hignett and Griffiths 2005). Possible consequences of physical restraints have been lower cognitive and ADL performance, higher walking dependency, more falls, pressure ulcers, urinary and faecal incontinence, depression, aggression and even death (Hamers et al. 2004, Kirkevold et al. 2004, Hofmann and Hahn 2014). On the other hand, lower ADL, problems of mobility, cognitive impairment, NPSs or history of multiple falls increase the risk of physical restraining (Castle et al. 1997, Kirkevold et al. 2004, Hofmann and Hahn 2014). Due to this complexity, the use of restraints can be regarded as an ethical problem for nursing staff (Saarmio et al. 2009). Although the risk of fatal entrapment has been lower than one in ten million admissions in hospitals (National Patient Safety Agency 2007), the importance of adequate fitting and maintenance of bedrails should not be neglected. Their use may also impact negatively on a person’s dignity, autonomy and integrity and may cause a traumatic experience (Gallinagh et al. 2001, Gastman and Milisen, 2006).

Restraining by the straps, particularly around the body, is associated with a lack of independency, causing isolation and barriers to social life (Berzlanovich et al. 2012). Regular and long-lasting restraining may cause or exacerbate existing muscular atrophy (Gastman and Milisen 2006). Due to immobilization, the ability to stand and move independently may be
impaired after the period of restraint and may result in falls. Physical restraints increase the risk of decubitus ulcers, pneumonia and leg vein thrombosis (Gastman and Milisen 2006). A negative effect of immobilization on cognitive skills has been reported (Wang and Moyle 2005). Incorrect use of restraining straps may cause cutaneous abrasions, bruises, soft tissue compression, neural lesions or even fractures. Berzlanovich et al. (2012) found that deaths due to physical restraints do occur, although they are rare.

The use of physical restraints is regulated strictly in many countries, whereas in others there is no specific legislation concerning their use. Even stern regulations as in Switzerland, have not succeeded in reducing the use of restraints (Hofmann et al. 2015). In Finland, the legislation covers their use only in mental health care services. Only one-third of wards providing residential care for older persons had written guidelines concerning their use (Saarnio et al. 2009).
3 Aims of the thesis

The use of anti-dementia and psychotropic drugs in regular home care and residential care, and their associations with Neuropsychiatric Inventory-defined NPSs and personal characteristics were examined. Also investigated was the use of physical restraints in residential care.

Specific aims were as follows:

1) To compare the users and non-users of anti-dementia drugs and examine the associations of drugs with NPSs in persons with dementia (Study I),

2) To evaluate the use of antipsychotics among persons with cognitive impairment and associations with NPSs (Study II),

3) To explore the physical restraints used in residential care and the associations with psychotropic drug use and NPSs (Study III) and

4) To investigate the prevalence of non-pharmacological approaches for NPSs in residential care.
4 Methods

4.1 SETTING AND DATA COLLECTION

The catchment area of the South Savo Hospital District has 105,000 inhabitants. In 2011, it consisted of 11 municipalities and had the largest proportion of aged individuals in Finland; 24% were aged 65 years or more (Statistics Finland 2012). We identified 68 residential care units in the district, 66 of which responded (Figure 1). In addition, of the 22 home care units, 21 responded.

![Diagram of study population recruitment](image)

*Figure 1. Recruitment of the study population.*

The data were gathered with the assistance of municipal and regional authorities. Nurses and doctors in charge were contacted and the study questionnaires were mailed to them with written instructions on how to implement the assessments. The cross-sectional data collection was accomplished in May 2011. Questionnaires included the basic demographic information of each patient, e.g. municipality, service unit or residential care unit, age and gender, followed by questions concerning current regularly used medications. The ADL (Barthel Index) score was included in both care settings, whereas Lawton and Brody IADL scores (Lawton and Brody, 1969) concerned home care only. Nurses assessed the NPSs according to the modified symptom list of Cummings et al. (1994) and Kaufer et al. (2000). Cognitive functioning was assessed by detecting the diagnoses of dementia from the medical records or classifying the cognition into four categories by nurses' observation.

In this study, residential care included all services in institutional care services and long-term wards in health centres. There is a novel kind of service between these traditional settings, i.e. assisted living facilities, which is divided into ordinary or intensified care with a 24-hour service. In the latter, nursing and medical facilities are available 24/7 and we included them in the category of long-term residential care. We identified and contacted all institutions providing
long-term residential care to older persons, comprising both private and municipal NHs, 24/7 sheltered housing services and LTC in health centres.

Regular home care included nurse visits at least once a week. Auxiliary services might also be available (e.g. meals-on-wheels, transportation). With the assistance of regional and municipal authorities, all home care units providing regular home care were identified.

The study population in Study I comprised all individuals diagnosed with dementia in residential care (n=774) and home care (n=410) (Figure 2). Of these 1184 persons, 791 used anti-dementia drugs.

![Figure 2. Population of Study I, users and non-users of anti-dementia drugs among persons with dementia.](image-url)
Study I subjects comprised long-term residential care to older persons, comprising both private and municipal NHs, 24/7 sheltered housing services and LTC in health centres. Regular home care included nurse visits at least once a week. Auxiliary services might also be available (e.g. meals-on-wheels, transportation). With the assistance of regional and municipal authorities, all home care units providing regular home care were identified.

The study population in Study I comprised all individuals diagnosed with dementia in residential care (n=774) and home care (n=410) (Figure 2). Of these 1184 persons, 791 used anti-dementia drugs.

Study II subjects comprised cognitively impaired persons. A person was classified as cognitively impaired if he or she had a diagnosis of dementia in medical records. In addition, nurses classified the patient’s cognition into four levels (normal, slightly impaired, moderately impaired, severely impaired). A category “cognitively impaired” was then formed from all persons who had the diagnosis or who were classified by a nurse to be slightly to severely cognitively impaired (Figure 3).
The original study population of *Study III* comprised 1439 persons in residential care. Because of missing information on restraint use, data were only gathered for 1386 persons. Of these, 721 persons (52%) were exposed to physical restraints during the preceding 24 hours (Figure 4).

*Figure 4.* Population of Study III, restrained and non-restrained persons.
The original study population of Study III comprised 1439 persons in residential care. Because of missing information on restraint use, data were only gathered for 1386 persons. Of these, 721 persons (52%) were exposed to physical restraints during the preceding 24 hours (Figure 4).

Figure 4. Population of Study III, restrained and non-restrained persons.

Restrained persons (in 24 hours)  
\[ n = 721 \]

Non-restrained patients  
\[ n = 665 \]

Residential care  
\[ n = 1386 \]

Residential care  
\[ n = 1439 \]

Missing data of restraints  
\[ n = 53 \]

The study population for the use of non-pharmacological treatments comprised 1439 persons in residential care. At least one non-pharmacological approach was used for 744 individuals who had at least one NPS (52%) (Figure 5). The assessed methods were verbal assurance, giving time and comfort, assessing somatic condition, using music, team assistance, animals or toys, discussions with relatives, occupational therapy and physical exercise or outdoor activities.

4.2 MEASUREMENTS

Nurses in residential care and home care facilities collected all data. They filled in the questionnaires according to written instructions. MK was designated as the contact person for additional information concerning the evaluation of patients. Nurses did not receive specific training to fill out the evaluations.

4.2.1 ADL functioning and cognition

Nurses assessed each patient’s basic ADL by the Barthel Index (BI), which was first introduced by Mahoney and Barthel (1965). The BI is a distinguished scale to assess physical functional deficits in people with dementia. It has been widely translated and validated and takes only five minutes of the informant’s time (Sheehan 2012). It comprises ratings on ten areas of ADL and mobility, including personal hygiene, bathing, feeding, toileting, stair climbing, dressing, bowel control, bladder control, ambulation and chair/bed transfer. Each performance item is rated on this scale with a given number of points assigned to each level. The original BI score then range from 0 to 100, but a widely adopted modification by Collin et al. 1988) revised the score to then ranging from 0 to 20. The accuracy of the BI was further improved after ten years (Shah et al. 1989). A higher score is associated with a greater degree of ADL independence. The BI is regarded
as a reliable scale (Collin et al. 1988), feasible not only in residential care facilities, but also in home care and in the community. Although the BI is a recommended scale to use, notable uncertainties remain, particularly when used on older people with many chronic diseases (Sainsbury et al. 2005).

Nurses in home care assessed the IADL by the Lawton and Brody scale, which has been regarded as an appropriate tool to assess independent living skills. The items are ability to use the telephone, managing laundry, shopping, food preparation, transportation, housekeeping, responsibility for own medications and ability to handle finances. It is fast to administer, taking only 10-15 minutes, and is ideal for community-dwelling older adults (Graf 2008). It is used as a screening instrument, but can be used to identify changes over time. The eight domains are rated with a summary score from 0 (low functioning) to 8 (high functioning). The validity of the IADL scales has been studied by Vitteng et al. (2006) who found the IADL to have a strong association with cognitive functioning (Tomburgh and McIntyre 1992).

Cognition was assessed in three ways. Firstly, nurses retrieved physician-made diagnoses of dementia from medical records. Secondly, nurses classified based on their own assessment patients’ cognition into four categories (normal, slightly impaired, moderately impaired, severely impaired). Persons from the last three categories were subsequently classified as “cognitively impaired”, as were persons diagnosed with dementia. Cognition was also assessed from the latest Mini Mental State Examination (MMSE) (Folstein et al. 1975) if carried out in 2010 or 2011. This 30-point evaluation is the most commonly used tool for cognition. It consists of 30 items and tests, each of which yields one point if the person answers correctly. It assists in estimating the level of cognitive impairment and in following the progression of cognitive changes of a person over time. The results were collected from medical records. Administration of the assessment takes 5-10 minutes and examines the functions of registration, attention and calculation, recall, language, ability to follow simple commands and orientation (Tuil et al. 2012).

4.2.2 Drug use
The comprehensive data on drug use was retrieved from the electronic medical records of each patient. Electronic medical records concerning drug use in residential care and home care were reliably managed and updated by a nurse. Antipsychotics were classified according to the Anatomical Therapeutic Chemical (ATC) Classification of Medicines recommended by the WHO (2013). Conventional antipsychotics were the group N05A in the ATC classification: chlorpromazine (N05AA01), levomepromazine (N05AA02), fluphenazine (N05AB02), perphenazine (N05AB03), pericazine, (N05AC01), haloperidol (N05AD01), flupentixol (N05AF01), chlorprothixene (N05AF03) and zuclopenthixol (N05AF05). Atypical antipsychotics were clozapine (N05AH02), olanzapine (N05AH03), quetiapine (N05AH04), risperidone (N05AX08), aripiprazole (N05AX12), sertindole (N05AE03) and ziprasidone (N05AE04). Sulpiride (N05AL01) was also included in atypical antipsychotics.

TCIs included clomipramine (N06AA04), trimipramine (N06AA06), amitriptyline (N06AA09), nortriptyline (N06AA10) and doxepin (N06AA12). SSRIs were fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08) and escitalopram (N06AB10). SNRIs comprised venlafaxine (N06AX16) and duloxetine (N06AX21). Other antidepressants included mianserin (N06AX03), trazodone (N06AX05), mirtazapine (N06AX11), bupropion (N06AX12), milnacipran (N06AX17), reboxetin (N06AX18), agomelatin (N06AX22) and moclobemid (N06AG02).

BZRD included the long-acting BZDs diazepam (N05BA01), chlordiazepoxide (N05BA02), alprazolam (N05BA12) and nitrazepam (N05CD02) together with medium- and short-acting BZDs oxazepam (N05BA04), lorazepam (N05BA06), triazolam (N05CD05) and temazepam (N05CD07). BZD-related drugs included zopiclone (N05CF01), zolpidem (N05CF02) and zaleplon (N05CF03). Mood stabilizers were lithium (N05AN01), sodium valproate (N03AN01) and carbamazepine (N03AF01).

Use of drugs administered pro re nata was not included in this study.
4.2.3 NPSs and subgrouping of symptoms
NPSs were assessed based on the NPI questionnaire. A brief version (NPI-Q) contains only the screening question, severity rating and caregiver distress rating of the original NPI, but the present study utilized only the screening questions of the brief version. Validity between NPI-Q and the NPI has been good (Kaufer et al. 2000). The NPSs enquired about included the following: agitation/aggression, irritability, disinhibition, aberrant motor behaviour, hallucinations, delusions, depression, anxiety, euphoria, apathy and problems in eating or sleeping.

The nurses assessed which NPSs were present during the preceding 24 hours in those care facilities providing nursing care 24/7 and during the preceding week in home care due to the at least weekly visiting schedules. The original NPI instrument has established psychometric properties in clinical trials. It assesses behavioural changes in neurological illnesses based on a standardized caregiver interview. The NPI also includes an integrated caregiver distress scale to evaluate caregiver distress associated with the patient’s behavioural changes. The symptoms include psychotic symptoms as delusions and hallucinations. Aggression might be physical or verbal. An agitated patient is easily upset, repeats questions, argues or complains, exhibits pacing, inappropriate screaming, rejects bathing or dressing or escapes from home. Other hyperactive symptoms include irritability and motor disturbances that may be purposeless actions or roaming. Apathy includes lack of motivation. Depression or dysphoria was evaluated as was anxiety. Elevation of mood and problems with sleep, appetite or eating were also assessed.

NPSs were divided into three subgroups: 1) hyperactivity, 2) psychosis and 3) mood and apathy. Aalten et al. (2003) found that agitation/aggression, aberrant motor behaviour, disinhibition and euphoria clustered together in the hyperactivity subgroup, whereas delusions and hallucinations formed the psychosis subgroup. In that study, depression, loss of sleep and appetite and apathy formed the mood and apathy subgroup, and anxiety clustered alone. However, according to van der Linde and colleagues (2014), also clinical judgement based on the occurrence of NPSs in the clinic and hypotheses regarding aetiology may be used to group symptoms. Following their suggestion, anxiety and euphoria were categorized in the mood and apathy subgroup in the present study.

4.2.4 Non-pharmacological treatments
Non-pharmacological approaches for NPSs were asked about in residential care services. Nurses reported whether the following approaches had been used during the last 24 hours (yes/no): 1) verbal reassurance, 2) time and comfort, 3) assessing somatic condition, 4) music, 5) using team to assist, 6) use of animals or toys, 7) discussions with relatives, 8) occupational therapy, gardening, etc., 9) physical exercise or outdoor activities.

4.2.5 Physical restraints
According to a widely accepted definition, physical restraints are “any devices, materials or equipment attached to or near a person’s body that cannot be controlled or easily removed by the person and that deliberately prevent or are intended to prevent a person’s free body movement to a position of choice and/or a person’s normal access to the body” (Retsas et al.1998). Nurses assessed restraint use in the residential care facilities. The alternatives were bedrails on both sides or on one side, restriction of the movement of the body (e.g. garments used to tie a patient to a chair, magnetic belt used to tie to a bed), restriction of movement of limb(s) (e.g. hand strap or a bond), boarding of the chair to prevent movement (e.g. associated with geriatric chair or, table), removing mobility aids, locking the door, using a soundproofed room, use of physical force, alarm mat, motion sensor, other choices or none of the above.
4.2.6 Main causes of care
Nurses were requested to assess the patient’s most important medical condition resulting in the need for residential care or regular home care. Only one alternative could be selected. Alternatives included 1) cognitive impairment (e.g. AD, vascular dementia, cerebrovascular disease), 2) other neurological condition (e.g. Parkinson’s disease, epilepsy), 3) musculoskeletal disorder (e.g. rheumatoid arthritis, osteoarthritis), 4) cardiovascular disease (myocardial infarction, coronary artery disease, valvular heart disease, arrhythmia), 5) any type of malignancy, 6) psychiatric disorder (e.g. depression, schizophrenia, paranoia), 7) accident and sequelae, 9) diabetes, 10) long-term lung disease (e.g. asthma, chronic obstructive pulmonary disease), 11) acute inflammatory disease (e.g. urinary tract infection, pneumonia, erysipelas, herpes zoster), 12) mental retardation, 13) other (e.g. gastric ulcer, varicose ulcer, thyroid dysfunction) and 13) none of the above.

4.3 STATISTICS
The data in Study I were described using proportions and means with standard deviation (SD). Statistical comparisons between users and non-users of anti-dementia drugs were conducted using the Chi-square test and independent samples t-test or one-way analysis of variance, with p≤0.05 considered significant. Univariate and multivariate forward stepwise regression analyses were performed to recognize such demographic subgroups as age, gender, care setting and NPS subgroups associating with the use of anti-dementia drugs. Results were indicated as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs). The data were analysed by using the Statistical Package for Social Sciences (SPSS) 19.0 software.

The data in Studies II and III were presented as means with SD, medians with interquartile ranges or numbers with percentages. Statistical comparisons between groups were performed using analysis of variance, t-test, Chi-square test or Fisher’s exact test, as appropriate. In case of a violation of assumptions (e.g. non-normality), a bootstrap-type test was used. The normality of the variables was tested using the Shapiro–Wilk W-test. Odds ratios (ORs) (95% CIs) were estimated using univariate and and multivariate forward stepwise logistic regression models. The Data Analysis and Statistical Software (STATA) 13.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

4.4 ETHICAL ASPECTS
The Ethics Committee of the South Savo Hospital District approved the study design on 8 September 2010. Because the study was based on medical records, without identification of individual patients or therapeutic interventions, no informed consents from patients or their family members were required. Local health authorities supported the participation in the study resulting in no incentives being needed to promote the response rate.
5 Results

5.1. STUDY POPULATION

5.1.1 Characteristics of study population
The study population in the South Savo Hospital District consisted of 2821 persons, 68.1% (n=1921) of whom were women (Table 6). The mean age was 80.9 years; 82.0 years in institutions and 79.8 years in home care settings. Only 8% (n=224) were younger than 65 years. Of those living at home, 81% were living alone. In the total study population (n=2821) (Figure 1), a physician-made diagnosis of dementia was found in 44% (n=1184), in 56% in residential care and in 31.1% in home care. In Study I, the population comprised the persons with diagnosed dementia (n=1184) (Figure 2). In the Study II, patients with cognitive impairment assessed by nurses regardless of whether or not diagnosed by a physician were categorized as cognitively impaired (n=1909) (Figure 3); they formed 68% of the whole study population. The Study III comprised the whole population in residential care (n=1439) (Figure 4). In the whole study population, the ADL functioning was significantly lower in residential care setting (mean BI 36.9) than in home care (BI 80.8). The MMSE was obtained only from 50% (n=1415) of the patients, the mean being 17.6 (SD 7.2); 21.3 in home care and 14.5 in residential care. The mean Lawton and Brody IADL score in home care was 3.3 (scale 0–8), with a higher score indicating better function. The main cause of care was dementia in both care settings, followed by cerebrovascular diseases in residential care and cardiovascular diseases in home care.

Table 6. Characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=2821)</th>
<th>Residential care (n=1439)</th>
<th>Home care (n=1382)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>1921 (68.1)</td>
<td>995 (69.1)</td>
<td>926 (67.0)</td>
<td>0.223</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>80.9 (10.1)</td>
<td>82.0 (9.8)</td>
<td>79.8 (10.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years, n (%)</td>
<td>224 (8)</td>
<td>89 (6)</td>
<td>135 (10)</td>
<td></td>
</tr>
<tr>
<td>65-74 years, n (%)</td>
<td>354 (13)</td>
<td>172 (12)</td>
<td>182 (13)</td>
<td></td>
</tr>
<tr>
<td>75-84 years, n (%)</td>
<td>1053 (37)</td>
<td>511 (36)</td>
<td>545 (40)</td>
<td></td>
</tr>
<tr>
<td>85-94 years, n (%)</td>
<td>1055 (37)</td>
<td>579 (40)</td>
<td>476 (34)</td>
<td></td>
</tr>
<tr>
<td>95 years or more, n (%)</td>
<td>132 (5)</td>
<td>88 (6)</td>
<td>44 (3)</td>
<td></td>
</tr>
<tr>
<td>Diagnoses and functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed dementia, n (%)</td>
<td>1184 (43.8)</td>
<td>774 (56.0)</td>
<td>410 (31.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADL score (mean, SD)</td>
<td>58.4 (34.3)</td>
<td>36.9 (30.8)</td>
<td>80.8 (20.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IADL score (mean, SD)</td>
<td></td>
<td>3.30 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE (mean, SD)*</td>
<td>17.6 (7.2)</td>
<td>14.5 (7.6)</td>
<td>21.3 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Main causes of care, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>1061 (37.6)</td>
<td>706 (49.1)</td>
<td>355 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>313 (11.1)</td>
<td>93 (6.5)</td>
<td>220 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>336 (11.9)</td>
<td>209 (14.5)</td>
<td>127 (9.2)</td>
<td></td>
</tr>
</tbody>
</table>

ADL = Activities of Daily Living, IADL = Instrumental Activities of Daily Living, MMSE = Mini Mental State Examination, SD = Standard Deviation
*MMSE for 743 persons (52%) in residential care and for 672 persons (49%) in home care.

5.1.2 Number of drugs used
Use of drugs was frequent in the total population. The mean number of drugs was 8.7 (Table 8). In home care the figure was 8.8 and in residential care 8.6. The majority of patients in both care
settings used more than six different drugs. It was common to use ten or more drugs, but only a few used 20 or more drugs.

**Figure 6.** Total number of drugs used by persons in residential care and home care.

### 5.1.3 NPSs and their subgroups

Among the cognitively impaired subpopulation (n=1909), no NPSs were detected in 43% of patients in residential care and 46% of patients in home care (Table 7). In home care, one NPS was somewhat more common, while several NPSs occurring simultaneously in the same person were more common in residential care, where one-fifth of patients suffered from 2-3 NPSs and 6% from four or more NPSs concomitantly. In home care, 16% of persons had 2-3 NPSs and 5% suffered from four or more NPSs simultaneously. Hyperactivity subgroup symptoms were more abundant in residential care (37%) than in home care (20%), whereas mood and apathy subgroup symptoms occurred more frequently in home care (32% vs. 39%). The frequency of psychotic symptoms did not differ significantly: 11% in residential care and 13% in home care. Of distinct NPSs, agitation/aggression was detected in 210 persons (18%) in residential care and in 58 persons (9%) in home care. Depression was the most common NPS in home care, present in 140 persons (21%), compared with 133 persons (12%) in residential care. Sleeping disturbances were common in home care (15%) and in residential care (10%). Eating problems were found in 6% of patients in both settings. Apathy was detected only in 3% of patients in home care and in 5 of patients in residential care.
Table 7. Frequency of NPSs (n, %) and subgroups in cognitively impaired patients* by setting.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Residential care (n=1149)</th>
<th>Home care (n=684)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of NPSs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>489 (42.6)</td>
<td>312 (45.6)</td>
<td>0.031</td>
</tr>
<tr>
<td>1</td>
<td>354 (30.8)</td>
<td>231 (33.8)</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>233 (20.3)</td>
<td>106 (15.5)</td>
<td></td>
</tr>
<tr>
<td>4 or more</td>
<td>73 (6.4)</td>
<td>35 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Subgroups of NPSs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>agitation/aggression</td>
<td>210 (18.3)</td>
<td>58 (8.5)</td>
<td></td>
</tr>
<tr>
<td>disinhibition</td>
<td>112 (9.8)</td>
<td>12 (1.8)</td>
<td></td>
</tr>
<tr>
<td>irritability</td>
<td>203 (17.7)</td>
<td>86 (12.6)</td>
<td></td>
</tr>
<tr>
<td>aberrant motor behaviour</td>
<td>80 (7.0)</td>
<td>11 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>delusions</td>
<td>61 (5.3)</td>
<td>48 (7.0)</td>
<td></td>
</tr>
<tr>
<td>hallucinations</td>
<td>78 (6.8)</td>
<td>53 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Mood symptoms and apathy</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>depression</td>
<td>367 (31.9)</td>
<td>268 (39.2)</td>
<td></td>
</tr>
<tr>
<td>anxiety</td>
<td>133 (11.6)</td>
<td>140 (20.5)</td>
<td></td>
</tr>
<tr>
<td>sleeping problems</td>
<td>95 (8.3)</td>
<td>54 (7.9)</td>
<td></td>
</tr>
<tr>
<td>eating problems</td>
<td>116 (10.1)</td>
<td>107 (15.6)</td>
<td></td>
</tr>
<tr>
<td>elation</td>
<td>67 (5.8)</td>
<td>40 (5.8)</td>
<td></td>
</tr>
<tr>
<td>apathy</td>
<td>19 (1.7)</td>
<td>12 (1.8)</td>
<td></td>
</tr>
</tbody>
</table>

NPS = Neuropsychiatric Symptom
* Missing NPS data for 76 persons

5.2 USE OF ANTI-DEMENTIA AND PSYCHOTROPIC DRUGS

Anti-dementia drugs were used by 32% (n=901) of the whole study population (n=2821) (Table 8). AChEIs were used by a total of 735 persons (26%), 391 (27%) in residential care and 344 (25%) in home care. Dementia diagnosis was found in 1184 patients. Donepezil formed half of the drug prescriptions. Of patients in residential care, 9% used combinations of AChEIs and memantine and 4% in home care, this figure was 4%.

Antipsychotics were used by 28% (n=797) of the total population, by 36% (n=520) in residential care and by 20% (n=270) in home care. Atypical antipsychotics were used by 666 persons (24%), 454 (33%) in residential care and 212 (15%) in home care. Atypical antipsychotics formed the majority of antipsychotic prescriptions, risperidone being the most abundant (11%). Conventional antipsychotics were used by less than 5% of the whole study population.

Antidepressants were used by 25% of the total population (n=711); the use was similar in the two settings, 26% (n=379) in residential care and 24% (n=332) in home care. SSRIs were used by 14%, and citalopram formed more than half of the use. Mirtazapine was used by almost one-tenth of the patients in both care settings.
Mood stabilizers were used by 7% (n=210) of the total population. BZRD were used by 383 patients (27%) in residential care and by 271 patients (17%) in home care. Less than 1% of patients in both settings used no drugs (Figure 6).
Table 8. Psychotropic drug use in the total population, in residential care patients and in home care patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=2821</th>
<th>Residential care n=1439</th>
<th>Home care n=1382</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of drugs, mean (SD)</td>
<td>8.7 (3.8)</td>
<td>8.6 (3.7)</td>
<td>8.8 (3.9)</td>
</tr>
<tr>
<td>Anti-dementia drug users, n (%)</td>
<td>901 (31.9)</td>
<td>516 (35.9)</td>
<td>385 (27.9)</td>
</tr>
<tr>
<td>AchEIs, n (%)</td>
<td>735 (26.1)</td>
<td>391 (27.2)</td>
<td>344 (24.9)</td>
</tr>
<tr>
<td>donepezil, n (%)</td>
<td>382 (13.5)</td>
<td>187 (13.0)</td>
<td>195 (14.1)</td>
</tr>
<tr>
<td>rivastigmine, n (%)</td>
<td>215 (7.6)</td>
<td>150 (10.4)</td>
<td>65 (4.7)</td>
</tr>
<tr>
<td>galantamine, n (%)</td>
<td>138 (4.9)</td>
<td>54 (3.8)</td>
<td>84 (6.1)</td>
</tr>
<tr>
<td>Memantine n (%)</td>
<td>356 (12.6)</td>
<td>254 (17.7)</td>
<td>102 (7.4)</td>
</tr>
<tr>
<td>AChEI and memantine</td>
<td>190 (6.7)</td>
<td>129 (9.0)</td>
<td>61 (4.4)</td>
</tr>
<tr>
<td>Antipsychotic users, n (%)</td>
<td>790 (28.3)</td>
<td>520 (36.1)</td>
<td>270 (19.5)</td>
</tr>
<tr>
<td>Conventional antipsychotics, n (%)</td>
<td>176 (6.2)</td>
<td>98 (6.8)</td>
<td>78 (5.6)</td>
</tr>
<tr>
<td>Levomepromazin</td>
<td>37 (1.3)</td>
<td>18 (1.2)</td>
<td>19 (1.4)</td>
</tr>
<tr>
<td>Atypical antipsychotics, n (%)</td>
<td>666 (23.6)</td>
<td>454 (32.7)</td>
<td>212 (14.7)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>319 (11.1)</td>
<td>216 (15.0)</td>
<td>103 (7.5)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>270 (9.6)</td>
<td>193 (13.4)</td>
<td>77 (5.6)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>78 (2.8)</td>
<td>45 (3.1)</td>
<td>33 (2.4)</td>
</tr>
<tr>
<td>Mood stabilizer users, n (%)</td>
<td>210 (7.4)</td>
<td>135 (9.4)</td>
<td>75 (5.4)</td>
</tr>
<tr>
<td>Lithium</td>
<td>15 (0.5)</td>
<td>6 (0.4)</td>
<td>9 (0.7)</td>
</tr>
<tr>
<td>Antidepressant users, n (%)</td>
<td>711 (25.2)</td>
<td>379 (26.3)</td>
<td>332 (24.0)</td>
</tr>
<tr>
<td>TCAs</td>
<td>53 (1.9)</td>
<td>26 (1.8)</td>
<td>27 (1.9)</td>
</tr>
<tr>
<td>SSRIs</td>
<td>390 (13.8)</td>
<td>214 (14.9)</td>
<td>176 (12.7)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>206 (7.3)</td>
<td>113 (7.9)</td>
<td>93 (6.7)</td>
</tr>
<tr>
<td>SNRIs</td>
<td>55 (1.9)</td>
<td>23 (1.6)</td>
<td>32 (2.3)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>31 (1.1)</td>
<td>13 (0.9)</td>
<td>18 (1.3)</td>
</tr>
<tr>
<td>Others</td>
<td>257 (9.1)</td>
<td>130 (9.0)</td>
<td>127 (9.2)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>242 (8.6)</td>
<td>123 (8.6)</td>
<td>119 (8.6)</td>
</tr>
<tr>
<td>BZD users, n (%)</td>
<td>654 (23.2)</td>
<td>383 (26.6)</td>
<td>271 (19.6)</td>
</tr>
<tr>
<td>Long-acting BZDs</td>
<td>88 (3.1)</td>
<td>49 (3.4)</td>
<td>39 (2.8)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>44 (1.6)</td>
<td>26 (1.8)</td>
<td>18 (1.3)</td>
</tr>
<tr>
<td>Medium- and short-acting BZDs</td>
<td>416 (14.7)</td>
<td>266 (18.5)</td>
<td>150 (10.9)</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>194 (6.9)</td>
<td>133 (9.2)</td>
<td>61 (4.4)</td>
</tr>
<tr>
<td>BZD-related drugs</td>
<td>205 (7.3)</td>
<td>95 (6.4)</td>
<td>110 (8.0)</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>174 (6.2)</td>
<td>76 (5.3)</td>
<td>98 (7.1)</td>
</tr>
</tbody>
</table>

AChEI = Acetylcholinesterase Inhibitor, BZD= Benzodiazepine, BZRD= Benzodiazepines and Related Drugs, SNRI= Serotonin and Noradrenaline Reuptake Inhibitor, SSRI= Serotonin Reuptake Inhibitor, TCA= Tricyclic Antidepressant
5.3 USERS AND NON-USERS OF ANTI-DEMENTIA DRUGS AND ASSOCIATIONS WITH NPSS (STUDY I, N=1184)

The majority, 67%, of persons with diagnosed dementia (n=1184) used anti-dementia drugs (n=791) (Table 9). There were some differences in the prevalences of NPSs and subgroups between users and non-users of anti-dementia drugs. More than half of the users and non-users of anti-dementia drugs were suffering from one or more NPSs. Users of anti-dementia drugs had more frequently two to three NPSs compared with non-users (p=0.016). Some 6% of both groups had four or more NPSs. The mean ADL score was 58 (SD 31.5) in users versus 29.8 (SD 34.5) in non-users of anti-dementia drugs. The mean MMSE scores were 16.0 (SD 6.6) and 14.7 (SD 8.0), respectively.

Table 9. Frequency of NPSs and subgroups, ADL functioning and cognition among patients with diagnosed dementia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Users of anti-dementia drugs n=791</th>
<th>Non-users of anti-dementia drugs n=351</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of NPSs**, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>320 (40.4)</td>
<td>162 (46.1)</td>
<td>0.098</td>
</tr>
<tr>
<td>One symptom</td>
<td>252 (31.8)</td>
<td>114 (32.5)</td>
<td></td>
</tr>
<tr>
<td>Two to three symptoms</td>
<td>171 (21.6)</td>
<td>55 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Four or more symptoms</td>
<td>48 (6.1)</td>
<td>20 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Any NPS, n (%)</td>
<td>471 (59.5)</td>
<td>189 (53.8)</td>
<td>0.771</td>
</tr>
<tr>
<td>Subgroups, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>264 (33.3)</td>
<td>116 (33.0)</td>
<td>0.936</td>
</tr>
<tr>
<td>Psychosis</td>
<td>105 (13.2)</td>
<td>36 (10.3)</td>
<td>0.155</td>
</tr>
<tr>
<td>Mood symptoms and apathy</td>
<td>299 (37.6)</td>
<td>90 (25.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADL score, mean (SD)</td>
<td>58.0 (31.5)</td>
<td>29.8 (34.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE***, mean (SD)</td>
<td>16.0 (6.6)</td>
<td>14.7 (8.0)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*Ch-square test for categorical variables and Student’s t-test for continuous variables, **NPS data missing for 42 persons, ***MMSE detected in 832 patients

Anti-dementia drug use was associated with the mood and apathy subgroup symptoms and combination therapy with the hyperactivity symptoms (Table 10). In multivariate analysis, the use of anti-dementia drugs was associated with the NPS subgroup of mood symptoms and apathy. The combination of AChEI and memantine was associated with hyperactivity, but not with psychotic symptoms. ADL functioning was associated with any kind of anti-dementia drug use. Age was associated with use of either an AChEI or memantine, but not with the combination therapy.
Table 10. Univariate and multivariate associations between patient characteristics, subgroups and anti-dementia drug use.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AChEI only Univariate OR (95% CI)</th>
<th>Multivariate* OR (95% CI)</th>
<th>Memantine only Univariate OR (95% CI)</th>
<th>Multivariate* OR (95% CI)</th>
<th>AChEI + memantine Univariate OR (95% CI)</th>
<th>Multivariate* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.02 (1.00-1.04)</td>
<td>1.04 (1.01-1.06)</td>
<td>1.03 (1.00-1.07)</td>
<td>1.05 (1.02-1.08)</td>
<td>0.99 (0.96-1.01)</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>1.06 (0.78-1.43)</td>
<td>1.48 (0.93-2.33)</td>
<td>1.01 (1.01-1.02)</td>
<td>1.02 (1.01-1.03)</td>
<td>1.00 (0.67-1.48)</td>
<td></td>
</tr>
<tr>
<td>ADL score</td>
<td>1.03 (1.02-1.03)</td>
<td>1.03 (1.02-1.04)</td>
<td>1.01 (1.01-1.02)</td>
<td>1.02 (1.01-1.03)</td>
<td>1.02 (1.02-1.04)</td>
<td></td>
</tr>
<tr>
<td>Residential care</td>
<td>0.31 (0.24-0.40)</td>
<td>1.37 (1.04-1.80)</td>
<td></td>
<td></td>
<td>1.13 (0.79-1.56)</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>0.83 (0.61-1.12)</td>
<td>0.91 (0.60-1.38)</td>
<td></td>
<td></td>
<td>1.69 (1.17-2.45)</td>
<td>2.03 (1.36-3.04)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1.15 (0.73-1.97)</td>
<td>1.24 (0.67-2.26)</td>
<td></td>
<td></td>
<td>1.93 (1.16-3.23)</td>
<td></td>
</tr>
<tr>
<td>Mood symptoms and apathy</td>
<td>1.66 (1.22-2.25)</td>
<td>1.44 (1.03-2.02)</td>
<td>1.87 (1.24-2.83)</td>
<td>1.77 (1.15-2.72)</td>
<td>1.91 (1.30-2.80)</td>
<td>1.56 (1.03-2.34)</td>
</tr>
</tbody>
</table>

AChEI = Acetylcholinesterase Inhibitor, ADL (Activities of Daily Living) score = Barthel Index, scale 0-100, CI = Confidence Interval, NPS = Neuropsychiatric Symptom, OR = Odds Ratio

*Forward selection. Variables included in the multivariate model are shown.
5.4 ANTIPSYCHOTIC USE AND ASSOCIATIONS WITH NPSS AMONG PERSONS WITH COGNITIVE IMPAIRMENT (STUDY II, N=1909)

Antipsychotics were used by one-third of cognitively impaired persons. The majority of cognitively impaired persons (n=1909) lived in residential care. Antipsychotics were used by 15.9% of persons living at home and by 37.7% of those in residential care. Antipsychotic users (n=563) were younger, had poorer cognition, lower ADL score and they lived more frequently in residential care setting than non-users of antipsychotics (n=1188) (Table 11). The three most frequently administered antipsychotics were risperidone, quetiapine and olanzapine. Altogether 105 persons used other antipsychotics, mainly conventional ones. At least two concomitant antipsychotics were used by some 5% of persons. The frequencies of all NPS subgroups were higher among the users of antipsychotics than among the non-users. Likewise, BZRD were more common among the users of antipsychotics than the non-users, but there was no significant difference in the use of antidepressants.

Table 11. Characteristics, NPSS and use of psychotropic drugs and anti-dementia drugs in cognitively impaired users and non-users of antipsychotics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Users of antipsychotics n=563</th>
<th>Non-users of antipsychotics n=1346</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, mean</td>
<td>80.4 (9.8)</td>
<td>83.3 (8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>386 (69)</td>
<td>938 (70)</td>
<td>0.61</td>
</tr>
<tr>
<td>Residential care, n (%)</td>
<td>448 (80)</td>
<td>740 (55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE*, mean (SD)</td>
<td>45.1 (32.1)</td>
<td>52.1 (35.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADL score, mean (SD)</td>
<td>14.3 (7.5)</td>
<td>17.3 (16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NPS subgroups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity, n (%)</td>
<td>254 (46)</td>
<td>300 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>150 (27)</td>
<td>118 (9)</td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>77 (14)</td>
<td>47 (4)</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>125 (23)</td>
<td>164 (13)</td>
<td></td>
</tr>
<tr>
<td>Aberrant motor behaviour</td>
<td>40 (7)</td>
<td>51 (4)</td>
<td></td>
</tr>
<tr>
<td>Psychosis, n (%)</td>
<td>101 (18)</td>
<td>110 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delusions</td>
<td>51 (9)</td>
<td>58 (5)</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>65 (12)</td>
<td>66 (5)</td>
<td></td>
</tr>
<tr>
<td>Mood and apathy, n (%)</td>
<td>223 (41)</td>
<td>412 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>86 (16)</td>
<td>187 (15)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>72 (13)</td>
<td>77 (6)</td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td>13 (2)</td>
<td>18 (1)</td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>33 (6)</td>
<td>46 (4)</td>
<td></td>
</tr>
<tr>
<td>Sleeping problems</td>
<td>74 (13)</td>
<td>149 (12)</td>
<td></td>
</tr>
<tr>
<td>Eating problems</td>
<td>34 (6)</td>
<td>73 (6)</td>
<td></td>
</tr>
<tr>
<td>Drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>151 (27)</td>
<td>326 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BZRD</td>
<td>207 (37)</td>
<td>285 (21)</td>
<td></td>
</tr>
<tr>
<td>Anti-dementia drugs</td>
<td>255 (45)</td>
<td>622 (46)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

AChEI = Acetylcholinesterase inhibitor, ADL (Activities of Daily Living) score = Barthel Index, scale 0-100, BZD = benzodiazepines, BZRD = Benzodiazepines and Related Drugs, MMSE = Mini Mental State Examination, scale 0-30
*missing data on MMSE n=770
In both univariate and multivariate analyses, use of antipsychotics was associated with living in residential care and use of BZRD (Table 12). In univariate analysis, all hyperactivity symptoms and psychotic symptoms as well as anxiety and apathy in the mood and apathy subgroup were positively associated with antipsychotic use. Such NPSs as agitation/aggression, disinhibition and hallucinations were associated in the multivariate analysis, but a negative association was found between MMSE, age and antipsychotic drug use.

Table 12. Associations of antipsychotic drug use with characteristics of persons, use of other psychotropic drugs and anti-dementia drugs and NPSs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Odds ratio (95% CI)</th>
<th>Multivariate* Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.96 (0.95-0.97)</td>
<td>0.97 (0.95-0.99)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.95 (0.77-1.17)</td>
<td></td>
</tr>
<tr>
<td>Residential care</td>
<td>3.19 (2.53-4.02)</td>
<td>2.78 (1.97-3.91)</td>
</tr>
<tr>
<td>ADL score</td>
<td>0.98 (0.97-0.99)</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>0.94 (0.92-0.96)</td>
<td>0.98 (0.95-0.99)</td>
</tr>
<tr>
<td>Anti-dementia drugs</td>
<td>0.96 (0.79-1.17)</td>
<td></td>
</tr>
<tr>
<td>Other psychotropic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antidepressants</td>
<td>1.15 (0.92-1.44)</td>
<td></td>
</tr>
<tr>
<td>BZRD</td>
<td>2.16 (1.74-2.69)</td>
<td>2.03 (1.48-2.80)</td>
</tr>
<tr>
<td>NPS subgroups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>3.73 (2.85-4.87)</td>
<td>1.70 (1.16-2.48)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>4.31 (2.95-6.28)</td>
<td>2.33 (1.31-4.15)</td>
</tr>
<tr>
<td>Irritability</td>
<td>2.02 (1.56-2.61)</td>
<td></td>
</tr>
<tr>
<td>Aberrant motor behaviour</td>
<td>1.91 (1.24-2.92)</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delusions</td>
<td>2.17 (1.47-3.21)</td>
<td>1.71 (1.01-2.91)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>2.48 (1.74-3.55)</td>
<td>2.77 (1.69-4.55)</td>
</tr>
<tr>
<td>Mood and apathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>1.09 (0.83-1.44)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.37 (1.69-3.23)</td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td>1.71 (0.83-3.51)</td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>1.73 (1.09-2.73)</td>
<td></td>
</tr>
<tr>
<td>Sleeping problems</td>
<td>1.19 (0.88-1.60)</td>
<td></td>
</tr>
<tr>
<td>Eating problems</td>
<td>1.10 (0.72-1.67)</td>
<td></td>
</tr>
</tbody>
</table>

ADL score = Barthel Index, scale 0-100, BZRD = Benzodiazepines and Related Drugs, CI = Confidence Interval, MMSE = Mini-Mental State Examination, NPS = Neuropsychiatric Symptom

*Forward selection. Variables included in the model are shown
5.5 PHYSICAL RESTRAINTS AND ASSOCIATIONS WITH PSYCHOTROPIC DRUG USE AND NPSS WITH SUBGROUPS IN RESIDENTIAL CARE (STUDY III, N=1439)

Half of the patients were restrained with bedrails (n=671, 49%) (Table 13). In addition, 93 persons were restrained with a tray table in a wheelchair, 44 persons with a belt around the trunk and 3 persons with binding of one or more extremities with straps. Locking the door was used in 73, removing a walking or standing aid in 11 and physical force in four persons in the preceding 24 hours. Bedrails were used for 96% of bedridden and for 40% of non-bedridden persons, but other restraints were much rarer. The use of multiple restraints was more common among persons with hyperactivity. Hyperactivity subgroup symptoms were more frequently present among those restrained than among non-restrained persons (37% vs. 29%, p<0.001).

Table 13. Physical restraints used in the preceding 24 hours in residential care.

<table>
<thead>
<tr>
<th>Physical restraints used</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedrails</td>
<td>671</td>
<td>(48.4)</td>
</tr>
<tr>
<td>Belt around trunk</td>
<td>44</td>
<td>(3.2)</td>
</tr>
<tr>
<td>Binding extremities</td>
<td>3</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Restraining with tray table</td>
<td>93</td>
<td>(6.7)</td>
</tr>
<tr>
<td>Locking door</td>
<td>73</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Removing walking aid</td>
<td>11</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Using physical force</td>
<td>4</td>
<td>(0.3)</td>
</tr>
</tbody>
</table>

Some form of physical restraint was used for 721 persons (52%) during the preceding 24 hours in residential care facilities (Table 14). Restrained persons were slightly older, had much lower ADL and were more often cognitively impaired than non-restrained individuals. Restrained persons used less often antipsychotics, antidepressants and anti-dementia drugs than the others. Bedrails (on one or both sides) were used for a total of 671 persons (49%).

Table 14. Characteristics of persons, NPSSs and use of psychotropics and anti-dementia drugs among non-restrained and restrained persons in residential care.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-restrained n=665</th>
<th>Restrained n=721</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>470 (71)</td>
<td>490 (68)</td>
<td>0.29</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>81 (10)</td>
<td>83 (9)</td>
<td>0.003</td>
</tr>
<tr>
<td>ADL score, mean (SD)</td>
<td>59 (26)</td>
<td>16 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bedridden, n (%)</td>
<td>8 (1)</td>
<td>196 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cognitive impairment, n (%)</td>
<td>494 (75)</td>
<td>655 (91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NPS subgroups, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>190 (29)</td>
<td>266 (37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosis</td>
<td>75 (11)</td>
<td>71 (10)</td>
<td>0.39</td>
</tr>
<tr>
<td>Mood and apathy</td>
<td>206 (31)</td>
<td>217 (30)</td>
<td>0.72</td>
</tr>
<tr>
<td>Psychotropics, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>278 (42)</td>
<td>234 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BZRD</td>
<td>194 (29)</td>
<td>231 (32)</td>
<td>0.25</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>194 (29)</td>
<td>175 (24)</td>
<td>0.039</td>
</tr>
<tr>
<td>Anti-dementia drugs</td>
<td>283 (43)</td>
<td>220 (31)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ADL score = Barthel Index, scale 0-100, BZRD = Benzodiazepines and Related Drugs, NPS = Neuropsychiatric Symptom

In the multivariate analysis, restraint use was associated with the NPS psychosis subgroup and use of BZRD (Table 15). BZRD were associated with the risk of being restrained. ADL score and use of antipsychotics or antidepressants were negatively associated with restraint use. No association was found between restraints and anti-dementia drug use. Concomitant use of two
or more restraints was associated with higher prevalence of hyperactivity and psychosis symptoms. No such relationship was seen with the symptoms of the mood and apathy subgroup. Better ADL functioning was associated with a lower risk of restraining, and those who were bedridden were most often exposed to physical restraints.

Table 15. Associations of restraint use with NPS subgroups and use of psychotropic and anti-dementia drugs among persons in residential care in multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>0.82 (0.58-1.17)</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.99-1.02)</td>
</tr>
<tr>
<td>ADL score</td>
<td>0.93 (0.92-0.93)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>1.16 (0.70-1.93)</td>
</tr>
<tr>
<td>NPS subgroups</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>1.37 (0.97-1.93)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1.94 (1.14-3.31)</td>
</tr>
<tr>
<td>Mood and apathy</td>
<td>1.14 (0.81-1.61)</td>
</tr>
<tr>
<td>Psychotropics</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>0.62 (0.44-0.87)</td>
</tr>
<tr>
<td>BZRD</td>
<td>1.69 (1.18-2.41)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>0.64 (0.45-0.90)</td>
</tr>
<tr>
<td>Anti-dementia drugs</td>
<td>0.81 (0.58-1.14)</td>
</tr>
</tbody>
</table>

BZRD = Benzodiazepines and Related Drugs, CI = Confidence Interval, NPS = Neuropsychiatric symptom

5.6 NON-PHARMACOLOGICAL APPROACHES FOR NPSS IN RESIDENTIAL CARE

Non-pharmacological treatments were frequently used in residential care to alleviate NPSs; 54% (n=774) of the patients in residential care had received some form of this treatment in preceding 24 hours. Persons with at least one detected NPS were treated with various approaches (Table 16). Altogether 483 persons (65%) were verbally assured to alleviate NPSs, both sexes in a similar manner. It was more common to give time and comfort to female patients (55% vs. 39%) (p<0.001). In assessing somatic condition there seemed to be no substantial sex differences; every fifth person was assessed somatically. Apparently, NPSs were then often related to a somatic condition, e.g. pain or discomfort. Physical exercise was used for every tenth patient with at least one NPS. Music was utilized in the treatment of 103 persons (14%). Team assistance to alleviate NPSs was reported in only 18 cases. Discussions with relatives were employed in 14% of cases (n=107), equally often among the sexes. Hobby crafts, gardening or arts were used in 2% of cases.
Table 16. Use of non-pharmacological approaches for NPSs in residential care for females and males.

<table>
<thead>
<tr>
<th>Variable (n, %)</th>
<th>Total* n=1386</th>
<th>Female n=744</th>
<th>Male n=642</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal reassurance</td>
<td>483 (65.1)</td>
<td>341 (66.3)</td>
<td>142 (62.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Time and comfort</td>
<td>371 (50.0)</td>
<td>282 (54.9)</td>
<td>89 (39.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Assessing somatic condition</td>
<td>155 (20.9)</td>
<td>108 (21.0)</td>
<td>47 (20.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>Music</td>
<td>103 (13.8)</td>
<td>68 (13.2)</td>
<td>35 (15.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Discussion with relatives</td>
<td>107 (14.4)</td>
<td>75 (14.6)</td>
<td>32 (14.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Physical exercise or going outdoors</td>
<td>86 (11.6)</td>
<td>52 (10.1)</td>
<td>34 (11.8)</td>
<td>0.060</td>
</tr>
<tr>
<td>Using animals or toys</td>
<td>19 (2.6)</td>
<td>14 (2.7)</td>
<td>5 (1.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Using team to assist</td>
<td>18 (2.4)</td>
<td>12 (2.3)</td>
<td>6 (2.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hobby crafts, gardening, arts</td>
<td>16 (2.2)</td>
<td>10 (1.9)</td>
<td>6 (2.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>Other means</td>
<td>40 (5.4)</td>
<td>32 (6.2)</td>
<td>8 (3.5)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*p-value* indicates statistical significance of the differences between genders.

Table 17. NPS subgroups, use of psychotropic and anti-dementia drugs and use of physical restraints in patients treated or not treated with non-pharmacological approaches in residential care.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=1386</th>
<th>Users of non-pharmacological approaches n=744</th>
<th>Non-users of nonpharmacological approaches n=642</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPS subgroups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity, n (%)</td>
<td>456 (32.9)</td>
<td>433 (58.2)</td>
<td>23 (3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychosis, n (%)</td>
<td>146 (10.6)</td>
<td>139 (18.7)</td>
<td>7 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mood and apathy, n (%)</td>
<td>423 (30.5)</td>
<td>381 (51.2)</td>
<td>42 (6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychotropic drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics, n (%)</td>
<td>512 (37.0)</td>
<td>345 (46.4)</td>
<td>167 (26.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antidepressants, n (%)</td>
<td>369 (26.6)</td>
<td>203 (27.3)</td>
<td>166 (25.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>BZRD, (%)</td>
<td>425 (30.7)</td>
<td>253 (34.0)</td>
<td>172 (26.8)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Anti-dementia drugs, n (%)</td>
<td>503 (36.3)</td>
<td>315 (42.3)</td>
<td>188 (29.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical restraints, n (%)</td>
<td>721 (52.0)</td>
<td>406 (54.6)</td>
<td>315 (49.1)</td>
<td>&lt;0.041</td>
</tr>
<tr>
<td>ADL score, mean (SD)</td>
<td>37.0 (30.7)</td>
<td>35.9 (29.6)</td>
<td>38.1 (31.9)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

ADL score: Barthel Index, scale 0-100, BZRD = Benzodiazepines and Related Drugs, NPS = Neuropsychiatric Symptom.
6 Discussion

6.1 MAIN FINDINGS

More than 50% of persons in both care settings suffered from at least one NPS. In residential care facilities, one-fifth and in home care 15% of patients had two to three NPSs concomitantly. One-fifth of the home care population suffered from depressive symptoms. Hyperactivity symptoms, such as agitation/aggression and irritability, were detected in every third person, and psychotic symptoms in every tenth person. Non-pharmacological treatments for NPSs were used for more than half (54%) of the patients in residential care. The prevalence of NPSs during the preceding 24 hours in residential care and during the preceding week in home care was 51% and 50%, respectively.

The use of anti-dementia drugs and psychotropic was scrutinized in the aged population receiving residential or regular home care in the South Savo Hospital District. Anti-dementia drugs were frequently used, presumably according to the national treatment guidelines, and their use was associated with the hyperactivity and psychosis NPS subgroups. Diagnosed dementia was found in 56% of persons in residential care, and anti-dementia drugs were used by 36%. Two-thirds of the total population was evaluated to be cognitively impaired which is in line with previous studies (Björk et al. 2016). In home care, dementia had been diagnosed in 31%, and the proportion of anti-dementia drug users was 28%. The use of any anti-dementia drug or combinations of AChEIs and memantine were associated with the mood and apathy subgroup. A combination therapy was associated with hyperactivity symptoms. Antipsychotics were used by one-third of cognitively impaired persons, 38% in residential care and 16% in home care settings.

Antipsychotic drug use was associated in the multivariate analysis with residential care, BZRD use and symptoms of agitation/aggression, disinhibition and psychosis. Half of the patients in residential care were exposed to physical restraints, with bedrails being the most common. Psychotic symptoms were associated with a higher risk of physical restraints, and hyperactivity was common when multiple restraints were used. The use of antipsychotics or antidepressants was associated with a lower risk of being restrained, but use of BZRD was associated with a higher risk. Better ADL was associated with a lower risk of restraining, and bedridden persons were most often exposed to physical restraints. Such non-pharmacological treatments as verbal assurance and giving time and comfort to patients were commonly used to alleviate NPSs.

6.2 DISCUSSION OF RESULTS

6.2.1 Users and non-users of anti-dementia drugs and associations with NPSs in dementia (Study I)

Two-thirds of persons with diagnosed dementia used anti-dementia medications. In home care, anti-dementia drugs were used by 28% of patients, and in residential care this figure was 36%. In the population with diagnosed dementia, use of anti-dementia drugs was associated with the mood and apathy subgroup. Hyperactivity symptoms associated with the concomitant use of AChEIs and memantine. Psychotic symptoms were not associated with the use of AChEIs, memantine or their combinations. Mood symptoms and apathy symptoms was the most prevalent NPS subgroup among the users of anti-dementia drugs. As the study was cross-
sectional, conclusions could not be drawn concerning the causality between the drug use and NPSs and their subgroups.

A recent study from Swedish NHs showed 56% of residents were ADL-dependent and 67% had cognitive impairment (Björk et al. 2016). In Finland, NPSs were present in 77% of patients with very mild AD and in 85% of patients with mild to moderate AD (Karttunen et al. 2011). The prevalences of NPSs were lower in the present study than in Sweden, where 92% of NH residents had NPSs during the preceding week (Björk et al. 2016). NPSs were assessed here based on a brief questionnaire examining the presence or absence of the NPSs during one week in home care and during 24 hours in residential care.

The prevalences of NPSs appeared to be somewhat lower than in many studies (Steinberg et al. 2008, Zhao et al. 2016), possibly due to the narrower time-window of detection of NPSs than in the many studies. In contrast of most studies, apathy was seldom found. Apathy and depression have previously been the most common NPSs (Lyketsos et al. 2002), and they are not easy to distinguish (Benoit et al. 2012). Most patients with dementia and apathy had concomitant depression, but less than one-third of depressed patients had concomitant apathy (Starkstein et al. 2005). Depression and apathy are overlapping and apathy may be mixed with depression (Hölttä et al. 2012). Apathy in AD has been consistently associated with relatively more severe cognitive deficits, more severe impairments in ADL, higher levels of burden and distress in caregivers and increased resource utilization (Landes et al. 2001). The use of specific structured interviews and valid diagnostic criteria to assess and diagnose apathy in AD will improve the identification. In everyday practice, rating scales for NPSs are not routinely used by physicians (Cummings et al. 2015).

As Nowrang et al. (2015) concluded, cluster analyses have consistently identified three to five subgroups of NPSs in dementia such as the behavioural dysfunction or hyperactivity subgroup, including agitation and aggressiveness, the psychosis subgroup and the mood disturbance subgroup, including depression and apathy. Thus, in the mood and apathy subgroup, there is poor identification and possible mixing with depression.

NPSs in home care and residential care were assessed using different time windows (previous week vs. preceding 24 hours) due to different observational possibilities, which may have to some extent affected the prevalence of NPSs. However, the relations of prevalences of NPSs other than apathy were comparable with many previous studies in residential care and home care facilities (Steinberg et al. 2008, Karttunen et al. 2011), taking into account the variability in the time window of different studies. NPSs are more prevalent in persons in residential care than in individuals in community settings (Ropacki and Jeste 2005, Selbaek et al. 2013).

The efficacy of AChEIs in the management of NPS in AD is limited. In some studies, anti-dementia drugs have improved depressive symptoms in mild to moderate dementia, regardless of the effect on cognition (Wilcock et al. 2008). Here, there was no association was between depressive symptoms and anti-dementia drug use. An association has been found between the use of anti-dementia drugs and aggression (Gustafsson et al. 2013a).

A recent study in Finland investigated the prevalence of use of anti-dementia drugs, treatment duration and concomitant use of AChEIs and memantine together with factors associated with the discontinuation of AChEI therapy during 2006–2009 (Taipale et al. 2014a). In the four-year follow-up, 84% of patients used AChEIs, 47% memantine and 22% both drugs concomitantly, and the median time for AChEI use was over three years. According to them, the low discontinuation rate was in accordance with the Finnish treatment guideline of memory disorders (Finnish Medical Society Duodecim 2010), but in contrast to previously reported results (Amun et al. 2010, van der Bussche et al. 2011).

Some RCTs of memantine in persons with moderate to severe dementia showed some benefit in NPSs such as decreased delusions and agitation/aggression (Gauthier et al. 2008, Wilcock et al. 2008). These results have later been questioned by Fox et al. (2012), who examined the efficacy of
memantine on AD with agitation, but found no benefit over placebo. In the present study, psychotic symptoms (delusions and hallucinations) were found in every tenth patient, but no associations emerged between the use of anti-dementia drugs and psychotic symptoms. Persons with psychotic symptoms may have been treated with anti-psychotic drugs rather than with anti-dementia drugs. Combining memantine with AChEIs has increased efficacy in cognition, but the effectiveness on NPSs has been disputed and new studies indicate that this combination has no clinically significant effects on disruptive behaviours (Rabins et al. 2014). Despite inconsistencies in various studies, treatment guidelines support the use of AChEIs to treat mild to moderate NPSs in patients with dementia (Finnish Medical Society Duodecim 2010, NICE 2013, Press et al. 2017).

In the South Savo Hospital District, anti-dementia drugs appear to have been implemented effectively and in accordance with Finnish treatment guidelines. Interestingly, only 20% of the Swedish dementia patients received anti-dementia drugs in NHs, whereas at the same time more than half of them used antidepressants (Gustafsson et al. 2013c). This finding may be due to different treatment guidelines; the Swedish national guideline recommends antidepressants before antipsychotics or other drugs in the management of NPSs (Läkemedelsverket 2013).

6.2.2 Antipsychotic use and associations with NPSs among persons with cognitive impairment (Study II)

Study II indicated that antipsychotic use was strongly associated with such NPSs as hallucinations, disinhibition and agitation/aggression. These kinds of associations between NPSs and antipsychotic use have previously been found in residential care settings. Earlier studies have noted associations between use of antipsychotics and delusions, hallucinations and signs of depression (Alanen et al. 2008b), aggressive, verbally disruptive, attention-seeking and hallucinatory symptoms, and psychosis, agitation and sleeping problems (Lövheim et al. 2006, Gustafsson et al. 2013a). In a European study 33% of the persons in residential care used antipsychotics and the use had the strongest relationship with severe NPSs, increasing the likelihood of antipsychotic drug use by 2.8-fold (Foebel et al. 2014). In the present study, the observed association between antipsychotic drug use and hyperactive and psychotic subgroup symptoms may reflect the known, relatively small positive effect of these drugs on NPSs. A representative study of persons with dementia (Maust et al. 2015, indicated associations of NPSs with use of antipsychotics and BZRD, but not with antidepressants (Maust et al. 2016).

In Finland and internationally, there has been long-standing concern about psychotropic drug use in older persons and for treating NPSs in dementia patients. Psychotropic drugs have frequently been used for extended periods in older community-dwelling persons (Rikala et al. 2011). Persistent use of antipsychotics may originate from organizational rather than person-related factors (Alanen et al. 2006), Huybrechts et al. 2012, Kales et al. 2015). There is also a substantial variation in prevalences of antipsychotic use between facilities within countries, indicating differences in patient populations, but potential inappropriate prescribing cannot be ruled out (Alanen et al. 2006). In the aforementioned study, however, cognitively intact patients were also included, thus differing from study population of the present study.

Atypical antipsychotic drugs were substantially used in our study population. In residential care, the use was in a high end of use in Europe (Foebel et al. 2014), and in line with findings in USA (Kamble et al. 2009) and Japan (Okumura et al. 2014). In the present study, the use of antipsychotics in home care was less than half of that in residential care, which is consistent with earlier results (Alanen et al. 2006, Alanen et al. 2008b). The prevalence of antipsychotic use in home care in several European countries varied from 3% in Denmark to 12.4% in Finland (Alanen et al. 2008a). The lower use of antipsychotics may be due to better ADL scores and a lower proportion of late-stage dementia among persons in home care. About half of the users of antipsychotics used anti-dementia drugs concomitantly, but due to the cross-sectional design of
this study it cannot be concluded whether increased anti-dementia drug use has affected the utilization of antipsychotics.

Many persons with hyperactivity symptoms and antipsychotics were subsequently treated with other psychotropic drugs, mainly BZDs. These drug combinations can be used in patients with severe symptoms and to keep doses moderate, but the co-use of several psychotropics should be avoided. Instead of using antipsychotics to alleviate all subgroups of NPSs, we should concentrate on treating only psychotic symptoms and severe agitation and aggression with these drugs for a limited time to avoid adverse effect (Press et al. 2017). In addition, some of NPSs vanish spontaneously (APA 2015). Small-scale trials of treatment with antidepressants and mood stabilizers have produced similar results as antipsychotics in the treatment of hyperactivity subgroup symptoms, especially agitation and aggression (Ballard et al. 2009a). A recent review of Soto et al. (2015) of medication development for agitation and aggression in AD found that RCTs are very heterogeneous regarding drug use for NPSs in this condition; definitions for agitation and aggression varied, as did choice of outcome measures and caregiver participation.

High use of antipsychotics in both residential care and home care is a concern. In previous studies the prevalence of use for persons with dementia has varied between 20% and 50% in NHs and other residential care (Kamble et al. 2009, Chen et al. 2010, Azermai et al. 2011, Zuidema et al. 2011, Foebel et al. 2014). Although the Finnish clinical care guideline recommends antipsychotics only for severe NPSs, antipsychotic drug use was frequent, especially in residential care, but also in regular home care. This supports the assumption that the treatment practices in Finland prefer antipsychotic use. It has been admitted that the tight time schedule of health care personnel has been acknowledged to favour a drug prescription as the first line of action for NPSs, despite the well-known risks of, for instance, antipsychotic drug use (Schneider et al. 2005, Gill et al. 2007) In recent studies, mortality risk was even higher than in previous studies (Maust et al. 2015). Atypical antipsychotics as a group increased dose-adjusted mortality risk, which was 3.5% higher in those receiving high doses than in the low-dose group. Relative to quetiapine, dose-adjusted mortality risk was increased with both risperidone and olanzapine (Maust et al. 2015).

Compared with patients in home care, those in residential care are claimed to receive poorer care, less advantageous drug treatment together with inappropriate or unnecessary drugs and inadequate follow-up of somatic condition (Fahey et al. 2003).

Recent trials of antipsychotics in NPSs support the use of non-pharmacological and environmental approaches instead of routine use of antipsychotics (Rabins et al. 2014). In most cases, discontinuation of antipsychotics can be done without significant risk of return of NPSs (Rabins et al. 2014). A finding from Sweden stated that even when use of psychotropics declined among older persons with cognitive impairment in residential care, it did not result in increased NPSs (Gustafsson et al. 2016). However, there may be a proportion of patients who benefit from long-term treatment (Devanand et al. 2012). In general, the dose of antipsychotics should be kept minimal and the duration of medication as short as possible (Alexopoulos et al. 2004, Zuidema et al. 2015). As the time allocation of doctors in long-term wards is a few minutes per week per patient in our country (Karppi et al. 2006), the majority of psychotropic drug prescriptions in LTC and in home care are assumed to arise from the observations and requests of the nursing staff. According to Zuidema et al. (2011), staff distress together with NPSs is associated with increased psychotropic drug prescriptions, especially for antipsychotics and anxiolytics. Kales et al. (2015) have proposed that in the community, instead of using financial resources for psychotropics, first aid and hospital stays, more proactive measures, e.g. non-pharmacological approaches to treat dementia patients with NPSs, should be introduced and developed.

Contrary to the findings of various studies (Alexopoulos et al. 2004, Gareri et al. 2014, Zuidema et al. 2015), and the recommendations (APA 2015) concerning the need for regular re-evaluation of antipsychotic use (APA 2015), resistance has been high among nurses and doctors in NHs to discontinue the use of antipsychotics (Azermai et al. 2014.) Thus, there is an urgent need to include discontinuation as a regular part of the standard procedures in both residential and home care. The cognitive status and choice of outcome measures and caregiver participation.
care facilities by multidisciplinary interventions. Discontinuation should be implemented through tapering when the NPSs have at least partly resolved (Zuidema et al. 2015). This is especially important in Finland, where up to 40% of patients in LTC have been administered antipsychotics, most of them without any psychiatric diagnosis (Alanen et al. 2006).

6.2.3 Physical restraints and associations with psychotropic drug use and NPSs with subgroups in residential care (Study III)

In residential care settings, more than half of the residents were exposed to physical restraints in the preceding 24 hours, a finding that is at the upper range of the prevalence found elsewhere in Europe (Castle and Engberg 2009, Beerens et al. 2014, Hofmann et al. 2015) and in USA (Hamers and Huizing 2005). Although in the studies based on the RAI, bedrails for bedridden persons are not regarded as restraints but instead considered as safety measures, in many studies they are included as restraints. They have been the most frequently used restraints in most studies (Meyer et al. 2009, Saarnio et al. 2009, Hofmann et al. 2015).

However, there have been marked differences in the use of bedrails and other restraints in the NHs between and within countries (Meyer et al. 2009, Köpke et al. 2012, Foebel et al. 2016). No RCTs were available of the risks of bedrails, but the review of Healey et al. (2008) concluded that serious direct injury from bedrails was usually related to use of outdated equipment and incorrect assembly, and bedrails did not appear to increase the risk of falls or injuries related to falls.

In the study of Meyer et al. (2009), the prevalence of an NH resident with at least one physical restraint was 26% (4% to 59%). Hofmann et al. (2015) found even greater variation within the same country (2.6-61%), and bilateral bedrails were most frequently used, on one- fifth of the residents. In the present study, also bedrails on one side were included in the definition restraints, which increased the number of restrained persons.

In line with findings of the present study, the use of physical restraints has most often been associated with low ADL and low cognitive status (Heinz et al. 2012, Hofmann et al. 2015). The restraints are used for the most vulnerable and disabled persons with serious mobility problems (Hamers and Huizing 2005, Saarnio et al. 2009, Hofmann et al. 2015). Practically all bedridden persons (98%) in our study were restrained. Bedrails formed the majority of all used restraints used in this study, consistent with the findings of Köpke et al. (2009), Meyer et al.(2009) and Hofmann et al. (2015). In addition, bedrails have been the most commonly used physical restraints also in home care, where two-thirds of nursing staff had used bedrails at some point (de Veer et al. 2009). Restraint use in home care may ethically and practically be even more complex than their use in residential care (Scheepmans et al. 2014).

The use of antipsychotic drugs was associated with a lower risk of restraining. This is consistent with the finding that the public obligatory reporting of physical restraints in USA decreased restraining, while the use of antipsychotics simultaneously increased (Konetzka et al. 2014). The concurrent use of restraints and antipsychotics increases functional and cognitive decline in association with physical restraints (Foebel et al. 2016). However, no association was found between physical restraining and administration of antipsychotics in patients newly admitted to LTC (Foebel et al. 2015). In this study, antidepressant drug use was associated with a lower risk of being restrained. Whether depressive patients are more apathetic, diminishing the need for restraining, warrants discussion. However, antidepressants have been used not only to treat depression but also to reduce psychotic and hyperactivity symptoms (Seitz et al. 2011).

Restrained persons here were a slightly older, had much lower ADL and were more often cognitively impaired than non-restrained individuals. As the ability to understand language decreases as dementia progresses, aggressive behaviour has been found to increase markedly (Volcier et al. 2007), possibly increasing the risk of being restrained. In the present study, the restrained persons used less often antipsychotics, antidepressants and anti-dementia drugs than the others. Whether the proper medication to treat NPSs could reduce the need for physical
restraining should be evaluated. On the other hand, psychotropics can be used as a chemical restraint (Kivelä 2010).

Permanent restlessness, which easily leads to physical restraining, and use of hypnotics have been positively associated (Richter et al. 2012). The association between BZRD use and physical restraints found here is in line with previous results (Saarnio and Isola 2010). Despite the common use of BZDs to treat such behavioural problems as anxiety, agitation and sleep problems and their potential risks (sedation, ataxia, falls, cognitive clouding and paradoxical reactions), they have not to date been systematically studied in treating NPSs (Casey 2015). In hospitalized patients using anxiolytics, the functional decline was substantial, supporting restraining from anxiolytic use in cognitively impaired persons with NPSs (Alanen et al. 2015).

Restricted residents have often been aggressive, disoriented or delirious (Pellfolk et al. 2010). In line with the present study, the high prevalence of hyperactivity symptoms (aggressive behaviour and repeated verbal and physical agitation) has been associated with the use of physical restraints (Karlsson et al. 2001, Kirkevold et al. 2004). Hyperactivity symptoms may increase physical restraining, or vice versa, limiting mobility may increase hyperactivity symptoms (Scherder et al. 2010). The use of restraints has predicted aggressive (Ryden et al. 1999) and self-injurious (de Jonghe-Rouleau et al. 2005) behaviour. The use of multiple restraints in the present study was especially common among persons with hyperactivity symptoms, possibly reflecting the difficulties in managing these symptoms in LTC facilities. Nevertheless, studies on the associations between psychotic symptoms and restraint use in residential care are scarce.

Such elements as underlying principles, organization, economy and legislation of residential care services and the selection of alternative care facilities in each country may contribute to variability in findings concerning the use of restraints (Pekkarinen et al. 2006). Designated organizational and resident characteristics predicted the rate of physical restraint use consistently between countries (Feng et al. 2009). However, it is possible to change restraint practices in residential care and improve the work environment of the nursing staff by increasing knowledge of alternative methods (Pellfolk et al. 2010, Köpke et al. 2012, Gulpers et al. 2013).

6.2.4 Non-pharmacological approaches for NPSs in residential care (unpublished findings)

According to Kales et al. (2015), non-pharmacological treatments may include general approaches, e.g. enhancing communication, or a targeted approach, e.g., physical activity and music as tailored activities. To my knowledge, this is the first study evaluating the use of non-pharmacological approaches in residential care in a geographically defined area. The most regularly used non-pharmacological approach was verbal assurance, administered to two-thirds of the persons treated with non-pharmacological means, while giving time and comfort was used for half of them. Both of these approaches are unspecific and easily accomplished without any special education or effort. Interestingly, time and comfort was a method more commonly used for females than males. Whether this arises from the fact that the majority of nursing staff were women warrants discussion. In previous studies, some gender differences have been found in drug use. Men have been at higher risk of receiving antipsychotics whereas antidepressants have been administered to women more often (Fernandez et al. 2000, Ott et al. 2000). These studies did not find gender differences in the use of non-pharmacological approaches.

Using verbal assurance is in line with the recommendations of Kales et al. (2015), according to which the most important non-pharmacological intervention is enhanced communication.

Other non-pharmacological treatments were seldom used. Music was used for 14%, physical exercise for 12% and hobby crafts for 2% of patients. Animals and toys were quite seldom utilized. Detecting any somatic condition underlying NPSs is fundamental in newly occurring NPSs. It was performed for 21% of patients during the preceding 24 hours. However, most NPSs may be more long-standing, and in at least some of the somatic assessments of newly occurring NPSs were conducted earlier.
Although only one percent of the non-users of non-pharmacological treatments suffered from psychotic symptoms, more than every fourth of them used antipsychotics. This finding is in line with previous studies indicating very loose connection of antipsychotic drug use with accepted indications of use (Alanen et al. 2006, Chen et al. 2010). A recent study indicated strongly that persons with dementia do benefit the reduction of antipsychotics only if effective non-pharmacological interventions were simultaneously implemented (Ballard et al. 2016). Antipsychotic review with social engagement reduced antipsychotic use and mortality without a worsening of NPSs, and physical exercise improved NPSs. Nevertheless, antipsychotic reduction without the implementation of effective non-pharmacological approaches worsened NPSs, still reducing mortality. In the same study, agitation was not affected by exercise (Ballard et al. 2016).

Nursing staff and family members of persons with dementia may be uncertain regarding which non-pharmacological approaches would be most applicable (Kales et al. 2015). In the present study, some of the key strategies of non-pharmacological approaches for NPSs were used actively and some neglected. Even if staff were adequately trained, the possibilities in the present care facilities in most countries do not allow sufficient time for non-pharmacological treatments which makes a prescription for a drug the most common action for NPSs (Kales et al. 2015). Nevertheless, only a few non-pharmacological treatments have been transferred from theory to clinical management and standard care (Kales et al. 2015). Thus, in the treatment of NPSs, the non-pharmacological approaches are potentially underused (Bradford et al. 2012, Kales et al. 2015), while antipsychotics and antidepressants seem to be overused. It has been recognized also that there is an underlying prescribing culture in NHs, which influences antipsychotic treatment choices (Huybrechts et al. 2012). BZDs for NPSs should be avoided (Hugo and Ganguli 2014).

Understanding of the link between neuropathology and non-pharmacological treatments is limited. The relationships between dementia, dementia subtypes and behavioural treatments thus warrant further investigations (Lyketsos et al. 2011). In the present study it was possible to explore what kind of approaches and non-pharmacological treatments nurses used to manage NPS. More detailed information is needed to evaluate the tailored approaches of nonpharmacological interventions. However, even in this rough approximation of the use is valuable in developing the care of NPSs in residential care setting.

6.3 STRENGTHS AND LIMITATIONS OF THE STUDY

6.3.1 Strengths of the study
The most important strength of this study was the nearly 100% coverage of the targeted study population receiving long-term residential care or regular home care services in the South Savo Hospital District. All private and municipal residential care facilities were contacted and 66/68 responded to the study. Of municipal home care services, 21/22 answered the questionnaires. The data on regularly used drugs were gathered in a consistent and reliable means utilizing the computerized drug lists of each unit. The gathered data give reliable point prevalence information about demographic characteristics, used medications, ADL scores, most NPSs, use of restraints and use of non-pharmacological managements for NPSs. The BI is regarded as a reliable tool for assessing basic ADL functioning in older persons (Collin et al. 1988).

To increase point prevalence reliability, NPSs were detected during the preceding 24 hours in residential care and during the preceding week in home care, resulting in somewhat lower
prevalences (51% and 50%, respectively) than in a recent Swedish study reporting NPSs, prevalence rates of NPSs 92% in NHs (Björk et al. 2016). In residential care, restraint use, NPSs and non-pharmacological treatments for NPSs were evaluated over the previous 24 hours, also increasing the reliability of the data. The cross-sectional design enabled the evaluation of associations between NPSs and patient characteristics of the patients as well as uses of medication and physical restraints at a specific time point.

6.3.2 Limitations of the study
Due to high the number of institutions and home care units, it was not possible to evaluate the interrater reliability. The cross-sectional design of the study did not enable assessments of to causality between drug use and NPSs, nor could the indications of psychotropic drug use or the possible risk for chemical restraining be assessed. The dates of dementia diagnosis, the initiation of anti-dementia or psychotropic drugs and the duration of detected NPSs or restraining could not be assessed. In the present study, the doses of the used drugs were not taken into account, but merely the use or non-use of a psychotropic or an anti-dementia drug.

The assessment of NPSs was based on merely determining the presence or absence of NPI-defined NPSs. However, the same pattern is followed in NPI-Q, which has had good concordance with the NPI, and has been shown to be a reliable tool in assessing NPSs in dementia (Kaufer et al. 2000). As a limitation, assessment of the severity into three categories (mild, moderate, severe) was not done here. Furthermore, the number of nurses rating the NPSs was high. In this study, apathy was not recognized by the nurses as well as other NPSs. Apathy appears to be difficult to identify in clinical practice, as it may be difficult to distinguish from depression due to overlapping of NPSs (Starkstein et al. 2005). However, apathy is very common and persistent in depressed older persons (Yuen et al. 2015). Concerning the BI, it is well documented and validated for stroke patients, but there have been some uncertainties when used with older people with many chronic diseases (Sainsbury et al. 2005).

A physician-made diagnosis of dementia from medical records collected by a nurse is not always indicative of a clinically verified diagnosis. In fact, up to 30% of dementia diagnoses in LTC are missing, and of NH residents, as many as 90% may have dementia (Lithgow et al. 2012). The classification of patients’ cognition into four categories (normal, slightly impaired, moderately impaired and severely impaired) by nurses is not comparable with standardized questionnaires; however, it was done by skilled nurses who knew the patient. Since a recent MMSE was available for less than half of the patients, it was used as a characteristic, not as a classification tool.
7 Conclusions

In conclusion, a comprehensive overview of persons in home care and residential care in a geographically defined area was achieved in terms of drug use, physical restraints, ADL functioning and prevalence of NPSs. Most of these individuals had some degree of cognitive impairment. Both anti-dementia drugs and psychotropics seemed to be used frequently. The use of antipsychotics was high in both care settings.

1. Anti-dementia drugs were commonly used in the both care settings, long-term residential care and home care. AChEI and/or memantine use was associated with the mood and apathy subgroup symptoms. Combination therapy with both AChEI and memantine associated with the hyperactivity subgroup symptoms. Non-users of anti-dementia drugs had two to three NPSs less than the users, and their ADL scores were higher than those who used anti-dementia drugs. Further studies are needed on the effectiveness of anti-dementia drugs to ensure effective and safe pharmacotherapy for our vulnerable patients with dementia.

2. Antipsychotics were commonly used in cognitively impaired persons in home care (16%), but especially common they were in the same group in residential care (39%). Their use was associated with hallucinations, disinhibition and agitation/aggression as well as BZRD use and living in residential care. Instead of using antipsychotics to alleviate all NPSs, antipsychotics should be used only for the most severe NPSs at the lowest effective dose and their need should be reviewed regularly.

3. Half of the persons in residential care were exposed to physical restraints in preceding 24 hours, mostly bedrails. Psychotic symptoms were associated with the restraint use as well as concomitant use of at least two restraints with hyperactivity subgroup symptoms. BZRD were associated with the increased risk, but the use of antipsychotics or antidepressants was associated with a lower risk of being restrained. Better ADL scores were related to a lower risk of restraining, and bedridden persons were most often exposed to physical restraints. The need for and use of restraints should always be tailored individually, and the need should be re-assessed regularly.

4. The most frequently used non-pharmacological approaches in residential care were verbal assurance (65%) and giving time and comfort (50%), both of which are unspecific and easily accomplished treatments. More targeted non-pharmacological strategies should be employed.
8 Implications for future

1. Combinations of AchEI and memantine were common in our area. However, the studies of their efficacy on NPSs are relatively scarce. More RTCs are needed to evaluate their usefulness.

2. The widespread and common use of antipsychotics among older persons with cognitive impairment warrants studies to analyze the risks associated with chemical restraining. Educational interventions on medical staff may have a substantial decreasing impact on prescribing of antipsychotics.

3. Because of the common use of physical restraints in residential care, we need further studies to implement restraint-free practices at all levels of health care, in the future even in home care. The improvement of the care towards restraint-free services requires improvement in co-operation between general practitioners, nurses and specialists.

4. The assessment of NPSs should be an important part of comprehensive dementia care. It is essential to continue to standardize the evaluation of NPSs for different populations of individuals because definitions of these symptoms, subgroups and syndromes remain inconsistent.

5. Future interventions for NPSs should focus on long-term implementation of staff training on non-pharmacological approaches. It is essential to understand how unmet needs, communication problems, understimulation and emotional discomfort relate to NPSs. Further studies are required to compare pharmacological and non-pharmacological treatments for NPSs and to define the treatments most suited to be carried out by both families and professional caregivers.
Implications for future

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9 References


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APPENDICES
### Asiakaskartoitus/ Iäkkäiden lääkehoito ja toimintakyky Etelä-Savossa

**KOTIHOITO**

1. Asiakkaan ikä täysinä vuosina
   -  
2. Sukupuoli
   - 1  mies
   - 2  nainen
3. Hoidon luonne
   - 1  säännöllinen kotihoito (vähintään yksi hoitajan käynti viikossa)
   - 2  tilapäinen kotihoito (esim. leikkausten jälkeinen hoito)
4. Syöminen, ateriointi
   - 1  ei kykene syömään
   - 2  tarvitsee apua ruoan paloittelussa, voin levittämisessä jne.
   - 3  itsenäinen
5. Siirtyminen (vuoteesta tuoliin ja takaisin)
   - 1  ei kykene, ei istumatasapainoa
   - 2  tarvitsee huomattavaa apua (yksi tai kaksi ihmistä, fyysistä apua), pystyy istumaan
   - 3  tarvitsee pientä apua (sanallista tai fyysistä)
   - 4  itsenäinen
6. Henkilökohtainen siisteys
   - 1  tarvitsee apua kasvojen pesussa, hiusten kampaamisessa, hampaiden harjauksessa, parranajossa yms.
   - 2  itsenäinen
7. WC:n käyttö
   - 1  riippuvainen avusta
   - 2  tarvitsee jonkin verran apua (istuimelle ja pois, pukeminen, pyyhkiminen)
   - 3  itsenäinen
8. Peseytyminen
   - 1  tarvitsee apua (koko kehon pesussa)
   - 2  itsenäinen
9. Liikkuminen sisätiloissa
   - 1  liikuntakyvytön
   - 2  pyörätuolia käyttäen itsenäinen
   - 3  tarvitsee yhden henkilön apua, ohjausta tai rollaattorin
   - 4  itsenäinen (saattaa käyttää apuvälinettä, esim. keppiä)
10. Portaissa liikkuminen
    - 1  ei kykene liikkumaan portaissa
    - 2  tarvitsee apua (sanallista, fyysistä, tavaroiden kantoapua)
    - 3  itsenäinen
Appendix 1. Questionnaire in home care.

Asiakaskartoitus/ lääkäiden lääkehoito ja toimintakyky Etelä-Savossa

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KOTIHOITO

1. Asiakkaan ikä täysinä vuosina _______

Ympyröi oikea vaihtoehto

2. Sukupuoli
   1  mies
   2  nainen

3. Hoidon luonne
   1  säänrällleen kotihoito (vähintään yksi hoitajan käynti viikossa)
   2  tilapäinen kotihoito (esim. leikkausten jälkeinen hoito)

4. Syöminen, ateriointi
   1  ei kykene syömään itsenäisesti
   2  tarvitsee apua ruoan palotteluessa, voin levittämisessä jne.
   3  itsenäinen

5. Siirtyminen (vuoteesta tuoliin ja takaisin)
   1  ei kykene, ei istumatasapainoa
   2  tarvitsee huomattavaa apua (yksi tai kaksi ihmistä, fyysistä apua), pystyy istumaan
   3  tarvitsee pientä apua (sanallista tai fyysistä)
   4  itsenäinen

6. Henkilökohtainen siisteys
   1  tarvitsee apua kasvojen pesussa, hiusten kampaamisessa, hampaiden harjauksessa, parranajossa yms.
   2  itsenäinen

7. WC:n käyttö
   1  riippuvainen avusta
   2  tarvitsee jonkin verran apua (istiimelle ja pois, pukeminen, pyyhkiminen)
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8. Peseytyminen
   1  tarvitsee apua (koko kehon pesussa)
   2  itsenäinen

9. Liikkuminen sisätiloissa
   1  liikuntakyvytön
   2  pyörätuolia käyttäen itsenäinen
   3  tarvitsee yhden henkilön apua, ohjausta tai rollaattorin
   4  itsenäinen (saattaa käyttää apuvälineitä, esim. keppiä)

10. Portaissa liikkuminen
    1  ei kykene liikkumaan portaissa
    2  tarvitsee apua (sanallista, fyysistä, tavaroiden kantoapua)
    3  itsenäinen
11. Pukeutuminen
1 riippuvainen avusta
2 tarvitsee apua, mutta pystyy osin pukeutumaan
3 itsenäinen (mukaan lukien napit, vetoketjut, kengännauhat jne.)

12. Ulosteen pidätyskyky
1 ei kykene pidättämään
2 ajoittain vahinkoja
3 kykenee pidättämään

13. Virtsanpidätyskyky
1 ei kykene pidättämään (katetri, cystofix tai vaippa)
2 ajoittaisia vahinkoja (esim. pikkuvippa)
3 kykenee pidättämään

14. Muistitoiminta
1 ei ainakaan merkittävästi muistamattomuutta
2 lievästi muistamaton (tarvitsee muistamattomuuden takia ajoittaisa apua vaikeissa tehtävissä)
3 keskiväkeasti muistamaton (tarvitsee muistamattomuuden takia säännöllistä apua)
4 vaikeasti muistamaton (tarvitsee jatkuvasti apua ja valvontaa muistamattomuuden takia)

15. MMSE
Vuoden 2010 tai 2011 aikana tehdyn viimeisen MMSE-tutkimuksen kokonaispisteet

16. Muistisairausdiagnoosi tehty
1 kyllä
2 ei

17. Sairaus (Merkitään tärkein hoidon ja avun tarvetta aiheuttava sairaus, vain yksi.)
1 muistisairaus (esim. Alzheimerin tauti, verisuoniperäinen demencia)
2 aivo-verenkiertosairaus tai sen jälkitiila
3 muu neurologinen sairaus (esim. Parkinsonin tauti, epilepsia)
4 tuki- ja liikuntalinsiirrostaidetta
5 sydänvahingot (esim. sydämiirin, sepelvaltimotauti, läppäviika, rytmihäiriöt)
6 syöpäsairaus
7 psykikinen sairaus (esim. masennus, skitsofrenia, vainoharhaisuus)
8 tapaturma ja sen jälkitiilit (esim. muurumaat)
9 diabetes ja sen jälkiseuraukset
10 pitkäaikaisten keuhkosairauksien (esim. astma, keuhkoaltaumat) diagnoosi
11 ääniin tulehdustaidetta (esim. virtsatietulehdus, keuhkokuuyme, ruusu, vyöruusu)
12 kehitysvammisaitu
13 muu (esim. mahahaava, säärihaava, kilpirauhasen toimintahäiriöt)
14 ei mikään

19. Tarvittavat lääkkeet viimeksi kuluneen vuorokauden (klo 00-24) aikana. (Katso täyttöohje! Tähän ei käy vastauksena tuloste lääkelista.)
18. Jatkuva lääkitys (Katso täyttöohje! Vaihtoehtona käy myös tuloste lääkelistasta tai lääkkeen-jako-listan kopio.)

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19. Tarvittavat lääkkeet viimeksi kuluneen vuorokauden (klo 00-24) aikana. (Katso täyttöohje! Tähän ei käy vastauksena tuloste lääkelista.)

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Ympyröi oikea vaihtoehto

20. Asuminen
   1 yksin
   2 toisen kanssa

21. Puhelimen käyttö
   1 käyttää oma-aloitteisesti, etsii ja valitsee numerot
   2 soittaa muutamia tuttuihin numeroihin (valitsee numerot)
   3 vastaa puhelimeen muttei soita
   4 ei kykene käyttämään puhelinta

22. Kaupassa käynti
   1 hoitaa kaikki ostokset oma-aloitteisesti
   2 tekee itsenäisesti pienet ostokset (päivittäiset taloustavarat, maito, leipä, voi yms.)
   3 tarvitsee jonkun avukseen kaikilla ostosmatkoilla
   4 täysin kykenemätön tekemään ostoksia

23. Ruoan valmistus
   1 suunnittelee, valmistaa ja tarjoilee asianmukaiset ateriat itsenäisesti
   2 valmistaa asianmukaiset ateriat, jos ainekset on annettu etukäteen
   3 lämmittää valmiita ruokia
   4 ruoka pitää valmistaa ja tarjoilla

24. Siivoustyöt
   1 tekee taloustyöt itsenäisesti, lukuun ottamatta apua raikaimmissa töissä, kuten ikkunoiden pesussa ja mattojen tamppauksessa
   2 suorittaa kevyet päivittäiset toimet (tiskaus, vuoteiden sijaus)
   3 pyrkii suorittamaan kevyitä päivittäisiä toimia, mutta ei kykene riittävään siisteystaa
   4 tarvitsee apua kaikissa siivoustöissä
   5 ei osallistu siivoustöihin

25. Pyykinpesu
   1 pesee kaiken henkilökohtaisen pyykkinsä itse
   2 pesee ns. pikkupyykin
   3 kaikki pyyikki pestään muiden toimesta

26. Liikkuminen kulkuvälineillä
   1 käyttää itsenäisesti yleisiä kulkuvälineitä tai ajaa autoa
   2 kulkee itsenäisesti taksilla, mutta ei muuten käytä yleisiä kulkuvälineitä
   3 kulkee yleisillä kulkuvälineillä ainoastaan toisen avustamana tai seurassa
   4 matkustaa taksilla tai pikkuautolla ainoastaan toisen seurassa
   5 ei liiku kulkuvälineillä lainkaan

27. Lääkkeistä huolehtiminen
   1 huolehtii itse omista lääkkeistään (oikea annos oikeaan aikaan)
   2 ottaa lääkkeensä ajallaan, jos ne on annosteltu etukäteen
   3 ei pysty itse huolehtimaan

28. Raha-asioiden hoito
   1 hoitaa kaikki raha-asisanssa itsenäisesti
   2 hoitaa päivittäiset raha-asiat, mutta tarvitsee apua pankkeissa ja isompien
   3 summien käsitelyssä
   4 kyvytön hoitamaan raha-asioitaan

29. Neuropsykiatriset oireet
   1 harhaluulot, esim. myrkytyspelot
   2 aistiharhat, esim. kuulo- ja näköharhat
   3 levottomuus tai aggressiivisuus
   4 masentuneisuus tai alakuloisuus
   5 ahdistuneisuus
   6 kohonnut mieliala tai epäasianmukainen iloisuus
   7 apaattia tai välinpitämättömyys
   8 estottomuus, huutelu
   9 ärtyneisyys tai mielialan vaihtelua
   10 poikkeava motorinen käyttäytyminen (esim. heijaaminen, harominen)
   11 unen häiriöt (unettomuus, unen katkeilu, liikaunisuus)
   12 ruokahalun tai syömisen häiriöt (esim. ahmiminen, syömättömyys)
   13 ei psyykkisiä tai käytöshäiriöitä
29. Neuropsykiatriset oireet (Ympyröi viimeksi kuluneen viikon aikana asiakaalla ilmenneet neuro-psykiatriset oireet.)

1. harhaluulot, esim. myrkytyspelot
2. aistiharhat, esim. kuulo- ja näköharhat
3. levottomuus tai aggressiivisuus
4. masentuneisuus tai alakulollisuus
5. ahdistuneisuus
6. kohonnut mielisdeja tai epäasianmukainen iloisuus
7. apatia tai välinpitämättömyys
8. estottomuus, huutelu
9. ärtynyyisyys tai mielisdeja vaihtelu
10. poikkeava motorinen käyttäytyminen (esim. heijastaminen, harominen)
11. unen häiriöt (unettomuus, unen katkeilu, liikaunisuus)
12. ruokahalun tai syömisen häiriöt (esim. ahmiminen, syömätömyys)
13. ei psykkisiä tai käytöshäiriöitä
Appendix 2. Questionnaire in residential care

Asiakaskartoitus/lääkäiden lääkehoito ja toimintakyky Etelä-Savossa

LAITOKSET JA PALVELUTALOT

1. Asiakkaan ikä täysinä vuosina __________

Ympyröi oikea vaihtoehto

2. Sukupuoli
   1 mies
   2 nainen

3. Hoidon luonne
   1 pitkäaikaishoito
   2 lyhytaikainen ympärivuorokauden laitos
   3 akuuttihoito (myös ns. kriisihoito)
   4 tehostettu palveluasuminen

4. Syöminen, ateriointi
   1 ei kykene syömään itsenäisesti
   2 tarvitsee apua ruoan paloitelussa, voin levittämisessä jne.
   3 itsenäinen

5. Siirtyminen (vuoteesta tuoliin ja takaisin)
   1 ei kykene, ei istumata
   2 tarvitsee aktiivista apua (yksi, kaksi ihmistä), pystyy istummaan
   3 tarvitsee vähän apua (sanallista, fyysistä)
   4 itsenäinen

6. Henkilökohtainen siisteys
   1 tarvitsee apua kasvojen pesussa, hiusten kampaamisessa, hampaiden harjauksessa, parranpesussa yms.
   2 itsenäinen

7. WC:n käyttö
   1 riippuvainen avusta
   2 tarvitsee jonkin verran apua (yksi, kaksi ihmistä, fyysistä apua), pystyy istummaan
   3 tarvitsee vähän apua (sanallista, fyysistä)
   4 itsenäinen

8. Peseytyminen
   1 tarvitsee apua (koko kehon pesussa)
   2 itsenäinen

9. Liikkuminen sisätiloissa
   1 liikuntakyvyttöön
   2 pyörätuolin käyttäen itsenäinen
   3 tarvitsee yhden henkilön apua, ohjausta tai rollaattorin
   4 itsenäinen (saattaa käyttää apuvälineitä, esim. keppilä)

10. Portaissa liikkuminen
    1 ei kykene liikkumaan portaissa
    2 tarvitsee apua (sanallista, fyysistä, tavaroiden kantoapua)
    3 itsenäinen
11. Pukeutuminen
1 riippuvainen avustaa
2 tarvitsee apua, mutta pystyy osin pukeutumaan
3 iskenen (mukaan lukien napit, vetoketjut, kengänhaat jne.)

12. Ulosteen pidätyskyky
1 ei kykene pidättämään
2 ajottain vahinkoja
3 kykenee pidättämään

13. Virtsanpidätyskyky
1 ei kykene pidättämään (katetri, cystofix tai vaippa)
2 ajottaisia vahinkoja (esim. pikkuvaippa)
3 kykenee pidättämään

14. Muistitoiminta
1 ei ainaakaan merkittävästi muistamattomuutta
2 lievästi muistamaton (tarvitsee muistamattomuuden takia ajoittaista apua vaikeissa tehtävissä)
3 keskivaikeasti muistamaton (tarvitsee muistamattomuuden takia säänollistä apua)
4 vaikeasti muistamaton (tarvitsee jatkuvasti apua ja valvontaa muistamattomuuden takia)

15. MMSE
Vuoden 2010 tai 2011 aikana tehdyen viimeisen MMSE-tutkimuksen kokonaispisteet

___________ / 30

16. Muistisairausdiagnosto tehty
1 kyllä
2 ei

17. Sairaus (Merkitään tärkein hoidon ja avun tarvettava sairaus, vain yksi.)
1 muistisairaus (esim. Alzheimerin tauti, verisuoniperäinen demetia)
2 aivoverenkiertosairaus tai sen jälkitila
3 muu neurologinen sairas (esim. Parkinsonin tauti, epilepsia)
4 tuki- ja liikuntaelinsairaus (esim. nivelreuma, nivelrikko)
5 sydänpsiirit skitsfrenia, vainoharhaisuus)
6 syöpäsairaus
7 psyykkinen sairaus (esim. masennus, skitsofrenia, vainoharhaisuus)
8 tapaturma ja sen jälkitila (esim. murtamat
9 diabetes ja sen jälkiseuraukset
10 pitkäaikainen keuhkosairaus (esim. astma, keuhkohtaumatauti)
11 äkillinen tulehdus (esim. virtsatietulehdus, keuhkokuumme, ruusu, vyöruusu)
12 kehitysvammaisuus
13 muu (esim. mahahaava, säärihaava, kilpia nhând toimintahäiriöt)
14 ei mikään
### 18. Jatkuva lääkitys (Katso täyttöohje! Vaihtoehtona käy myös tuloste lääkelistasta tai lääkkeenjako-listan kopi.)

<table>
<thead>
<tr>
<th>Lääkkeen nimi</th>
<th>vahvuus</th>
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### 19. Tarvittavat lääkkeet viimeksi kuluneen vuorokauden (klo 00-24) aikana. (Katso täyttöohje! Tähän ei käy vastauksena tuloste lääkelista.)

<table>
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<th>Lääkkeen nimi</th>
<th>vahvuus</th>
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</table>
20. Neuropsykiatriset oireet (Ympyröi viimeksi kuluneen vuorokauden (klo 00-24) aikana asiakkaalla ilmeneet neuropsykiatriset oireet.)

1. harhaluolot, esim. myrkytyspelot
2. aistiharhat, esim. kuolo- ja näköharhat
3. levottomuus tai aggressiivisuus
4. masentuneisuus tai alakuloisuus
5. ahdistuneisuus
6. kohonnut mielilääta tai epäasianmukainen iloisuus
7. apatie tai välinpitämättömyys
8. esittömuus, huutelu
9. ärtyneisyys tai mielialalan vaihtelu
10. poikkeava motorinen käyttäytyminen (esim. heijaaminen, harominen)
11. unen häiriöt (unettomuus, unen katkeilu, liikaunisuus)
12. ruokahalun tai syömisen häiriöt (esim. ahmiminen, syömättömyys)
13. ei psykikkisiä tai käytöshäiriöitä

21. Neuropsykiatristen oireiden lääkkeetön hoito (Ympyröi viimeksi kuluneen vuorokauden (klo 00-24) aikana käytettyt lääkkeet ilman lääke- ja toimintakirjaco.)

1. asiakastauttui sanallisesti
2. asiakkaalle annettiin aikaa ja läheisyyttä
3. selvitettiin somaattisen syyn mahdollisuus (esim. nälkä, jano, kipu, kylmä, tulehdus)
4. käytettiin musiikkia hoitomuotona
5. käytettiin työryhmää apuna tilanteen selvittämisessä
6. käytettiin askartelu-, taide- tai puutarhaterapiaa
7. käytettiin apuna eläimiä tai leikkialäimiä tai nukkeja
8. keskusteltiin asiakkaan/omaisten kanssa tilanteesta
9. säännöllinen ulkoilutus tai muu liikunta
10. muita, mitä ____________________________
11. ei käytetty mitään edellä mainituista

22. Turvatoimet (Ympyröi seuraavista turvatoimista ne, joita on tämän potilaan kohdalla käytetty viimeksi kuluneen vuorokauden (klo 00-24) aikana. Ympyröi kaikki käytetyt turvatoimet.)

1. sängynlaidat molemmilla puolilla
2. sängynlaita toisella puolellalla
3. vartalon liikumisen rajoittaminen (esim. sitominen tuoliin vaatekappaleella, sitominen vuoteeseen magneettivyöllä)
4. yhden tai useamman raajan liikumisen rajoittaminen (esim. käsi- tai sidos)
5. tuolista nousemista estäminen (esim. geriatriseen tuoliin liitetty pöytä)
6. liikumisen apuvälineiden, vaatteiden tai sittokellon poistaminen
7. huoneen oven sulkenminen tai lukitseminen
8. äänieristetty huone
9. fyysisen voiman käyttö
10. hälytysmatto
11. liiketunnistin
12. muita, mitä ____________________________
13. ei mitään edellä mainituista
ORIGINAL PUBLICATIONS (Studies I-III)
Use of antidementia drugs in home care and residential care and associations with neuropsychiatric symptoms: a cross-sectional study

Kuronen M, Koponen H, Nykänen I, Karppi P and Hartikainen S


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I

Use of anti-dementia drugs in home care and residential care and associations with neuropsychiatric symptoms: a cross-sectional study

Kuronen M, Koponen H, Nykänen I, Karppi P and Hartikainen S


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Marja Kuronen 1*, Hannu Koponen 2, Irma Nykänen 3,4, Pertti Karppi 1 and Sirpa Hartikainen 3,4

Abstract

Background: The number of people with dementia is increasing alongside the aging population, and most of these patients manifest with neuropsychiatric symptoms (NPS). The objective of this study was to investigate anti-dementia drug use and its associations with NPS.

Methods: Questionnaires on demographic information, current drug use, activities of daily living and NPS were sent to all municipal home care producers and to all institutions providing long-term residential care in the South Savo Hospital District, Finland.

Results: The study population comprised 2821 persons. Their mean age was 81 years and 68% were female. Dementia had been diagnosed in 31% (n = 410) in home care and in 56% (n = 774) in residential care. Anti-dementia drugs were used by 69% of patients with dementia. Hyperactivity symptoms were common in residential care patients (n = 456, 33%), while problems with mood and apathy dominated in home care patients (n = 486, 54%). In multivariate regression analysis, the mood symptoms and apathy subgroup was associated with use of an acetylcholinesterase inhibitor (AChEI) (OR 1.44; 95% Cl 1.03–2.02), memantine (OR 1.77, 95% Cl 1.15–2.72) or their combinations (OR 1.56, 95% Cl 1.03-2.34). Hyperactivity symptoms were associated with combination therapy of this type (OR 2.03, 95% Cl 1.36–2.34).

Conclusions: The use of anti-dementia drugs was common in both care settings. The use of any anti-dementia drug or combination was associated with the mood and apathy subgroup. The hyperactivity subgroup was associated with combination use of memantine and AChEI.
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Background

Dementia contributes one-tenth of the years spent with disability in people aged over 60 years. This is more than the proportion of stroke, cardiovascular disease or cancer [1]. An estimated 42.3 million people globally will suffer from dementia by the year 2020 and over 80 million by 2040 [1], not only in high-income but also low- and middle-income countries [2]. The annual costs of dementia are estimated to be 600 billion US dollars [3]. Neuropsychiatric symptoms (NPS) occur in 80–90 % of persons with dementia [4]. They may be more disruptive to patients and their caregivers than the decline of cognition [5]. NPS are associated with decline in global functioning, increased use of medications and frequent hospitalization [6]. Agitation, aggression and psychosis are the most distressing NPS and correlate with early transfer to institutional care [7].

Many attempts have been made to form subgroups or symptom clusters of NPS [8–12]. In a large multicenter study with 2 354 outpatients with Alzheimer’s disease, four NPS subgroups were found: hyperactivity, psychosis, affective symptoms and apathy [13]. Petrovics and co-workers identified four factors based on the Neuropsychiatric Inventory (NPI) [14], namely psychosis factor, psychomotor factor, mood liability factor and instinctual factor [10]. Most studies agree that NPS form...
three to five subsyndromes consisting of hyperactivity symptoms, mood symptoms, psychotic symptoms and apathy [12, 13].

Anti-dementia drugs are used not only to improve cognitive functions but also to treat behavioral symptoms [15]. They are either AChEIs (donepezil, rivastigmine and galantamine) or memantine. AChEIs are recommended for use in mild to moderate dementia and to reduce NPS, and memantine in moderate to severe dementia and to diminish behavioral symptoms [16]. The concomitant use of memantine and AChEI is not recommended by NICE 2011, although there may be a small benefit on NPS at six months after the initiation of treatment [17]. Most studies exploring the effect of anti-dementia drugs on NPS have been primarily designed to evaluate their effect on cognition [18]. The effect on NPS may be limited [19].

As the number of people with dementia is increasing and most of these patients manifest with NPS, the aim of this study was to investigate the use of anti-dementia drugs and the prevalence of NPS in two different populations and the associations between anti-dementia drug use and NPS.

**Methods**

**Study design and participants**

We identified with the help of local and regional authorities all public home care units (n=21) providing regular care (a nurse visiting a home-dwelling patient at least once a week) and all institutions (n=68) giving long-term residential care to older people, including both private and municipal residential care facilities, nursing homes and long-term wards in municipal hospitals. The catchment area of the South Savo Hospital District is 105,000 inhabitants [20]. Due to strong support from the local authorities, we had an excellent response rate. Twenty out of 21 municipal home care units responded, and 66 out of 68 residential care units responded (Fig. 1).

General information about the study and the questionnaires were mailed to the nurses and doctors in charge who were responsible for instructing the nurses on the field. Written instructions on how to carry out the assessments were included, and the staff were given the name and telephone number of the first writer if additional guidance was needed. The study was carried out in May 2011.

**Fig. 1 Flowchart of the study**
Questionnaires
The basic demographic information of each patient, e.g. municipality, service unit or residential care unit, age and sex, was followed by questions concerning current regularly used medications, which were obtained from electronic medical records. Activities of daily living (ADL) were assessed by the Barthel Index (scale 0–100) [21]. On this scale, the higher the score, the better the functioning. Cognitive functioning was assessed in two ways. Firstly, we inquired about the results of the latest Mini Mental State Examination (MMSE, scale 0–30) [22] if carried out in 2010 or 2011. Cognition had been assessed by MMSE in 743 patients (51.6 %) in residential care and in 627 patients (45.2 %) in home care services. Nurses reported whether dementia had been diagnosed by a physician, but we did not sort out different dementia types. Secondly, we asked the nurse to assess each patient’s memory by direct observation and assign it to one of four categories by the clinical dementia rating (normal, slightly impaired, moderately impaired, or severely impaired) [23]. We did not ask the dates of dementia diagnosis, start of the anti-dementia drugs or the beginning of NPS.

Each patient was evaluated by a nurse who knew the patient, and NPS were listed according to a symptom list based on the Neuropsychiatric Inventory (NPI). The scale was originally developed to assess behavioral and psychological symptoms in dementia and it consists of 12 items, each of which is scored for frequency and severity. Nurses reported all NPS of each patient during the preceding week in home care (due to visiting procedures at least once a week in home care) and during the preceding 24 h in residential care (observation and care available 24/7). The assessment gave only the presence or absence of the symptom, not the severity or the effects on carers. The interrater reliability was not assessed, but the nurses had written instructions to evaluate the symptoms. We organized the NPS into three subgroups [8]: 1) hyperactivity consisting of agitation or aggression, disinhibition, irritability and aberrant motor behaviour, 2) psychosis consisting of delusions and hallucinations, and 3) mood symptoms and apathy consisting of depression, anxiety, sleeping disturbances, eating disturbances, apathy and euphoria. Fifty-three patients in home care and 89 patients in residential care had no data concerning NPS. These 142 patients were excluded from all NPS or subgroup analyses.

Classification of medication
Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification of medicines recommended by the World Health Organization (WHO) [24]. The anti-dementia drugs included memantine (N06DX01) and the AchEIs: (N06D) donepezil (N06DA02), rivastigmine (N06DA03) and galantamine (N06DA04).

Ethics
The study design was accepted by the Ethics Committee of the South Savo Hospital District. The use of current medication was obtained from medical records, without identification of individual patients. Other data were obtained from a special questionnaire form, which was sent to the institutions and home care services. Informed consents were not needed in our study, because data did not contain birth dates or other material by which a person could have been identified. In addition, ad hoc questionnaire did not include other identification than municipality, service unit or residential care unit, age and gender. As participation in the study was supported by local health authorities, no incentives were needed to promote the response rate.

Data analysis
Differences in characteristics of patients by setting, prevalence and number of NPS among users of anti-dementia drugs were described using proportions and means with standard deviation (SD). Statistical comparisons between groups were conducted using Chi-square test and independent samples t-test or one-way analysis of variance, with p ≤ 0.05 considered significant. Univariate and multivariate (stepwise, forward selection) regression analyses were performed to identify demographic (age, sex and home care/residential care) and neuropsychiatric subgroups (hyperactivity, psychotic symptoms, mood symptoms and apathy) associated with anti-dementia drug use. Results were expressed as odds ratios (ORs) with corresponding 95 % confidence intervals (95 % CIs). In the Tables 3 and 4 the missing p-values of NP were due to confidentiality matters. Data were analyzed using SPSS 19.0 software.

Results
The study population comprised 2821 persons, 68.1 % (n = 1921) of whom were women (Table 1). The mean age of participants was 80.9 (SD 10.1) years, 82.0 (SD 9.8) years in residential care and 79.8 (SD 10.4) years in home care. Only 8 % (n = 224) were younger than 65 years. Of home care patients, 81 % lived alone. Dementia had been physician-diagnosed in 1184 patients (43.8 %), 56.0 % in residential care and 31.1 % in home care. ADL were worse in residential care (mean Barthel Index 36.9, SD 30.8) than in home care (mean 80.8, SD 20.9, p < 0.001). Bedridden persons constituted 0.9 % of patients in home care, and 15.4 % in residential care. Anti-dementia drugs were used by 31.9 % (n = 901) of the study population. AchEIs were used by 19.3 % of patients and memantine by 8.7 % of residential care and
3 % of home care patients. Combination therapy with AChEI and memantine was used by 9.0 % of residential care and 4.4 % of home care patients.

Neuropsychiatric symptoms
More than half of the patients in both settings suffered from NPS (Table 2). In residential care 19.1 % and in home care 15.1 % of patients suffered from two to three simultaneous NPS, and 5.7 % and 4.5 % suffered from at least four symptoms, respectively. The most common NPS subgroup was mood symptoms and apathy (n = 908). Hyperactivity subgroup symptoms occurred in 684 patients and psychotic symptoms in 278 patients. In residential care, the most common subgroup was hyperactivity (32.9 %), while in home care mood symptoms and apathy predominated (54.4 %). The most common distinct symptoms were agitation/aggression, irritability and depression in residential care, but depression, sleeping problems and irritability in home care. Disinhibition was seldom seen (2.0 %) in home care, whereas it was reported in almost one-tenth (8.9 %) of patients in residential care.

Patients with diagnosed dementia
Of persons with diagnosed dementia (n = 1142), altogether 66.8 % (n = 791) used anti-dementia drugs (Table 3). Of these 58.8 % used AChEIs, 18.3 % memantine and 22.9 % combinations of an AChEI and memantine. Users of anti-dementia drugs had higher mean ADL (58.0 vs. 29.8) and MMSE score (16.0 vs.14.7) than non-users. The prevalence of NPS was about the same in both groups.

The frequency of NPS did not differ between the three groups studied: users of AChEI only, memantine only or combination of both (Table 4). In multivariate analyses, any kind of anti-dementia drug use appeared to be independently associated with the subgroup of mood symptoms and apathy, and the use of a combination therapy was associated with hyperactivity but not with psychotic symptoms (Table 5). The ADL score was associated with

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Table 1 Characteristics, functioning and anti-dementia drug use of patients by setting

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 2821)</th>
<th>Residential care (n = 1439)</th>
<th>Home care (n = 1382)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>1921 (68.1)</td>
<td>995 (69.1)</td>
<td>926 (67.0)</td>
<td>0.223</td>
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<tr>
<td>Mean age, years (SD)</td>
<td>80.9 (10.1)</td>
<td>82.0 (9.8)</td>
<td>79.8 (10.4)</td>
<td>&lt;0.001</td>
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<td>≤ 64, n (%)</td>
<td>224 (8.0)</td>
<td>89 (6.2)</td>
<td>135 (10.6)</td>
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<td>65-74, n (%)</td>
<td>354 (12.6)</td>
<td>172 (11.0)</td>
<td>182 (13.5)</td>
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<td>75-84, n (%)</td>
<td>1056 (37.6)</td>
<td>511 (35.6)</td>
<td>545 (39.7)</td>
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</tr>
<tr>
<td>≥ 85, n (%)</td>
<td>1174 (41.8)</td>
<td>664 (46.2)</td>
<td>513 (37.2)</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis and functioning

| Diagnosed dementia, n (%) | 1184 (43.8) | 774 (56.0) | 410 (31.1) | <0.001 |
| ADL score (SD), MMSE, mean (SD) | 58.4 (34.3) | 36.9 (30.8) | 80.8 (20.9) | <0.001 |
| Bedridden, n (%) | 233 (8.3) | 221 (15.4) | 12 (0.9) | <0.001 |

Drug use

| Total number of drugs, mean (SD) | 8.6 (4.7) | 8.5 (4.2) | 8.5 (5.3) | 0.437 |
| Anti-dementia drug users, n (%) | 901 (31.9) | 516 (35.9) | 385 (27.9) | 0.007 |
| AChEIs alone, n (%) | 545 (19.3) | 262 (18.2) | 283 (20.5) | 0.015 |
| Donepezil, n (%) | 291 (10.3) | 127 (8.8) | 161 (11.6) | |
| Rivastigmine, n (%) | 153 (5.4) | 99 (6.9) | 54 (3.9) | |
| Galantamine, n (%) | 107 (3.8) | 36 (2.5) | 69 (4.9) | |
| Memantine alone, n (%) | 166 (5.8) | 125 (8.7) | 41 (3.0) | 0.003 |
| AChEIs and memantine | 190 (6.7) | 129 (9.0) | 61 (4.4) | <0.001 |
| Donepezil + memantine, n (%) | 94 (3.3) | 60 (4.2) | 34 (2.5) | |
| Rivastigmine + memantine, n (%) | 63 (2.2) | 51 (3.5) | 12 (0.9) | |
| Galantamine + memantine, n (%) | 33 (1.2) | 18 (1.3) | 15 (1.1) | |

*Chi-square test for categorical variables and Student’s t-test for continuous variables
ADL score = Barthel Index, scale 0-100
AChEI Acetylcholinesterase inhibitor
Table 2 Frequency of NPS (n, %) and subgroups in patients by setting

<table>
<thead>
<tr>
<th>Frequency of NPS</th>
<th>Residential care ( n = 1386 ) (n, %)</th>
<th>Home care ( n = 1293 ) (n, %)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>643 (46.4)</td>
<td>642 (49.7)</td>
<td>0.014</td>
</tr>
<tr>
<td>One symptom</td>
<td>398 (28.7)</td>
<td>397 (30.7)</td>
<td>0.357</td>
</tr>
<tr>
<td>Two to three symptoms</td>
<td>265 (19.1)</td>
<td>195 (15.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Four or more symptoms</td>
<td>79 (5.7)</td>
<td>58 (4.5)</td>
<td>0.110</td>
</tr>
</tbody>
</table>

Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Residential care (n, %)</th>
<th>Home care (n, %)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity</td>
<td>456 (32.9)</td>
<td>228 (17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>224 (16.1)</td>
<td>92 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>123 (8.9)</td>
<td>26 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>220 (15.9)</td>
<td>144 (11.1)</td>
<td></td>
</tr>
<tr>
<td>A aberrant motor behaviour</td>
<td>83 (6.0)</td>
<td>21 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>146 (10.6)</td>
<td>132 (10.2)</td>
<td>0.788</td>
</tr>
<tr>
<td>Delusions</td>
<td>72 (5.2)</td>
<td>76 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>93 (6.7)</td>
<td>77 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Mood symptoms and apathy*</td>
<td>422 (30.5)</td>
<td>486 (34.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>157 (11.3)</td>
<td>271 (21.0)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>115 (8.3)</td>
<td>101 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Sleeping problems</td>
<td>130 (9.4)</td>
<td>179 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Eating problems</td>
<td>75 (5.4)</td>
<td>70 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Elation</td>
<td>20 (1.4)</td>
<td>18 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>69 (5.0)</td>
<td>40 (3.1)</td>
<td></td>
</tr>
</tbody>
</table>

Notes

*One person could suffer from several symptoms, thus total number of cases in the subgroups is not the same as the total number of patients suffering from at least one neuropsychiatric symptom (NPS). Missing cases: 53 in residential care and 89 in home care.

Discussion

In our large, geographically defined study population, the use of any anti-dementia drug was associated with the NPS subgroup of mood symptoms and apathy. In addition, hyperactivity subgroup symptoms were associated with the combination therapy of AChEI and memantine. Psychotic symptoms were not associated with the use of AChEIs, memantine or their combinations. To our knowledge, this is the only study investigating the associations between anti-dementia drug use and prevalence of NPS subgroups. Mood symptoms and apathy were the most common NPS in anti-dementia drug users. According to previous studies, anti-dementia drugs improve depressive symptoms in mild to moderate dementia, independent of any effect on cognition [25]. A Swedish study [26] reported no association between depressive symptoms and the use of anti-dementia drugs. Instead, they found an association between anti-dementia drug use and aggressive behaviour. The efficacy of AChEIs in the management of NPS in Alzheimer’s disease is limited [14]. Despite, anti-dementia drugs are recommended as a first-line pharmacological treatment for NPS just after non-pharmacological interventions [20]. In Finland, the National Treatment Guidelines recommend the use of AChEIs to treat NPS in patients with dementia [16].

Combination therapy of memantine and AChEI has growing evidence of efficacy in cognitive decline [27, 28], but the effect on NPS is controversial [29]. However, memantine alone has had some effect on hyperactivity symptoms [7]. Psychotic symptoms occurred in every tenth patient in our study. Although memantine has been found to have some benefits in treating psychotic symptoms [30] without an increased risk of mortality, which occurs with anti-psychotics [31], we found no association between the use of any anti-dementia medication and the psychosis subgroup. Persons with psychotic symptoms may have been treated with anti-psychotic drugs rather than with anti-dementia drugs. This may be due to evidence that risperidone, olanzapine and aripiprazole are superior to placebo in treating agitation and psychosis in dementia [32].

The use of anti-dementia drugs has increased in the last few years [33], and the proportion of AChEI users in long-term residential care varies from 3 % in Australia...
to 30 % in the United States [34, 35]. In Finland, during 2005–2009, 84 % of patients with Alzheimer’s disease used AChEi and 47 % memantine, 22 % using both of these concomitantly [36]. In our study, donepezil was the most commonly used anti-dementia drug, consistent with previous studies [36]. The use of memantine or combination therapy was common also in our study, whereas in Sweden, memantine was used in 2007 by only 3.1 % of patients with cognitive impairment [26].

The main strength of our study is the nearly 100 % coverage of the targeted study population, receiving long-term residential care or regular home care services in the South Savo Hospital District. We obtained comprehensive data concerning drug use, NPS profile and basic demographic characteristics of these patients, enabling a representative overview of the use of anti-dementia drugs and NPS in two different care settings. The study has also some limitations. We did not ask the dates of dementia diagnosis, start of the anti-dementia drugs or the beginning of NPS. This cross-sectional design forms a limitation, and allows us only to evaluate the correlations between NPS and use of anti-dementia drugs at a specific time point. The questionnaires also gave only an approximation of NPS, as the interrater reliability was not assessed, and nurses had only written instructions for evaluating the symptoms of patients. The assessment of only the presence or absence of the symptom forms a limitation. Different time windows to detect NPS in home care and residential care (previous week vs. preceding 24 h) due to different observational possibilities may also have affected the prevalence of NPS to some extent. However, there are only a few

Table 4 Frequency of NPS and subgroups, ADL functioning and cognition by use of anti-dementia drugs

<table>
<thead>
<tr>
<th></th>
<th>AChEi only</th>
<th>Memantine only</th>
<th>AChEi and memantine</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of NPS, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>202 (43.4)</td>
<td>60 (41.4)</td>
<td>58 (32.0)</td>
<td>0.065</td>
</tr>
<tr>
<td>One symptom</td>
<td>144 (31.0)</td>
<td>47 (32.4)</td>
<td>61 (33.7)</td>
<td>0.569</td>
</tr>
<tr>
<td>Two to three symptoms</td>
<td>97 (20.9)</td>
<td>28 (19.3)</td>
<td>46 (25.4)</td>
<td>0.296</td>
</tr>
<tr>
<td>Four or more symptoms</td>
<td>22 (4.7)</td>
<td>10 (6.9)</td>
<td>16 (8.8)</td>
<td>0.107</td>
</tr>
<tr>
<td>Any NPS, n (%)</td>
<td>263 (56.6)</td>
<td>85 (58.6)</td>
<td>123 (68.0)</td>
<td>0.029</td>
</tr>
<tr>
<td>Subgroups, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>136 (29.2)</td>
<td>45 (31.0)</td>
<td>83 (45.9)</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>54 (11.6)</td>
<td>18 (12.4)</td>
<td>33 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Mood symptoms and apathy</td>
<td>170 (36.6)</td>
<td>57 (39.3)</td>
<td>72 (39.8)</td>
<td></td>
</tr>
<tr>
<td>ADL score, mean (SD)</td>
<td>62.3 (31.5)</td>
<td>48.0 (31.7)</td>
<td>54.6 (28.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE, mean (SD)</td>
<td>17.2 (6.3)</td>
<td>14.4 (7.2)</td>
<td>13.9 (6.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ADL = Barthel Index, scale 0–100
NPS = Neuropsychiatric symptoms, AChEi = Acetylcholinesterase inhibitor, MMSE = Mini Mental State Examination
*Chi-square test for categorical variables and one-way analysis of variance for continuous variables

Table 5 Univariate and multivariate associations between patient characteristics, subgroups and anti-dementia drug use

<table>
<thead>
<tr>
<th>Variable</th>
<th>AChEi only</th>
<th>Memantine only</th>
<th>AChEi + memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate*</td>
<td>Univariate</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.02 (1.00 to 1.04)</td>
<td>1.04 (1.01 to 1.06)</td>
<td>1.03 (1.00 to 1.07)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.06 (0.78 to 1.43)</td>
<td>1.48 (0.93 to 2.33)</td>
<td>1.00 (0.67 to 1.48)</td>
</tr>
<tr>
<td>ADL score</td>
<td>1.03 (1.02 to 1.03)</td>
<td>1.03 (1.02 to 1.04)</td>
<td>1.02 (1.01 to 1.02)</td>
</tr>
<tr>
<td>Residential care</td>
<td>0.31 (0.24 to 0.40)</td>
<td>1.37 (1.04 to 1.80)</td>
<td>1.13 (0.79 to 1.56)</td>
</tr>
<tr>
<td>NPS subgroups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>0.83 (0.61 to 1.12)</td>
<td>0.91 (0.66 to 1.38)</td>
<td>1.69 (1.17 to 2.45)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1.15 (0.73 to 1.97)</td>
<td>1.24 (0.67 to 2.26)</td>
<td>1.93 (1.16 to 3.23)</td>
</tr>
<tr>
<td>Mood symptoms and apathy</td>
<td>1.66 (1.22 to 2.25)</td>
<td>1.44 (1.03 to 2.02)</td>
<td>1.87 (1.24 to 2.83)</td>
</tr>
</tbody>
</table>

ADL score = Barthel Index, scale 0–100
AChEi = Acetylcholinesterase inhibitor, NPS = Neuropsychiatric symptoms, OR = odds ratio, CI = confidence interval
*Forward selection. Variables included in the multivariate model are shown
studies about NPS in home-dwelling persons with dementia [37] and there are, to our knowledge, no other studies detecting NPS in a almost all persons receiving home care in a defined area.

Conclusions
The use of anti-dementia drugs was common both in long-term residential care and home care. The use of AChEIs and/or memantine was associated with the mood and apathy subgroup and combination therapy with the hyperactivity subgroup symptoms. As clinicians, we need more studies on the effectiveness of anti-dementia drugs to ensure effective and safe pharmacotherapy for our vulnerable patients with dementia.

Abbreviations
AChEI: Acetylcholinesterase inhibitor; ADL: Activities of daily living; ATC: Anatomical Therapeutic Chemical; CI: Confidence interval; MMSE: Mini mental state examination; NSAID: Non-steroidal anti-inflammatory drug; NPS: Neuropsychiatric symptoms; OR: Odds ratio; SD: Standard deviation; WHO: World Health Organization.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
MK designed the study, collected the data and wrote the first manuscript. IN carried out the statistical analysis and participated in the writing of the manuscript. HK and SH participated in planning the study design, and prepared and analysed the manuscript. All authors participated in interpreting the statistical analysis, read, added comments and approved the final manuscript.

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Dementia is pandemic. Almost all persons with dementia exhibit neuropsychiatric symptoms (NPSs) during the course of their illness. One-third of the care expenses of home-dwelling patients are due to these symptoms. NPSs such as aggression, agitation, delusions and depression increase the risk for institutionalization. Psychotropic drug use, especially use of antipsychotics, has been concerningly high in this vulnerable group of people. The aim of this study was to examine the use of anti-dementia drugs, antipsychotics, physical restraints and their associations with NPSs.