Neuropsychiatric symptoms in institutionalized residents with dementia:

Course and interplay with cognition, quality of life and psychotropic drug use.

Roland B. Wetzels

Colofon

This research presented in this thesis was performed by a researcher of the department of Department of Primary and Community Care, Centre for Family Medicine, Geriatric Care and Public Health, Radboud University Nijmegen, Medical Centre, the Netherlands and the Nijmegen UKON.

This work was financially supported by the Joannes de Deo Foundation, Netherlands Organisation for Health Research and Development (ZonMW), Foundation for the Promotion of Science in Nursing Home Care (SWBV), and the Department of Geriatric Care of the Radboud University Nijmegen.

Financial support for the printing of this thesis has been kindly provided by the department of elderly Care medicine of the Radboud University Nijmegen, Novartis

Lay-out

Druk

ISBN/EAN: 978-90-9026378-6

Neuropsychiatric symptoms in institutionalised residents with dementia:

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Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen op maandag 19 december 2011
om 15.30 uur precies

door

Roland Bernard Wetzels
geboren op 7 januari 1969
te Nijmegen

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An academic essay in
Medical Sciences

Doctoral Thesis

to obtain the degree of doctor
from Radboud Universiteit Nijmegen
on the authority of the Rector Magnificus prof. dr. S.C.J.J. Kortmann,
according to the decision of the Council of Deans
to be defended in public on Monday December 19, 2011
at 15.30 hours

by

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Contents

„ That was certainly most unexpected "

A Beautiful Mind

„ The Fat Man said that for gomers, doing nothing is the delivery of medical care "

#13 Laws of The House of God

<u>Voor</u> :

ter nagedachtenis aan mijn vader Drs. M.H. Wetzels

& Bettie

én

Barbara

…you are everything I hoped for…

…you are everything I need…

Chapter 1

General Introduction

Specialist ouderengeneeskunde:

"…. als dhr. begint te roepen, is het keihard en alles doordringend. Al maanden zoeken we naar de juiste aanpak, maar het wordt steeds indringender. Hoewel ik liever weinig medicatie voorschrijf heb ik alles uit de richtlijn probleemgedrag al geprobeerd… te vergeefs….
…Ik ga na mijn visite de deur uit, maar de medebewoners zitten er 24 uur per dag in en steeds meer onderlinge agressie en bezwaren van familie. Waarom we er niet meer aan doen…."

General introduction

Introduction

Dementia is a major cause of suffering and disability in the elderly. Dementia is a complex brain disease that affects many aspects of individual patients' lifes. The pleiotropic consequences of the illness have tremendous and devastating impact due to personality and emotional changes, decreasing intellectual capabilities and loss of fruitful social interaction with others. Since theres is no cure, patients have protracted disease courses.

Because dementia mostly affects the elderly, its prevalence is expected to rise steeply over the coming years [1]; therefore, it also has got a huge economic impact. In the Netherlands, it is currently estimated that 235.000 people with dementia life in our country and this figure is expected to raise to half a million in 2050 [2].

Dementia constitutes a number of heterogeneous diseases, of which Alzheimer's disease (AD) is the most frequent in the general population 70% [2]. Other common forms of dementia include vascular dementia (VaD) 15% [2], Lewy Body dementia (LBD), Parkinson's disease dementia (PDD) and frontotemporal dementia (FTD), each with their own onset, course over time and progressive cognitive symptomatology. Although onset and course can differ, initially, all dementia syndromes are characterized by progressive cognitive decline resulting in a slow but gradual decline in memory function, inability of perception and thinking, necessitating supervision and assistance with personal care.

Neuropsychiatric symptoms

Recent advances in dementia research have increased our insight in the symptomatology and have shifted focus toward the non-cognitive symptoms of dementia, also called dementia-related neuropsychiatric symptoms (NPS). Basically, NPS encompass a wide range of heterogeneous symptoms including the affective domain like depression, apathy and anxiety; behavioural domain like aggression, disinhibition, screaming, but also psychotic symptoms like delusions and hallucinations. Since NPS are ubiquitous and probably universal at some point during the course of the disease, they significantly contribute to the suffering of dementia due to their major impact on patient's and caregiver's lives. Consequently, NPS are increasingly recognized as important research outcome measures [3,4]; therefore, illustrating the need to explore the prevalence, course and correlates of NPS. Notably, to help clinicians and researchers to define NPS, guidelines on relevant aspects of NPS in statements involving definition [5] and treatment [6] have been formulated.

In community-dwelling patients with dementia [7,8], according to the Dutch Maastricht Study of Behaviour in Dementie (MAASBED-study) [9], NPS occur up to 50-80%. Apathy and depression are the most prevalent NPS in paticents with dementia living at home. Due to caregiver inabilities to tackle adequately the impact of NPS, they can ultimately result into (earlier) institutionalization [10,11].

Since the publication of the WAALBED-study (Waal (:major river in Nijmegen) Behaviour in Dementia), in which, after a single, large cross-sectional assessment, the prevalence and predictors of NPS had been determined in 1452 residents with dementia in 59 Dutch nursing homes, figures on the prevalence of NPS are known. In this WAALBED-study, prevalences of NPS show percentages up to 80% [12], and agitation/aggression and apathy were the most frequently observed behaviours with prevalences of 30-35% [12]. Also, comparable prevalences have been found in a similar study in Norway [13]. NPS represent a major challenge for clinician's, patients' families and nursing staff, which are faced with managing agitated and sometimes aggressive behaviors. NPS can therefore

result in increased demands on staff resources, increased job-related stress, burnout, and staff turnover. Moreover, NPS can result in the application of physical restraints [14] further diminishing the resident's ability to move freely and to engage in social interaction with his surroundings and therefore reducing residents' quality of life.

In addition, according to the WAALBED-study, NPS in patients with dementia in nursing homes can be grouped into five main clusters: agitation, psychosis, mood disorders, psychomotor agitation and apathy [15], indicating the interconnection but also the distinct nature of individual NPS.

As the rate and type of cognitive symptoms tend to vary across different types of dementia, so do NPS. According to several cross-sectional studies, sleep disturbances are encountered more frequent in vascular dementia (VaD) compared to AD [16], VaD is associated with less clinical relevant-NPS [17] and sleep disturbances, appetite changes and aberrant motor behaviour are found to be more prevalent and more severe in AD [18]. In addition, in more advanced stages of dementia, prevalence rates of NPS also vary across dementia aetiologies as well [16-18]. Furtheremore, it has also been demonstrated in the WAALBED-study that the emergence of NPS is associated with gender and dementia severity [19]. Besides these biological origins of NPS, it has been found that the environment, specifically the special care unit, also influence the emergence and clustering of NPS [20]. Indeed, these correlates demonstrate the complex nature of NPS and contribute to the growing notion that the biopsychosocial model [21] applies fully to this complex nature. This biopsychosocial model has been used to examine and explain the full range of consequences of the dementia [22] as well on NPS [23].

Although several studies have looked at the course of NPS in community-dwelling patients with dementia [9,24-26], most studies, however, have institutionalization as a primary endpoint. A detailed knowledge of the course of a wide range of NPS can help clinicians to better understand the clinical course of individual NPS; indicate causal relationships between these variables; to ensure more efficient therapeutic interventions and better treatment decisions of NPS; to provide continuous support to patients and caregivers and to inform them on prognosis. Longitudinal studies, however, on the course of NPS in patients with dementia in nursing homes are scarce.

Psychotropic drugs use in residents with dementia

Psychotropic drugs are frequently used among old, frail nursing homes population [12,13,27-29]. These drugs have only a modest beneficial effect in short-term treatment but limited benefit in longer-term therapy [30]. Their use is furthermore limited due to inefficacy and side-effects like the induction of somnolence. The use of these drugs is therefore under intense scrutiny and necessating a black box warning from the FDA [31].

Since the midnineties of the last century [32] and more recently since the publication of the aforementioned WAALBED-study, figures on the psychotropic drugs use (PDU) in nursing homes residents with dementia in the Netherlands are known and show prevalences up to 65% for any psychotropic drug [12]. Particularly, in this study, antipsychotics are prescribed up to 37% to residents with dementia in nursing homes, and antidepressants up to 27%. These data support the notion that residents with dementia in nursing homes are overtreated and that treatment guidelines are not observed to [28].

In addition, the effect that psychotropic drugs have on the quality of life of the individual residents with dementia has been of particular interest. It has been found that the prescription of PD per se negatively influence the quality of life of residents with dementia [33].

Given this high prescription, the limited beneficial effect of these psychofarmacological treatments and the negative impact on quality of life, prudent use of PD is a mainstay on quality of care. Indeed, the Ministry of Health, Welfare and Sport issues the prescription of PD has one of the main targets to evaluate individual nursing home practises.

Although an important issue, it is hardly known how prescription patterns for the main psychotropic drugs given in nursing homes are over time: antipsychotics, antidepressants, anxiolytics, hypnotics, antiepileptics and antidementia drugs.

Quality of Life in residents with dementia

In the past three decades, the focus of dementia care has shifted from somatic care and treatment to emotion-oriented care [34]. This led to the development of several approaches and support for people with dementia and has stimulated the development of several assessment instruments to measure a broader range of Quality of Life (QoL) indicators which is in fact a multidimensional construct. Apart from this, the mean goal for professional workers for treatment interventions is the improvement of QoL for the individual resident with dementia. Consequently, in research, QoL is increasingly recognized as a key consideration [35,36].
In general, nursing home residents with dementia have a lower QoL than community-dwelling patients with dementia [37-39]. For residents with dementia in nursing homes, QoL is of particular importance since they live their lifes in nursing homes and their QoL is much dependant of the quality of care. The determinants contributing to this lower QoL are largely unknown. Studying these determinants, however, can help to improve quality of care and therefore their lifes.

Nursing home medicine in the Netherlands.

In the Netherlands, large portions of patients with dementia reside in nusing homes on dementia special care unit (SCU) to receive special care. On a daily basis, patients are being taken care of by a multidisciplinary team using a multidisciplinary, problemoriented care plan based on the Chronic Care Model [40]. Elderly care physicians who completed a 3-year training programme, are responsible for the care of approximately 100 residents, are employed by the nursing home [41].
Recent debate on the small-scaling housing policy has gained some momentum in that it is not considered to be superior to regural ward size [42].

Aim of this thesis

Studies on the course of NPS in residents with dementia in nursing homes are scarce. While cross-sectional studies have been more widespread and underscore the importance of (individual) NPS in daily clinical work, a need exists to study a broad range of NPS in residents with dementia in nursing homes over time. Insight into the course of NPS can provide best practice for treating NPS, help clinicians to establish the prognosis of NPS, offer psycho-education, increase residents' quality of life, and help planning of healthcare facilities against reasonable costs.
Only recently, the topic of the longitudinal course has been the focus of more attention but -until now- none such study had been undertaken in the Netherlands. The aim of this research, which is labeled the WAALBED-II-study, since it is a continuation of the WAALBED-study, was to explore the course of NPS and prescription patterns of psychotropic drugs in residents with dementia in nursing homes and to explore its impact on QoL and relation with cognition.
The WAALBED-II-study studies the course and predictors of neuropsychiatric symptoms (NPS) in nursing home residents with dementia. The Waalbed-II-study sets research of NPS in institutionalized residents with dementia one-step further. NPS are studied in a longitudinal prospective observational cohort study, among 290 residents with dementia residing in nine different nursing homes in the Netherlands. During this two-year follow-up, successive measurements with a six-month interval were carried assessing several residents characteristics, prevalence and severity of NPS, quality of life, drug use (especially psychotropic drug use), ADL-functions and cognition. The CMO Arnhem-Nijmegen Medical Ethics Committee gave formal approval. Written informed consent was obtained from all residents' legal representatives.

Research questions and general outline

The following research questions are addressed:

1. *What is the course of NPS in people with dementia residing in long-term care facilities?*

In chapter 3, a systematic overview is given of the literature of studies found on the course of a wide range of NPS in longterm care settings.

In chapter 6, a detailed overview of the actual course over a 2-year period is given of NPS in the WAALBED-II-study. Since it is believed that individual NPS show different courses over time, also the prevalence and course of individual symptoms are studied and are described in this chapter. From a clinical and research point of view, important questions are: Do individual symptoms resolve over time or do they persist? What symptoms are the most prevalent? What symptoms are the most persistent? Do differences exist in the course of NPS between different types of dementia?

2. *What is the validity of Severe Impairment Battery-short version (SIB-s) in a sample of nursing home residents with dementia?*

In chapter 4, the first study to date is described that examined the validity of the SIB-s in a group of residents with dementia. When assessing the cognitive abilites of residents with dementia, the use of the mini mental state examination (MMSE) is widespread, but flooreffects hamper its usefulness in the advanced stages of dementia and limiting the interpretation of results of studies focusing on the treatment of cognitive functions. A clear need exists to tap cognitive functions in advanced stages of dementia and therefore identifying subgroups of residents who would normally be labeled as one group with the use of the MMSE. Factory analysis was also used to examine validity of the SIB-s and to gain insight in the possible subscales of the SIB-s.

3. *What are determinants of Quality of Life in residents with dementia in nursing homes?*

In chapter 5, a detailed study is described that looked for significant contributors in QoL. These contributors are important since they can focus treatment and can increase quality of care given to residents with dementia. This is the first study to include the impact of cognition on QoL assessed with the SIB-s.

4. *What are prescriptions patterns of psychotropic drugs over 2-year period?*

In chapter 7, a detailed overview is given for psychotropic drugs frequently used to treat resident with dementia in nursing homes. Psychotropic drugs use (PDU) was classified using the Anatomical Therapeutical Chemical - classification [43] and grouped into antipsychotics, antidepressants, hypnotics, anxiolytics, antiepileptics and antidementia medication. PDU was observed for a period of 2-years. The outcome measures were frequency parameters: point prevalence (baseline, follow-up, and cumulative), discontinuation, continuation, and (cumulative) new onset of PDU specified as users and non-users of the ATC-groups. Specifically, following research quenstions were considerd relevant: how often are the individual psychotropic drugs prescribed? For how long are these drugs prescribed? Do differences exist in prescriptions patterns between different types of dementia? In addition, PDU was analyzed across multiple indications.

Finally, chapter 8 summarizes the main findings and conclusions and these are discussed in the context of nursing home care practise. Methodological issues are also presented. The relevance of this study for further research and clinical practice is also discussed and implications are discussed.

Eerst verantwoordelijke verzorgende:

" …Het is een erg vervelend gezicht en gehoor om een goed uitziende dame te zien zitten, zich krampachtig vasthoudend aan de stoelleuningen met angstige, vragende en rusteloze ogen die continu roept/schreeuwt om verschillende mensen. Deze dame is niet te corrigeren met allerlei zaken wat is uitgeprobeerd. Het enige wat een beetje helpt is naast haar zitten en hand vasthouden en blijven inpraten op mevrouw. Dit dwingende en indringende roepen brengt veel onrust bij haar zelf en medebewoners; maar ook familieleden vinden het erg moeilijk. Dit betekent dat je hier ook een steun voor moet zijn. Het vergt zoveel tijd dat hier andere bewoners met minder aandacht moeten doen. Op een gegeven moment brengt dit te veel irritatie waardoor medebewoners erg boos reageren waardoor mevrouw niet snapt waarom iedereen boos is op haar.

Van de bewoners die boven ons wonen krijgen we iedere dag klachten met name in de avond en nacht omdat hun nachtrust wordt verstoord. Ook de afdeling op de begane grond geeft klachten. Al met al geeft het een machteloos gevoel om niets te kunnen doen dan alleen medicatie te geven waardoor mevrouw even suf is. Naast alle pillen wordt mevrouw ook gespoten: dit is een aangrijpend moment, ze kijkt je dan met radeloze ogen aan en vraagt dan ook de andere arm te doen op een bepaalde manier niet goed te plaatsen. En alles helpt maar even, als personeel ga je dan naar huis maar als bewoner ben je overgeleverd aan wat komen gaat.

Ik word hier wat radeloos van… "

Chapter 2

Design and Methods

Design and Methods

Design

The WAALBED-II-study studies the course and predictors of neuropsychiatric symptoms (NPS) in nursing home residents with dementia. The Waalbed-II-study sets research of NPS in institutionalized residents with dmenetia one-step further. NPS are studied in a longitudinal prospective observational cohort multicentred study, among residents with dementia residing in nine different nursing homes in the Netherlands. During this two-year follow-up, successive measurements with a six-month interval were carried assessing several residents' characteristics, prevalence and severity of NPS, quality of life, drug use (especially psychotropic drug use), ADL-functions and cognition. The CMO Arnhem-Nijmegen Medical Ethics Committee gave formal approval. Written informed consent was obtained from all residents' legal representatives.

Timetable and flowchart:

Characteristics	inclusion	T_0 (Baseline)	T_1 (6-months)	T_2 (12-months)	T_3 (18-months)	T_4 (24-months)
Age, gender, marital status, duration of stay	x					
Dementia diagnosis	x					
SCU characteristics	x					
Co-morbidity	x					
Dementia severity (GDS)		x	x	x	x	x
Cognition (MMSE)		x				
Cognition (s-SIB)		x	x	x	x	x
Communication (InterRAI)		x	x	x	x	x
ADL (InterRAI)		x	x	x	x	x
NPS (NPI-NH)		x	x	x	x	x
NPS (CMAI)		x	x	x	x	x
QoL (QUALIDEM)		x	x	x	x	x
Medication ATC-classification		x	x	x	x	x

Methods

Nursing home

Several nursing homes, as part of the Nijmegen University KnowledgeNetwerk Elderlycare Nijmegen (UKEN), took part in this study. The management staff selected several dementia special care units (SCU) to participate. After screening by the researchers, these SCU's selected reside residents with a formal diagnosis of dementia and these residents where admitted to the SCU according the Psychiatric Hospitals (Compulsory Admissions) Act (Wet bijzondere opnemingen in psychiatrische ziekenhuizen, BOPZ).

Residents

Residents were enrolled from SCU from nursing homes in the Netherlands in this prospective cohort study. Resident's elderly care physicians systematically screened all residents for inclusion. Residents were considered for inclusion provided they: (1) met the Diagnostic and Statistical Manual of Mental Disorders fourth edition criteria for dementia [44]; (2) had no history of life-threatening disease at the time of inclusion; and (3) had to reside in the nursing home for at least four weeks. Residents with dementia residing in so called outreaching nursing home care were not included in this study.

The following characteristics were registered: age, gender, marital status, admission date, duration of stay and in residents die during the follow up the date of death, cause(s) of death.

Assessment of types of dementia

Dementia diagnosis was determined according to the Dutch guideline 'diagnosis and treatment of dementia' [45] and international approved criteria [46,47] for Alzheimer disease (AD), vascular dementia (VaD), mixAD/VaD or other diagnosis. An etiological diagnosis was established by the elderly care physicians using international accepted criteria for AD, VaD, mixed AD/VaD [46,47], frontotemporal lobar degeneration [48] and dementia with Lewy bodies [49]. The author of this thesis independently checked the eligibility and diagnosis of all residents by examining the patient's clinical notes. When disagreement arose, consensus meetings were organized to ensure the inclusion of all residents who met the aforementioned criteria.

Procedure

All licensed vocational nurses, who have been specifically assigned to the individual residents, observed symptoms during a 2-week period prior to assessment, were interviewed by author of this thesis or the research assistant at each assessment at six-month intervals during a two-year period. All interviews were carried out by author of this thesis or the reseach assistant. Initially, information gathering took several days to interview all licensed vocational nurses from one SCU.

Assessment of NPS

NPS were assessed with the Neuropsychiatric Inventory Nursing Home version (NPI-NH) [50,51]. The nursing home version was developed for the use of professional caregivers within institutions and proved to be valid and reliable for trained nursing staff [52] and has been translated into Dutch [53]. The NPI-NH is a structured interview that includes 12 NPS: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, nighttime disturbances and appetite/eating change. Both the frequency (F) and severity (S) of each symptom are rated on a four- (1–4) and three-point (1–3) Likert scale, respectively. A separate score can be calculated for each symptom by multiplying the frequency and severity scores (FxS score), resulting values ranging from zero to 12 for each symptom. Summing FxS scores reveals a total score that ranges from 0–144. In order to reduce the number of predictor variables, we used five NPI-NH factor scores based on the findings of previous studies [15,54]. The following factors were selected for analysis: (1) agitation consisting of agitation/aggression, euphoria, disinhibition and irritability; (2) depression consisting of depression and anxiety; (3) psychosis consisting of hallucinations and delusions; (4) psychomotor agitation consisting of aberrant motor behavior and nighttime behavior; and (5) apathy consisting of apathy and eating disorders [15].

Agitation and aggression were assessed using the Cohen Mansfield Agitation Inventory (CMAI). This instrument, originally developed by Cohen-Mansfield [55], is designed to assess 29 agitated or aggressive behaviors and has been extensively used for assessment purposes in nursing homes. The original CMAI has been validated [56] and is the only instrument specifically addressing agitation or aggression that has been translated into Dutch. The Dutch CMAI (CMAI-D) has been validated [57]. The frequency of each symptom is rated on a seven-point scale (1–7) ranging from "never" to "several times an hour". Summing all symptomscores reveals a total score that ranges from 29–203.

Assessment of quality of life

Quality of life (QoL) was assessed with the Qualidem. This questionnaire, which is specifically designed for institutionalized residents with dementia, is rated by professional

caregivers [58,59]. It is a multidimensional scale with 37 items, with four response categories each (never, rarely, sometimes, frequently), that make up nine homogeneous, unideminsional subscales: 'Care relationship', 'Positive affect', 'Negative affect', 'Restless tense behaviour', 'Positive self image', 'Social relations', 'Social isolation', 'Feeling at home' and 'Something to do'). Qualidem can establish a QoL profile and a QoL total score. The reliability, internal structure and validity are satisfactory [58,59]. The authors of the Qualidem state that in very severe dementia six subscales can be applied using approximately half the items (18/37 items); the reliability is moderately sufficient [60]. Symptoms were observed by two licensed vocational nurses during regular care giving in a one-week observational period prior to assessment.

Dementia severity

The Global Deterioration Scale (GDS) rates was used to asses severity in dementia. This 7-point scale ranges from normal cognition (stage one) to very severe cognitive decline (stage seven) [61]. Stages four and higher are considered to represent subsequent dementia stages.

Cognition

Cognitive functioning was assessed with the Severe Impairment Battery-short version (SIB-s). The SIB-s is a cognitive assessment instrument able to test cognition into the later stages of dementia[62]. At baseline, the MMSE was also used to assess cognitive functioning [63]. As the MMSE is known to show floor effects with increasing cognitive decline, a better cognitive assessment instrument is required to assess cognitive function in the advanced stages of dementia. The SIB-s has been shown to enable reliable assessment of patients with severe dementia [62].

Assessment of activities of daily living (ADL)

ADL was assessed with the InterRAI Long Term Care Facility (LTCF) section G (2005, version 07). This observational scale measures resident self-involvement in the personal ADL. An hierarchy ADL-Scale includes 4 of the ADL items of the InterRAI LTCF, each with 6 response categories, and is scored according to a decision tree with 8 scale categories, ranging from 0 (independent) to 6 (totally dependent) and 8 (activity not seen). When first introduced, its reported psychometric properties were good to excellent (inter-rater reliability) and an internal consistency (Cronbach's alpha) of .90 [64]. Validity and reliability of the ADL scale are established in a study including Dutch nursing home residents with dementia [65].

Psychotropic drug use (PDU)

Data on PDU on the day of assessment were retrieved from the patients' medical and pharmacist files. Drugs were classified using the Anatomical Therapeutic Chemical classification (ATC) [43] and grouped into antipsychotics (AP; No5A…) anxiolytics (ANX; N05B…), hypnotics (HYP; N05C…), antidepressants (ADP; N06A…), anticonvulsants (AC; No3A…), anti-dementia drugs (ADM; N06A…), and any psychotropic drugs (either of the six aforementioned psychotropic drugs). Dichotomous categories of either "present" or "absent" were used to quantify PDU; prescriptions for incidental use (P.R.N.; pre re nata) were discarded.

Frequency parameters of course of dementia

The main outcome measures were frequency parameters and NPI-severity scores [9]. The following frequency parameters were calculated: prevalence, resolution, persistence, and incidence of NPS. Clinically relevant NPS (NPS-CR) measured with the NPI-NH were defined by a FxS

score for each individual symptom ≥4, as being likely to represent residents with clinically relevant behaviour [52]. Point prevalence was defined as the proportion of residents with specific CR-symptoms at each assessment. The cumulative two-year prevalence was defined as the proportion of residents developing a specific CR-symptom on at least one assessment over the two-year period. Resolution was defined as the proportion of residents who showed a specific CR-symptom at one assessment but not at the next assessment and was calculated for each two successive assessments. A CR-symptom was persistent if it was present on at least two subsequent assessments, and was calculated for any three and four consecutive assessments as well. Incidence was rated as the proportion of residents who developed a specific CR-symptom at one assessment but showed no CR-symptom on the preceding assessment. The cumulative incidence was rated as the proportion of residents who were symptom free at baseline, but developed the specific CR-symptom at next assessments. Prevalences were presented as percentages of total group. Frequency parameters are presented as percentages on subgroup level; by definition, persistence and resolution add up to 100%.

Chapter 3.

Course of neuropsychiatric symptoms in residents with dementia in long-term care institutions: A systematic review

R Wetzels S Zuidema I Jansen F Verhey R Koopmans

Eerste verantwoordelijke verzorgende:

"…Ik voel vaak onmacht als de cliënten onrustig zijn, en daarom geef ik vaak de medicatie voor de onrust van zonodig.
Ik wil het graag voorkomen en ben alert en ga onderzoeken waar het vandaan komt en schakel verschillende disciplines in…"

Abstract:

BACKGROUND: Neuropsychiatric symptoms (NPS) occur frequently in residents of long-term care institutions. The aim of this study was to systematically review the literature on the course of NPS in residents with dementia in long-term care institutions.

METHODS: A systematic literature search was conducted using Medline, PsychInfo, Embase and Cinahl. Search terms included dementia, long-term care institutions, NPS, longitudinal, and additional related terms. All titles and abstracts were independently assessed for inclusion and for methodological quality by two researchers, and the full texts of relevant papers were retrieved. Inclusion criteria were: dementia diagnosis, long-term care institutions, NPS, and longitudinal design.

RESULTS: The literature search revealed 1982 papers of which 18 met the inclusion criteria.

The patients were predominately female and were aged 75 years and over. The follow-up period ranged from three months to one-year. The number of assessments ranged from two to five, and 12 different assessment instruments were used to study NPS. Aberrant motor behaviour, depression, anxiety, and euphoria showed decline over time, and psychosis remained constant whereas apathy, agitation, irritability, and disinhibition increased over time. All symptoms showed specific intermittent courses. The methodological quality of the literature was limited by the small sample sizes, short follow-up periods, and lack of comprehensive neuropsychiatric assessment instruments.

CONCLUSIONS: In the reviewed studies, NPS in institutionalized residents with dementia showed a heterogeneous course, although methodological limitations and the diversity of the studies calls for caution in interpretation. Future research should focus on large prospective cohort studies with institutionalized residents with dementia, examining a wide range of NPS.

Introduction

Dementia encompasses several distinct progressive brain diseases, with Alzheimer dementia (AD) and vascular dementia (VaD) as the most prevalent types. During the course of the disease, patients become more dependent in their activities of daily life, which ultimately can result in institutionalization [10,11]. Because dementia mostly affects the elderly, its prevalence and costs are expected to rise steeply over the coming years [1]; given the limited funds to further expand care for institutionalized residents with dementia, it is urgent to develop best practices.

In addition to cognitive decline, patients with dementia show behavioral and psychological symptoms, also referred to as neuropsychiatric symptoms (NPS). NPS occur in up to half of community-dwelling patients with dementia [8,9,66], which can result into earlier institutionalization [10]. The prevalence of NPS in nursing homes residents with dementia is even higher at up to 80% [12,13]. In nursing homes, NPS include five main clusters: agitation, psychosis, mood disorders, psychomotor agitation and apathy [15]. These can result in increased demands on staff resources, increased job-related stress, burnout, and staff turnover. Furthermore, NPS can result in the application of physical restraints [14] and psychotropic drugs (PDs) use [29], which can lead to a decrease in the caregiver's and patient's quality of life [67]. PDs use, of which antipsychotics (APs) are the most frequently prescribed [27,68], has come under intense scrutiny. Recent evidence has indicated that APs have a limited benefit in long-term therapy and can cause severe side effects such as stroke and increased mortality [30,69].

Although several studies have looked at the course of NPS in community-dwelling patients with dementia [9,24-26], most studies, however, have institutionalization as a primary endpoint. A detailed knowledge of the course of a wide range of NPS can help clinicians to better understand the clinical course of individual NPS, to make better treatment decisions of NPS including the prudent use of psychotropic drugs, to provide continuous support to patients and caregivers and to inform patients and caregivers on prognosis. Therefore, this study specifically addresses the period after institutionalization. The objective of this study was to systematically review the literature on the course of a wide range of NPS in residents with dementia in long-term care institutions.

Methods

Search Strategy

A computerized search was carried out in MEDLINE (1966- September 2008), PsychInfo (1806- September 2008), EMBASE (1980- September 2008), and Cinahl (1982- September 2008). An extensive list of index labels (MESH-terms) and free text words, indicating a wide range of NPS, including agitation and other behavioural problems, depression, psychosis, anxiety and apathy, was searched to retrieve relevant papers (see Table 1). Additionally, the reference list of selected articles was screened to identify other relevant articles.

Table 1 Overview of computerized search strategy: terms used.

Index labels:
"Dementia"[MeSH] OR "Dementia, Vascular"[MeSH] OR "Dementia, Multi-Infarct"[MeSH] OR "Alzheimer Disease"[MeSH] OR "Lewy Body Disease"[MeSH] OR "Pick Disease of the Brain"[MeSH]
AND
"Activities of Daily Living"[MeSH] OR "Affect"[MeSH] OR "Aggression"[MeSH] OR "Anxiety"[MeSH] OR "Appetite"[MeSH] OR "Behavioral Symptoms"[MeSH] OR "Chronic Disease"[MeSH] OR "Cognition Disorders"[MeSH] OR "Comorbidity"[MeSH] OR "Communication"[MeSH] OR "Communication Disorders"[MeSH] OR "Delusions"[MeSH] OR "Depressive Disorder"[MeSH] OR "Eating Disorders"[MeSH] OR "Environment"[MeSH] OR "Euphoria"[MeSH] OR "Geriatric Assessment"[MeSH] OR "Geriatric Psychiatry"[MeSH] OR "Hallucinations"[MeSH] OR "Hearing"[MeSH] OR "Irritable Mood"[MeSH] OR "Language Disorders"[MeSH] OR "Marital Status"[MeSH] OR "Mental Disorders"[MeSH] OR "Mood Disorders"[MeSH] OR "Natural History"[MeSH] OR "Neurobehavioral Manifestations"[MeSH] OR "Neuropsychological Tests"[MeSH] OR "Neuropsychology"[MeSH] OR "Pain"[MeSH] OR "Personality"[MeSH] OR "Psychomotor Agitation"[MeSH] OR "Psychotic Disorders"[MeSH] OR "Psychiatric Status Rating Scales"[MeSH] OR "Quality of Life"[MeSH] OR "Race Relations"[MeSH] OR "Risk Factors"[MeSH] OR "Severity of Illness Index"[MeSH] OR "Sexual Behavior"[MeSH] OR "Social Behavior Disorders"[MeSH] OR "Sleep Disorders"[MeSH] OR "Vision"[MeSH]
AND
"Long-Term Care"[MeSH] OR "Nursing Homes"[MeSH] OR "Progressive Patient Care"[MeSH] OR "Skilled Nursing Facilities"[MeSH]
AND
"Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Longitudinal Studies"[MeSH] OR "Prospective Studies"[MeSH]
Free text words:
Alzheim* OR dement*
AND
aberrant motor behav* OR affect* sympt* OR aggression OR agitation OR anxiety OR apathy OR behav* sympt* OR biting OR cognitive sympt* OR complaining OR crying OR cursing OR delirium OR delusions OR demanding OR depress* OR disinhibition OR disrupt* OR eating disturban* OR emotional disturban* OR environment OR euphoria OR gender OR hallucinations OR hitting OR hoarding OR irritability OR kicking OR misidentification OR negativism OR neuropsychia* OR noncognitive OR non-cognitive OR pacing OR pain OR premorbid personality OR psycho geriatric OR psychopatholog* OR psychiatric sympt* OR psychosis OR psychotic behav* OR psychoger* sympt* OR psychol* sympt* OR quality of life OR repetition OR repetitive behav* OR screaming OR sleep disturban* OR restlessness OR sexual disinhibition OR sundowning OR troublesome OR uncooperative behave* OR verbal outburst OR vocal agitation OR violence OR wandering OR yelling
AND
alzheimer special care unit OR dementia special care OR chronic care OR long term care facilit* OR nursing home OR skilled nursing facilit* OR special care unit
AND
cohort OR follow-up OR longitudinal OR prospective

Inclusion criteria

Two reviewers (RBW & IJJ) independently screened all abstracts retrieved. Both reviewers used the following five criteria for inclusion:

(a) English or German-language

(b) Established diagnosis of dementia, by chart diagnosis or according to international accepted criteria (e.g. DSM-IV [70], NINCDS-ADRDA [47], NINCDS-AIREN [46]);

(c) residents had to be institutionalized in a (skilled) nursing home, a long-term care facility, a progressive patient care facility, dementia special care -, chronic care -, or (Alzheimer) special care unit;

(d) NPS had to be repeatedly measured in at least two consecutive measurements, and

(e) Papers had to have included at least 25 patients.

The two reviewers compared the initial lists of selected abstracts in order to reach a consensus. In cases of doubt all full text articles were retrieved, and a final list of selected papers was made after a consensus meeting. Also, the fully blinded-placebo groups of medication intervention studies conducted among institutionalized residents with dementia were also included but not the intervention groups. The follow-up of NPS in the placebo groups were believed to reflect the natural longitudinal course of NPS.

Exclusion criteria were: outpatients or community dwelling patients and cross-sectional studies looking at NPS.

Quality Assessment

The reviewers independently assessed the methodological quality of the selection of papers using two sets of criteria. The STROBE-statement [71] provides an extensive checklist on reporting observational studies and provides criteria for judging methodological quality. Although the STROBE-list has been designed to strengthen the reporting of observational studies, not all items applied to assess the quality of articles reporting the longitudinal course of NPS discussed in this review. Also, we incorporated another set of criteria that included the type of longitudinal design, length of the time lags between measurements, quality of the measures, statistical analysis, and non-responder analysis. [72,73].

Quality was assessed using both sets of criteria to ensure validity and generalizability for the papers ultimately selected for this review:

Study population:

-Homogeneity of study population and setting
Assessment instruments:
-Confirmation of dementia diagnosis, and description of dementia stage
-reliability of instruments used
Longitudinal design:
-Length of interval and duration of follow-up.
Statistical analysis:
-Non-response analysis at baseline and through measurements.

Data extraction

We grouped NPS into clinically meaningful clusters, i.e., agitation consisting of aggression, disinhibition, irritability, aberrant motor behavior, psychosis consisting of hallucinations and delusions, and mood disorders including depression, anxiety, sleep disorders, apathy, affect, anger, sadness, and euphoria.

From each selected paper, we extracted the following frequency parameters: baseline and follow-up prevalences, persistence, and cumulative incidences of NPS. The point prevalence was defined as the proportion of residents with NPS at any assessment. The cumulative prevalence was defined as the proportion of residents exhibited NPS on at least one assessment. The incidence was calculated as the proportion of residents who showed an NPS at one assessment but not on the preceding assessment. The cumulative incidence was calculated as the proportion of residents with no NPS at baseline who newly developed NPS in the follow-up assessments. An NPS was considered persistent if it was present on at least two subsequent assessments, and persistence was calculated as the proportion of residents who showed NPS at one assessment and again at the following assessment. Resolution was calculated as the proportion of residents who showed an NPS at one assessment but not at the following assessment.

Because some frequency parameters were missing from the reviewed studies, and we wanted to enhance the comparability of the studies' results as much as possible, we calculated the missing relevant parameters from the frequency parameters available or transformed some percentages into subgroup percentages instead of group percentages. In the majority of studies, however, frequency parameters could not be calculated.

Results

The search strategy initially resulted in 1982 abstracts including duplicates. After two consensus meetings, 18 papers met the inclusion criteria (Table 2).

Table 2 Residents characteristics and study design of 18 studies investigating the course of NPS in chronic care institutions

Author Year	Study design Aim	Number of patients In/exclusion Multi Centre	Patients characteristics	Diagnosis stage	Criteria	residence
Ballard *et al*, 2001	1-year follow-up P In of Agi Dep Psy	136 (208 started and 136 had two measurements) 6 centres	Age:83(7) Fe:77% MMSE9(0-21)	AGECAT CDR	AGECAT≥3 CDR≥1	3SC(29%) 3NH(71%)
Brodaty *et al*, 2003	RCT DB MC AGG AGI PSY NH-DP	114 completed trial I: DD+AB: E: medical or neurological conditions other than dementia that diminish cognitive function, other types of dementia, major depression and other criteria/14	Age:82.7(.64) Fe72.4% FAST:10.0(range:4-16) MMSE5.78(.46)	AD 59.6% VD 28.2% MD 12.2%	DSM-IV	NH
Burton, *et al*, 1995	LCS change in DB NHR treated Neu+ v. Neu-	201: 79 participants received neuroleptics during the year 122 did not 8 centres	Age:65<5.5% 65-74:10.0% 75-84:47.2% >85 36.8% Fe:84% MMSE17.9 12.2	DC+34.3% DC- 37.8% PD+10.4% PD-17.4%	MPSE DSM-III	NH/SNF
Chappell and Reid, 2000	SCU v. n-SCU comparison	323 patients MSD 51% SCU 49%IU I: RWD>65yrs, unlikely to move or die <12mths/77centres	Age:81.57(6.60) Fe:67%	AD/VD MSD	MR	ICF LTC
Frisoni *et al*, 1998	CCS BP in integrated model of care v traditional NH model	66 I:MMSE≤16; CDR>2 and <4 NPItotal≥24 or NPIsubscale=12 E: MMSE>22 extended CDR>4 long time between admission and communication, incomplete data	Age:81Fe:71%-80% MMSE:7(5:0-16) 8(5:0-16)	AD 37%-371% VD 10%-29% MD 19%-14% (SCU-TNH)	McKahn Roman McKeith	31SCC 35NH
Lawton *et al*, 1998	stimulation-retreat model	48control I: residents who were treated for 12 months and resided on unit for ≥1-month E: transfer of hospitalization >2weeks during project	GDS↓*** PSMS↓*** No figures on age gender	MDRS GDS		SCU NH
Payne *et al*, 2002	Dep In P LTCF in first year after admission	201 81 had past Dep 1center	Age79.7 Fe71.6%	AD59,7% VD12,4% MD7,5% other diagnosis20,4%	NINCDS-ADRDA NINDS-AIREN	LTCF
Reimer *et al*, 2004	compare QoL in RWD MSD over 1-year between TIF SCF	185: 62 SCF-group 123 TIF-group 28center	Age81.7(7.5) Fe73.5% GDS6.0(5-7)	GDS≥5		LTC
Rovner *et al*, 1996	RCT care program BD NHR v. usual NH care	39 controls I: DP BP PDRS≥2B ≥2/wk 1center	Age81.2(7.2) Fe67% MMSE9.0(6.1)	PDD MID	DSM-III-R	community ICF NH
Schultz *et al*, 2002	L psy symptoms + cognitive impairment on daily living skills	28 participated I: >65 LTR E: chronic schizophrenia bipolar disorder MR/3center	Age87,8(6.8[69-101]) CDR:1.2 1.7 MDRS:85.4 64.9	Mostly AD; some VD or LBD CDR MDRS	MMSE<26 CDR≥0,5	rural SNF
Selbaek *et al*, 2008	natural course of NPS + concomitant use PM NH PWD	633 completed study out of 933; I:≥14days/26	Age:84.5(7.5) 84.9(7.8) ♀♀:73.6% 75.7% CDR2+3:78.3%	CDR	MR	NH
Sival, 2000	PCS influence introduction behaviour rating scale In AGG psychogeriatric NH	64 patients were analyzed out of 75 I:>65years irreversible dementia and in need of support in daily activities E: patients who died or transferred during study/1center	Age:80.2(7.8) Fe:72%	D=54 D+Dep=1 AS=7 MR=1 schizophrenia=1	DSM-III-R	NH 2-wards
Sloane *et al*, 2005	LCS: health care functional outcome /health care utilization PWD RC v. ALF	243NH residents E: rehabilitation 166 RC/AL+ 40NH	Age84.9(7.5) Fe76.2% 15.3% mean length of stay 896.0(866.2)days mild:50.7% MSD:49.3%	DP: Az, senile dementia, organic brain syndrome VD Pick's disease	MR MDS-COGS≥2	RC/AL NH
Tariot *et al*, 2001	RCT DB PC donezil AD NH	78controls completed trail 105ADI:MMSE5-26 + NPI-F≥3E: neurological disease responsible for D major heart/lungdisease/CVA/27NH	Age85.9(65-102) Fe82% MMSE14.4(5.8;5-26)	CDR	NINCDS-ADRDA	
Testad *et al*, 2005	SB-RCT:BD+ use of restraints in DP in NH	87analyzed 96RWD 4NH	Fe72% CDR2.2(.9)	CDR		NH

Wagner *et al*, 1995	Investigate nature and change BP among residents in SCU's	289 patients who were available for at least three follow-up behavioural observations and who completely and accurately identified data 41 SCU of NH	Age:80(55-96) Fe:73% MMSE8.1(6.1)	D esp. AD	MR	SCU
Wancata *et al*, 2003	Frequency of NCDS in NH	86 residents completed T1 and T2; I:≥60years E: secondary psychiatric disorder were excluded from analysis: 150 residents were analyzed/10	Age:>80:69.9% Fe78.3%	Clinical severity (5-point scale)≥ 2	DSM-III-R	NH
Wettstein *et al*, 1997	Prospective study: clinical course B in DP pathologically verified	AD36 PD4 Course shown for patients who lived more than two-years and diagnosis confirmed with pa: I: pathology available, no floor effects on MMSE of ceiling effects on CDR E: known brain infarcts Hachinsky≥6	Fe:81% MMSE6.5(9.3) CDR:AD12.7(5.8) 1.6(4.5) 2.8(5.0)PD9.0(7.1) 1.0(3.9) 1.1(5.8)	AD36 PD4 CDR	DSM-IIIR + pathology	Hospital
Author Year	**Study design Aim**	**Number of patients In/exclusion Multi Centre**	**Patients characteristics**	**Diagnosis stage**	**Criteria**	**residence**

Study design/Aim: AB=aggressive behaviour, AD=Alzheimer dementia, AGG=aggression, AGI=agitation, ALF=assisted living facility, B=behaviour, BP=behavioral problems, CCS=case-control study, DB=disruptive behaviour, DB=double blind, D=dementia, DC-=dementia without complication, DC+=dementia with complication, Del=delirium, Dep=depression, Delu=delusions, DP=dementia patients, E=exclusion, Hal=hallucination, In=incidence, I=inclusion, L=longitudinal, LCS=longitudinal cohort study, LTCF=long term care facility, MC=multicentre, MSD=moderate to severe dementia, NCDS=non-cognitive dementia symptoms, Neu+=received neuroleptics, Neu-=received no neuroleptics, NH=nursing home, NHR=nursing home residents, NPS=neuropsychiatric symptoms, P=prevalence, PCS=prospective cohort study, PD+=psychiatric disorder, PD-=no psychiatric disorder, PM=psychotropic medications, Psy=psychosis, PWD=patient with dementia, QoL=quality of life, RC=residential care, RCT=randomized clinical trail, RWD=residents with dementia, SB=single-blind, SCF=special care facility, SCU=special care unit, TIF=traditional institutional facility.
Number of patients In/exclusion MC: CMAI=Cohen-Mansfield Agitation Inventory, CSDD=Cornell scale depression in dementia, DD=dementia diagnosis, E=exclusion, MMSE=mini mental state examination, NPI=neuropsychiatric inventory, PDRS= psychogeriatric dependency rating scale.
Patients characteristics: B=baseline, **B-ADL**=Barthel-ADL, **CDR**=clinical dementia rating, **F**=follow-up, **FAST**=functional assessment staging, **Fe**=female, **MDRS**=Mattis dementia rating scale, **PSMS**=physical self-maintaining scale.
Diagnosis/stage: AGECAT=computer based diagnostic system formulation 8 diagnostic clusters, AS=amnesic syndrome, CDR=clinical dementia rating, DD=dementia diagnosis, DSM=diagnostic statistical manual, GDS=global deterioration scale, LBD= Lewy Body disease, LTR=long term resident, MD=mixed dementia, MID=multi-infarct dementia, MR=mental retardation, MSD=moderate or severe dementia, PD=Parkinson dementia, PDD=primary degenerative dementia, MDRS=Mattis dementia rating scale, MR=medical record, VD=vascular dementia.
Criteria: DSM= diagnostic and statistical manual of mental disorders, MPSE=modified present state examination, MR=medical record, NINCDS-ADRDA=internationally accepted criteria for AD, NINDS-AIREN= internationally accepted criteria for VD.
Residence: AL=assisted living, **ALF**=assisted living facilities, **CF**=care facilities, **ICF**=intermediate care facilities, **IU**=integrated unit, **LTCI**=long term care institutions, **NH**=nursing home, **RC**=residential care, **SC**=social care, **SCF**=specialized care facilities, **SCU**=special care unit, **SNF**=skilled nursing facilities, **TCI**=traditional care institution.
*=p<.05**=p<.01***=p<.001****=p<.0001

Resident population

The residents were predominately female (ranging from 67 to 82%) and were aged 75 years and older. The number of included residents ranged from 26 to 323.

Assessment instruments

Twelve different assessment instruments were used to follow the course of NPS. Seven of these were used in more than one study: Cohen-Mansfield Agitation Inventory (CMAI)[74-80], Neuropsychiatric Inventory (NPI)[76,81-83], Cornell Scale of Depression in Dementia (CSDD)[76,80,84], Philadelphia Geriatric Centre Apparent Affect Rating Scale (PGCAARS), Behavioural Pathology in AD (BEHAVE-AD), Psychogeriatric Dependency Rating Scale (PGDRS), and Multidimensional Observation Scale for Elderly Subjects (MOSES). Although the CMAI was used in six studies, the comparison between these studies was difficult because different versions were used. Three different NPI-versions were used. An additional five different assessment instruments were used once in the remaining articles.

Longitudinal design

The follow-up period ranged from three months to one year. The number of assessments ranged from two to five. Several studies did not statistically analyze the same group of residents over time. Several studies showed only graphics instead of tables. Group ratings were reported in some articles instead of individual ratings, and aggregated symptom scores were described in several studies instead of specific symptoms.

The course of NPS

Agitation.

Ballard *et al.* [83] analyzed three types of agitation using the NPI-items aggression, aberrant motor behaviour, and overall agitation (either type of agitation). After one-year of follow-up, both types of agitation changed: prevalence of aggression decreased from 40% to 29%, and of aberrant motor behaviour from 33% to 24%. For individual patients, resolution was comparable for aggression (59%) and for aberrant motor behaviour (57%), as was persistence (41% v 43%), but in others newly development was different (22% vs. 14%), indicating that aggression showed a more intermittent course than aberrant motor behaviour. The cumulative prevalence of aggression was higher than aberrant motor behaviour (53% v 42%).

Burton *et al.* [85] studied nine types of agitation using the PGDRS including wandering, various types of verbal agitation, and various types of physically aggressive behaviour. Cumulative incidences ranged from 5.1% to 20% and cumulative prevalences ranged from 22% to 31.9%, pointing at an intermittent course of the different types of agitation. Overall, persistence was more stable ranging from 3.9% to 7%.

Selbaek *et al.* [81] studied agitation/aggression and related symptoms. Prevalences[a] over a one-year period showed variable courses. In individual patients, aberrant motor behaviour (20.8%-19.4%) remained stable as did aggression (27.4%-28.0%), disinhibition (22.2%-23.2%), and irritability (30.0%-33.4%).

[a] Percentages denote the prevalences at subsequent assessments

Wancata *et al*. [86] studied six aggressive-psychotic symptoms using the Clinical Interview Schedule (CIS) over a six-month observational period. The overall prevalences showed increases (17.5%-22.1%), although some patients showed low persistence (12.8%).

Psychosis.

Ballard *et al*. [83] studied the course of psychosis with the NPI-items of delusions and hallucinations using frequency parameters. The overall prevalence of delusions remained stable (15%-15%). In individual subjects, delusions persisted (43%) and in others it resolved fully (57%) or newly developed (10%). On the other hand, prevalence in hallucinations increased from 3% to 7%. In individual patients, hallucinations resolved (75%), in some it remained stable (25%) and others showed new onset (6%). Cumulative prevalences of 23% and 9% were found for delusions and hallucinations respectively.

Selbaek *et al*. [81] also studied psychosis with the NPI-items of delusions and hallucinations using frequency parameters. Prevalence for both delusions and hallucinations remained stable: 24.4%-23.5% for delusions, 12.6%-12.1% for hallucinations. In individual patients, resolution for delusions and hallucinations were comparable (55.9% respectively 57.9%), in other patients persistence was also comparable (44.1% and 42.1%), but in others new onset delusions (16.9%) developed more frequent than hallucinations (7.8%).

Mood disorders.

Ballard *et al*. [83] studied the course of depression using the NPI. The overall prevalence of depression decreased slightly (18%-15%), but in individual patients depression resolved fully (67%), in some it persisted (32%), whereas in others it newly developed (11%).

Selbaek *et al*. [81] studied the course of depression, anxiety, apathy and euphoria with the NPI. Overall, prevalence of depression and anxiety remained almost stable over time (20.8%-19.1% and 22.0%-19.2% respectively) as did euphoria (7.8%-5.3%). Apathy, on the other hand, increased (25.6%-28.2%) in individual patients, apathy persisted (52.2%), in some it resolved (47.8%), whereas in others newly onset was considerable (20.0%).

Payne *et al*. [84] studied depression using the Cornell Scale of Depression in Dementia over a one-year period with three measurements. They found in individual patients high resolution (85%), in some persistence (15%) and in others newly developed (3.7%).

Wancata *et al*. [86] studied five different depressive symptoms using the Clinical Interview Schedule. Overall symptom prevalence increased (22.1%-24.5%) and in individual patients, high persistence was found (63%).

Table 3 Course of NPS in residents with dementia in chronic care institutions (percentages are prevalences in subgroups).

Follow-up	Measures	Author Year	Assessment instruments	Informant	Agitation[a]	Psychosis[a]	Mood disorders[a]	Non-response analysis
		Wettstein *et al*, 1997	SVS	Doctor Nursing staff	↓≈			Mentioned:- Analyzed:-
3-months		Frisoni *et al*, 1998	NPI(9) CMAI CSDD		CMAI↓ NPI: agi↓*eup≈dis≈irr≈ABM↓	NPI:Hal↓***/Del↓	CSDD↓* NPI:anx↓sle↓**	Mentioned:- Analyzed:-
4-months	other	Wagner *et al*, 1995	MBPC-NH(41-BP)	RN LVN	Most behaviour≈	Most behaviour≈	Most behaviour≈	Mentioned:- Analyzed:-
	five	Brodaty *et al*, 2003	CMAI(29) BEHAVE-AD	Nurse	CMAI score TA↓ PA↓ VA↓ PNA↓ VNA↓	Overall↓ of psychotic symptoms		Mentioned:+ Analyzed:-
6-months	two	Rovner *et al*, 1996	PGDRS CMAI PS	RP RN	P BD↓			Mentioned:+ Analyzed:-
		Tariot *et al*, 2001	NPI-NH(12)		↓ but not significant change over time	↓ but not significant change over time	↓ but not significant change over time	Mentioned:+ Analyzed:-
		Testad *et al*, 2005	BARS		BARSscore≈			Mentioned:+ Analyzed:-
		Wancata *et al*, 2003[c]	CIS(23)	RP interview	Pre17.5→22.1 Res4.7 CP26.7 CI9.3 Per12.8	Del:Pre4.6→7.0 Res2.3 Per2.3 CI4.7 CP9.3 Hal:Pre2.4→1.2 Res1.2 Per1.2 CI0 CP2.4	Pre22.1→24.5 Res37 CP32.6 CI10 Per63	Mentioned:+ Analyzed:-
	four	Sival *et al*, 2000	SDAS(9) BOP	HN NS	frequency of Agg behaviour reported by nursing staff↑***			Mentioned:+ Analyzed:-
one-year	two	Ballard *et al*, 2001[b]	NPI(10 CR>3)	resident key worker	Amb:Pre32%-24% CP42% CI14% Per43% Res57% Agg:Pre40%-29% CP53% CI22% Per41% Res59% Overall:Pre54%-42% CP71% CI35% Per47% Res52.7%	Del:Pre15%→15% CP23% CI10% Per43% Res57% Hal:Pre3%→7% CP9% CI6% Per25% Res75%	Dep:Pre18%→15% CP27% CI 11% Per32% Res67% PerCM 38% Per CNM 18%	Mentioned:+ Analyzed:+
		Burton *et al*, 1995[b]	PGDRS	NA most familiar with the resident	W RES12% CP22% CI3.6% Per6% OBCI20% PR Per7% IS Res10% Per3.9% RtflCP31.9% CI14% Per7% HBS CP22% CI5.1% Per6% VA CP22% IN CI14%			Mentioned:- Analyzed:-
		Chappell and Reid, 2000	CMAI(14) FTQ MAS-R	RP	Agitation↓ ns		Affect↓**	Mentioned:+ Analyzed:+
		Schultz *et al*, 2002	CUSPDAD CDRS	Ra interview	Behavioural↓	DEL↓	DEP↑	Mentioned:- Analyzed:-

		Selbæk *et al*, 2008 [b]	NPI-10 (CR>3)	PC RN Interview	AgiPre27.4-28.0 Res47.1 Per52.9 CI18.6 Dis22.2-23.2 Res50.0 Per50.0 CI15.5 Irr30.0-33.4 Res42.0 Per58.0 CI23.0 Amb20.8-19.4 Res59.2 Per40.8 CI13.8 Significant↓ NPI-items severity scores***	Del:Pre24.4-23.5 Res55.9 Per44.1 CI16.9 Hal:Pre12.6-12.1 Res57.9 Per42.1 CI7.8 Significant↓ NPI-items severity scores***	Dep20.8-19.1 Res58.3 Per41.7 CI13.2 CP28 Anx22.0-19.2 Res55.5 Per44.5 CI12.1 CP31 Apa25.6-28.2 Res47.8 Per52.2 CI20.0 CP40 Eup7.8-5.3 Res71.4 Per28.6 CI3.3 Significant↓ NPI-items severity scores***	Mentioned:+ Analyzed:+
		Sloane *et al*, 2005	CMAI(14) CSDD	interview telephone	CMAI score ↑ both mild and MSD		CSDD/MOSES ↑ both mild and MSD	Mentioned:+ Analyzed:-
	three	Lawton *et al*, 1998	MOSES BRS BEHAVE-AD CMAI(29) ARS MDS PGAARS	CNA AT NP	CMAI PA↑ PNA↑ MOSES Irr↑ MDS PB↓ Behavior Stream PB↑ RB↓ Sociability:CNA↓TRS↓ social B↓ repB↓ MDS Social quality≈ time use≈ Behavior Stream gaze with interest↑	Psy behaviors≈	MOSES Dep↑ MDS Dep≈ AARS pleasure↓ interest↓ anger≈ sadness↓ anxiety↓	Mentioned:+ Analyzed:-
		Payne *et al*, 2002 [c]	CSDD(>12)				P19.9→6.0→4.5 AAR(CP)26.8 I3.7→3.9 Per15→50 Res85→0	Mentioned:+ Analyzed:-
	five	Reimer *et al*, 2004	CMAI(14) PES-AD MOSES PGAARS	RA	no figures shown only graphics: CMAI TS≈		PES↓ AARS-anx↑ AARS-interest≈ MOSES-withdrawn↑	Mentioned:+ Analyzed:-
Follow-up	**Measures**	**Author Year**	**assessment instruments**	**Informant**	**Agitation[a]**	**Psychosis[a]**	**Mood disorders[a]**	**Non response analysis**

Assessment instrument: ARS=activity rating scale, B=baseline, BARS=brief agitation rating scale, BEHAVE-AD=behavioural pathology in AD, BOP=validated Dutch version of the Stockton Geriatric Rating Scale, BRS=behavior rating scale, CIS=Clinical Interview Schedule, CSDD=Cornell scale depression in dementia, CMAI=Cohen-Mansfield Agitation Inventory, CUSPDAD=Columbia University scale psychopathology-AD, FAST=functional assessment staging, FTQ=feeling tone questionnaire, FU=follow-up, GMSS=geriatric mental state schedule, MASR=multi-focus Assessment Scale Revised, MBPC-NH=memory behaviour problems checklist-NH, MDRS=Mattis dementia rating scale, MDS-COGS=minimum data set cognition scale, MMSE=Mini Mental State Examination, MNCAS=modified nursing care assessment scale, MOSES=multidimensional observation scale for elderly subjects, NM=none mentioned, NPI=neuropsychiatric inventory, PES-AD=pleasant event scale-AD, PGCAARS=Philadelphia geriatric centre apparent affect rating scale, PGDRS= Psychogeriatric Dependency Rating Scale, SVS=Socialverhaltensskala.
Informant: AT=activity therapist, CNA=certified nurse aides, LVN=licensed vocational nurse, N=nurse, NP=nurse physician, PC=primary carers, RP=research personnel.
Agitation: Agi=agitation, Agg=aggression, Amb=aberrant motor behaviour, CI=cumulative incidence, CP=cumulative prevalence, DA=demanding attention, Dis=disinhibition, Eup=euphoria, HBS=hitting biting scratching, Irr=irritability, IS=interfering staff: preventing from doing their work, MIN=making intolerable noises, OB=objectionable behaviour, PA=physical aggression, PB=passive behaviour, per=persistence, PNA= physical non-aggression, PR=paces restlessly, RB=repetitive behaviour, Re=recurrence, Res=resolution, RtfI=refusing to follow instructions, TS=total score, VA=verbal aggression, W=wandering.
Psychosis: Delu=delusions Hal=hallucination.
Depression: Anx=anxiety, Apa=apathy, Dep=depression, Sle=sleep.
Predictors: PD=psychotropic drugs.
Medication/restrains: PD=psychotropic drugs.
Loss to follow-up: NCDS=non-cognitive dementia symptoms.
*=p<.05**=p<.01***=p<.001****=p<.0001
[a]: percentages denote prevalences at subsequent assessments
[b]: parameters were calculated out of the frequency parameters shown in the tables
[c]: parameters transformed to subgroup percentages instead of groups percentage

Discussion

This is the first systematic review on the longitudinal course of NPS in residents with dementia in long-term care institutions. Of the 18 included studies in this review, only six had the primary objective to study the course of NPS over time [81,83-87]. Only three of these evaluated a broad range of NPS [81,83,86]. Furthermore, pooling of data was impossible due to the heterogeneity of the resident populations studied and the methods used. However, we extracted frequency parameters whenever possible. We found that aberrant motor behaviour, depression, anxiety, and euphoria showed declines over time, but psychosis remained constant. Apathy increased as did agitation, irritability, and disinhibition. All symptoms showed specific intermittent courses. The high cumulative prevalence of agitation in particular underscores the importance of this symptom for residents in long-term care facilities.

The representation of the course of NPS in the selected articles needs some consideration. Generally, studies dealt with NPS according to the assessment instrument used. This can have a major drawback: symptoms not covered with the assessment instrument will not be assessed and therefore remains unaccounted for; for example, apathy was studied in only one study. The frequency parameters merely take into account the presence or absence of NPS instead of the actual severity. A loss of information is therefore unavoidable, as is encountered with the use of graphics instead of tables. In addition, there could be incomparability or misinterpretation when it is not transparent how parameters were calculated (e.g., cut-off points, percentages of groups or subgroups, observation period). General conclusions regarding the course of NPS can be made more accurately if patients are described clearly in terms of their residential setting, dementia diagnosis, etiological differentiation and dementia stage. Different NPS are represented according to the etiology of diagnoses [17,18] and might follow different courses over time. The objective of examining the course of NPS is to identify significant changes over time. Therefore, it is mandatory that the statistical analyses are carried out on the same group of residents instead of on different groups of residents [85]. In this review, the RCT-placebo groups were included as in these groups, the natural courses of NPS without interventions could be observed. Although this sounds reasonable on the surface, several drawbacks hamper the interpretation from such data. First, in RCTs, the extra attention the participants receive alone can be enough to act as an intervention to affect the natural course of NPS at subsequent measurements (Hawthorne-effect). Second, the administration of assessment scales *per se* is an intervention; therefore, a placebo group is not entirely free from any kinds of interventions [88]. And finally, regression to the mean could occur when a group of residents exhibiting a high frequency of a behavior or severe form of behavior is selected and followed over time [89]. Also noteworthy is the time between admission and inclusion in the study, since admission into a nursing home can be a stressful moment accompanied with NPS. After some adjustment to the new surroundings, a dementia patient might express less NPS. Several studies included residents within 14 days after admission [76,86], or required a minimum stay of 14 days [81], and another study included residents from whom CSDD was administered within one month after admission [84]. One can speculate about how the expression of NPS might have been influenced by this short time interval. Of particular interest and importance in interpreting change scores are the psychometric properties of the assessment instruments such as reliability, validity, and responsiveness to change [90]. The reliability and validity of most assessments instrument have been incompletely assessed, and longitudinal data is not available to assess responsiveness to change [91]. This lack of information might hamper clear and unambiguous interpretations of NPS change scores. And finally, NPS are frequently treated with psychotropic drug (PD). PD use can possibly influence the course or severity of NPS, which makes comparison to with non-PDU group difficult. On the other hand, previous studies question the influence of PD use on the actual course of NPS [81,83].

Results so far indicate that there are different courses over time for individual NPS. The implications for current practice are not obvious, but addressing the high persistence on the one

hand and trying to resolve or prevent the development of NPS on the other hand warrant constant monitoring of current pharmacological interventions.

There is a need to study a larger group of institutionalized residents with dementia looking at a broad spectrum of NPS over longer periods. Moreover, at this moment, studies have only observed NPS over time, but future longitudinal prospective cohort studies looking at the course of NPS should also account for their association with activities of daily living, cognition, PD uses, quality of life, and other clinical and personal characteristics and also identify subgroups. These studies should give detailed insights into the actual course of NPS in residents with dementia, indicate causal relationships between these variables, ensure more efficient therapeutic interventions, and help to enhance daily care given to residents and family members.

Validity of the Severe Impairment Battery Short Version

J de Jonghe R Wetzels A Mulders S Zuidema R Koopmans

Teamleidster psychogeriatrische afdeling:

"..In eerste instantie denk ik dat je al bij een discussiepunt komt over de vraag wat is probleemgedrag? De ene collega zal dit anders interpreteren dan de andere collega. Als er sparake is van probleemgedrag is mijn ervaring dat je eigen handelen en reageren daar een grote invloed op heeft.
Bij dementie is de benaderingen rust al van groot belang, en dus zeker ook bij probleemgedrag. Door diverse jaren ervaring met dementerenden en probleemgedrag merk ik dat ik zelf iets niet gauw als probleemgedrag omschrijf, mede omdat er vaak een oorzaak voor te achterhalen is. Dit is natuurlijk niet altijd goed omdat het voor een ander wel als "probleemgedrag" ervaren wordt. Ik kan/ mag mijn eigen benadering/ houding t.o.v. de cliënt niet altijd projecteren aan andere verzorgende. Ik denk dat je je zelf een aantal vragen moet stellen bij het ontstaan van probleemgedrag: Wat is mijn aandeel hierin geweest? Had ik het kunnen voorkomen? Waar komt dit gedrag vandaan, herkenbaar patroon, iets van vroeger? Wat kunnen doen om dit te voorkomen of het in ieder geval acceptabel te houden? (eventueel m.b.v. specialist ouderengeneeskunde en/ of psycholoog)
Het belangrijkste van alles vind ik dat we met z'n allen niet moeten vergeten dat we te maken hebben met dementerende cliënten, die wij hun gedrag net kwalijk mogen nemen en dat het vaak te verklaren is. Als je kennis hebt van het dementieproces zul je deze gedragingen ook beter kunnen begrijpen en accepteren…"

Abstract

Background. Efficient neuropsychological tests are needed to measure cognitive impairment in moderate to severe dementia.

Objective. To examine construct validity of the Severe Impairment Battery Short version (SIB-S) in nursing home patients with moderate to severe dementia, and to examine potential floor effects for the SIB-S.

Methods. Cross-sectional comparison of cognitive measures, dementia severity and functional dependency.

Results. A total of 290 patients were included 264 of whom had complete SIB-S protocols. Internal consistency of the SIB-S was very high (Cronbach's alpha=.97). Principle components analysis produced 3 factors, the first of which explained more than 50% of common score variance. Semantic memory items loaded highly on the first factor. Total SIB-S scores were associated with cognitive impairment (SIB-S - MMSE rho = .91, p<.001), and with functional dependency (SIB-S - ADL scale rho = -.61, P<.001). SIB-S total scores differentiated between dementia stages as measured with the Global Deterioration Scale (F=164.6 df:3,260, P<.001). Comparisons of SIB-S total score variance across patients with moderate to severe dementia and patients with below or above average Mini Mental State Exam scores, indicate absence of large floor effects.

Conclusion. In this first study examining an independently administered SIB-S, the scale proved to be a homogeneous and valid measure of cognitive impairment. The SIB short version can be used to assess moderately to severely demented patients, who may find it difficult to complete traditional, lengthier neuropsychological tests.

The Severe Impairment Battery (SIB) is a cognitive test developed specifically for assessment of patients who are cognitively too much impaired to be able to complete standard neuropsychological tests [92]. The SIB has become an important outcome measure in clinical trials involving patients with severe dementia [93-97]. It takes 30 minutes to complete the SIB and for some severely impaired patients, this time is at the upper end of their attention span. Recently, a short version of the SIB (SIB-S) was developed that takes 10-15 minutes to administer and it can be completed by more profoundly impaired patients [62]. Though content validity of the SIB-S was established in the development cohort, validity has not been examined in an independent patient sample.

Several studies from different countries have shown that the 51 items SIB scale is a reliable and valid measure of cognitive functioning across patient groups with varying degrees of dementia severity [62,98-104]. Results from three different studies show that SIB scale items are based on 4-8 underlying factors with a strong first factor explaining a large part of common score variance [62,101,105]. Patients in the development cohort of the SIB-S were assessed with the 51 item SIB. In the final SIB-S version, 26/51 original SIB scale items were retained [62]. SIB-S total scores were strongly associated with SIB and MMSE total-scores. A recent Korean study, conducting a secondary analysis of the 51 items SIB showed that the SIB-S was a reliable and valid measure for evaluating patients with severe dementia [106]. However, none of these studies examined psychometric properties of an independently administered SIB-S.
Ideally, a scale's psychometric properties are retained in the short version derived from it in a way that both measure the same aspects of behavior or cognition. Factor structure invariance across patient samples is one way of examining whether two scales measure the same cognitive abilities, thereby establishing construct validity.

This study examined cognitive functioning as measured with the SIB-S in nursing home patients with moderate to severe dementia. To our knowledge, it is the first time construct validity was examined in an independent patient sample. We hypothesized that the SIB-S factor structure would be invariant to the original SIB factor structure. Acknowledging, that every cognitive test may show floor effects along the continuum of dementia, our second hypothesis was that floor effects would be less evident for the SIB-S as compared to another well-known cognitive measure.

Methods

Study Design

This was a cross-sectional, observational study. Cognitive impairment, dementia severity and functional dependence were assessed in nursing home patients, allowing for a comparison between measures. The study is part of the WAAL BEhavior in Dementia (WAALBED)- part II study, a longitudinal study on the course of neuropsychiatric symptoms in nursing home patients with dementia. Approval of the regional research ethics committee was obtained. Relatives or legal guardians of all patients gave fully informed written consent.

Participants

Nine nursing homes in the Netherlands participated in the study. Resident nursing home physicians identified potentially eligible patients by systematically screening all inpatients from 14 dementia special care units. Patients were considered for inclusion provided they had dementia (defined with international criteria and Dutch consensus guidelines[17]) and were institutionalized for at least 4 weeks. Patients were ineligible if a life-threatening disease was

present. The second author (RW) independently checked eligibility against patients' clinical notes.

MEASUREMENTS AND PROCEDURES

Consensus meetings were organized to instruct and to ensure that standardized procedures were applied for all measures and assessments. Resident nursing home physicians or psychologists assessed cognitive impairment using the SIB-S and Mini Mental State Examination (MMSE) [63], and rated severity of dementia as defined by Global Deterioration Scale (GDS) criteria [61]. The MMSE is a well-known screening test for cognitive impairment and scores range 0-30. The Global Deterioration Scale (GDS) consists of descriptions of seven major, clinically distinguishable dementia severity stages, ranging from 'no cognitive decline' to 'very severe'. Licensed vocational nurses, who were assigned to individual patients and who were specifically instructed to observe patient behavior a few days prior to assessment, rated Activities of Daily Living (ADL) as defined by Inter Resident Assessment Instrument – Long Term Care Facilities section G (2005, version 07). The InterRAI LTCF-ADL is an observational scale for ADL-dependence, which measures resident self-involvement in the personal activities of daily life. It includes 4 of the ADL items of the InterRAI, each with 6 response categories and is scored based on a decision tree with 8 scale categories, ranging from 0 (independent) to 6 (totally dependent) and 8 (activity not seen). When first introduced, its reported psychometric properties were good to excellent (inter-rater reliability) and an internal consistency (Cronbach's alpha) of .90. [64] Validity and reliability of the ADL scale are established in a study including Dutch nursing home patients with dementia.[21]

The SIB has been used as a cognitive outcome measure in many clinical trials involving patients with severe dementia. SIB-S item selection is based on factor analysis of original SIB scale items and subsequent consensus discussions between authors of the SIB [62]. In the final version of the SIB-S 26/51 original SIB scale items were retained. All scale items except two are coded 0,1,2. The other two are coded 0,1 and the maximum possible score on the SIB-S is 50. The SIB is a highly reliable and valid cognitive test [107]. Two authors (AM and JJ) performed modifications on a provisional SIB Dutch version to suit the aims of this study. Subsequently, the SIB-S Dutch version was translated back independently. The primary author of the original SIB-S approved the SIB-S Dutch version after adjusting a few minor details.

ASSESSMENT

A total of 76% of patients were assessed with the SIB-S and MMSE on the same day, 90.4% had both tests within the same week, and for the remaining patients cognitive tests were administered 8-47 days apart. All data were collected on standardized patient record forms.

STATISTICAL ANALYSIS

Statistical calculations were performed using SPSS for Windows, version 11 (SPSS, Inc. Chicago, IL).

Complete test protocols were those with no more that 10% missing values per cognitive test. Whenever there were few missing values modal test item scores were used as substitutes. The internal consistency reliability of the SIB-S was examined using Cronbach's alpha. Calculation of the sample size was based on the assumption that 10:1 observations-variables are required in order for the correlation matrix to be sufficiently stable to be used in factor analysis: in case of a 26 items test, 260 patients.

Extracted factors with eigen values ≥ 1.0 were subsequently rotated orthogonally according to simple structure criterion and with the aim of clear factor interpretation. Item factor correlations determined assignment of the item to a factor, with a required minimum factor loading of .40, and provided the item-factor correlation was at least .10 higher than that with another factor. Construct validity was further evaluated by retaining SIB-S factor scores and using them as dependent variables in stepwise regression analysis with MMSE items as predictors. As some of the measures are ordinal scales and because scale scores were not normally distributed in this study, associations between SIB-S, MMSE and ADL total scales were examined using nonparametric Spearman rank correlations.

ONEWAY analysis of variance with Scheffe post hoc comparisons was used to examine group differences using cognitive test scores as dependent variables and dementia severity as independent variable. Diagnostic accuracy was examined by calculating the area under the curve (AUC) for SIB-S and MMSE total scores comparing GDS 4 and GDS 5, GDS 5 vs. 6 and GDS 6 vs. 7.

In the original SIB-S study, floor effects were examined by comparing mean SIB-S scores and variances in patients with MMSE scores below the 50^{th} percentile MMSE total score as compared to those with scores above the 50^{th} percentile.[7] We repeated the analysis by calculating the t-test statistic for comparisons of mean scores and we used Levene's homogeneity of variances test. Additionally, potential floor effects were examined by comparing mean SIB-S and MMSE scores and the homogeneity of score variances across patient groups in GDS 4-7 (t-test, Levene's test), and by examining proportions of patients who failed to take the test or who had a total test score of 0 using Chi^2 statistic.

Two-tailed *P* values of <0.05 were considered to indicate statistical significance.

Results

A total of 290 eligible patients were included in the study. Twenty-six patients had more than 10% missing data because they refused or were just too ill to take the SIB-S, or because of other reasons. Of the remaining 264 patients 36 had a score of 0 on the SIB-S. A total of 20/290 patients had missing data for the MMSE and 75/270 had a score of 0 on the MMSE. So, SIB-S total scores did not differentiate between 62/290 patients (21.4%) who were intended to be tested, as compared to 95/290 (32.8%) for the MMSE: a reduction of 34.7% (Chi-square 9.5, df:1, *P*=002).

Patients with missing values for the SIB-S total score did not differ from other patients on any of the demographic and clinical variables, except for vision impairment (*P*=.004), with more patients without vision impairment completing the SIB-S than those with mild to severe vision impairment.

As this is a study of the SIB-S and for reasons of simplicity, the data of 264 patients with complete SIB-S protocols are presented.

Table 1. Demographic and clinical characteristics nursing home patients n=264.

Age	83.5 (SD 6.9, range 59-102)
Male / female	61 / 203
Marital status %	
- married	25.0
- widow	51.5
- divorced	3.8
- unmarried	8.0
- missing values	11.7
Nationality %	
-Dutch	82.2
-other	3.0
-missing values	14.8
Education %	
- primary	26.9
- low vocational secondary	18.9
- mid vocational secondary	8.3
- high vocational secondary	2.3
- university	.8
- missing values	42.8
Length of stay nursing home	2.9 years (SD 2.3, range .1-14.3)
Length of stay nursing home unit	2.6 years (SD 2.3, range .04-14.3)
ADL	39.7 (SD 20.3, range 0-68)
Communication %	
- (almost) never makes him/herself clear	33.0
- (almost) never understands others	34.5
- severe hearing impairment	6.9
- severe vision impairment	7.8
GDS stage %	
- 4	6.1
- 5	23.5
- 6	42.4
- 7	28.0

SD: Standard Deviation.

Demographic and clinical characteristics are presented in table 1. The study sample is typical of Dutch psychogeriatric nursing home patients, with a preponderance of older residents, many of whom female, with low educational attainment, and with advanced dementia.

Table 2. Principal Component Analysis of SIB-S Items in Nursing Home Patients with Dementia.

	Items*	Factor I	Factor II	Factor III
1.	Shake hands	.81		
17.	Hat or cup	.80	*.31*	
19.	Blue block	.77	*.33*	
23.	Red block	.77	*.36*	
15.	Cup again	.76	*.35*	*.34*
13.	Picture cup	.75	*.30*	
4.	Your name?	.71	*.35*	
18.	Spoon	.70	*.43*	
11.	Digit span	.69	*.38*	*.41*
26.	Say patients name	.68	*.35*	
2.	Come to	.68	*.36*	
3.	My name	.60	*.38*	*.42*
8.	Cup	.55	*.30*	*.46*
5.	Write name	*.34*	.81	
24.	Draw square	*.33*	.80	
6.	Copy name opt	*.41*	.79	
9.	Read card	*.42*	.64	
10.	Other hand	*.53*	.61	
20.	Your blue block	*.57*	.59	
21.	Give back block	*.45*	.57	
22.	Different block	*.53*	.57	*.30*
25.	Remember cup		.52	*.37*
12.	Remember my name			.74
7.	This city?		*.34*	.56
14.	Use cup		*.48*	.53
16.	Use cup again	*.39*	*.47*	.48
	% explained variance	58.3	4.9	4.2

*: abbreviated item names.
Bartlett's Test of Sphericity (Chi-Square=6175.7. df=325. *P*=.001) and Kaiser-Meyer-Olkin measure of sampling adequacy (.96) indicate SIB-S data matrix is very well suited for factor analysis. Item loadings .30 or higher on more than one factor in italics.

CONSTRUCT VALIDITY

Average SIB-S total score was 25.9 (SD 17.3, range 0-50) and average MMSE total score was 7.1 (SD 6.6, range 0-25). Cronbach's alpha coefficient for the SIB-S was very high (α = .97). SIB-S item-rest correlations all were higher than .55, except for item 12 (Remembering investigator's name, item-rest correlation: .30).

Three principal components that explained 67.4% of score variance (table 2) were found. Scale items that reflect understanding gestures and verbal instructions, and items reflecting

recognizing and naming objects loaded highly on the first factor, which was called 'Aphasia-Agnosia'. The second factor consists of items reflecting writing and copy drawing and it was called 'Apraxia'. The third factor consists of items reflecting memory for newly learned material and it was called 'Episodic memory'. Notably, the first factor explains more than half of common variance, indicating the SIB-S is a homogeneous measure.

In regression analysis of SIB-S factor scores MMSE items reflecting verbal ability shared unique variance with the first SIB-S factor. MMSE items reflecting nonverbal performance were associated with the second factor and MMSE items reflecting episodic memory were associated with the third SIB-S factor.

Table 3. Regression analysis of MMSE and SIB-S factor scores.

SIB-S factor I	Partial r
MMSE item 6: naming pencil, watch	.39**
MMSE item 3: repeat 3word	.24**
MMSE item 1: time orientation	-.20***
	Model R^2 =.43
SIB-S factor II	**Partial r**
MMSE item 9: three step instruction	.38***
MMSE item 8: read this and do what it says	.25***
MMSE item 10: write sentence	.20***
MMSE item 6: naming pencil, watch	-.13*
	Model R^2 =.48
SIB-S factor III	**Partial r**
MMSE item 2: place orientation	.36***
MMSE item 5: 3 words recall	.19**
MMSE item 7: 'no ifs, ands or buts'	.15*
	Model R^2 =.27

Partial r: partial correlation. R^2: percentage explained variance.

CONCURRENT VALIDITY

Low scores on total SIB-S were associated with cognitive impairment as measured with the MMSE (Spearman rho = .91, p<.001) and with functional dependency as measured with total ADL scale (Spearman rho = -.61, P<.001).

SIB-S total scores were associated with dementia severity. Patients in GDS stage 7 had lower scores compared to patients GDS 6, and patients in GDS 6 had lower scores than those in GDS 4-5. Diagnostic accuracy of SIB-S as measured with the AUC was modest for mild to moderate stages of dementia, but it increased importantly for moderate to very severe stages (table 4).

Table 4: SIB-S and MMSE by Severity of Dementia (GDS 4-7) in Nursing Home Patients with Dementia.

	GDS 4 n=16	GDS 5 n=62	GDS 6 n=112	GDS 7 n=74	ANOVA	Scheffe's
SIB-S	44.9 (2.5)	40.7 (7.0)	28.6 (13.2)	5.3 (8.1)	F=164.6 df:3,260	4,5>6>7, P<.001
MMSE	15.8 (4.6)	13.3 (4.9)	6.7 (4.9)	.7 (1.6)	F=124.5 df:3,260	4,5>6>7, P<.001
AUC SIB-S						
-GDS 4 vs. 5	.664 (CI: .542-.786)					P=.04
-GDS 5 vs. 6	.797 (CI: .730-.863)					P=.001
-GDS 6 vs. 7	.917 (CI: .878-.956)					P=.001
AUC MMSE						
-GDS 4 vs. 5	.633 (CI: .473-.792)					P=.10
-GDS 5 vs. 6	.831 (CI: .770-.893)					P=.001
-GDS 6 vs. 7	.876 (CI: .826-.926)					P=.001

( ): Standard Deviation, unless indicated otherwise
AUC: Area under the receiver operating characteristic curve.

FLOOR EFFECTS

SIB-S total score variances were unequal across patient groups in different stages of dementia severity (Levene's test: F=22.9, df=3,260, P<.001) (table 4). Post hoc analysis showed that score variance was less in GDS 4 as compared to GDS 5 (F=10.8, df=2,312, P=.002), score variance was less in GDS 5 as compared to GDS 6 (F=32.1, df=6,738, P<.001) and variance was greater in GDS 6 as compared to GDS 7 (F=26.4, df=13,586, P<.001). Notably, in GDS 7 MMSE total score variance was about two thirds less than the score variance in GDS 4-6.

The 50th percentile MMSE total score was 6. The mean SIB-S total score for patients with a MMSE score $\leq$ 6 (n=129) was 11.2 (SD=11.8, range= 0-39). For patients with a MMSE score > 6 (n=135) the mean SIB-S was 40.0 (SD=6.8, range= 16-50). Additionally, the mean and variance of the SIB-S total score differed significantly between the two MMSE groups for each sample (two-sample test with unequal variances, t=24.2, df=202,750, P<0.001, Levene's test for equality of variances, F=77.8, P<.001). These results indicate the SIB-S does not show strong floor effects.

Discussion

This study evaluated validity of the SIB-S in nursing home patients with mild to severe dementia. Though principle component analysis produced 3 factors, the SIB-S is in fact a unidimensional measure of cognitive impairment. Cognitive impairment as measured with the SIB-S was associated with dementia severity and with functional impairment. Moreover, it was associated with another cognitive screening test and the SIB-S showed only modest floor effects.

These findings may have implications for neuropsychological evaluations of patients with advanced dementia. Few patients failed to take this relatively short cognitive test or had a total score of 0. The proportion of patients that did score 0 or failed to take the test was almost 35% lower than that for the MMSE. The wide range of test scores found for patients in the severe stages of dementia opens up the possibility of testing those who are usually considered not testable, without risking high drop out rates due to lengthy assessment procedures.

Though most of our results are in accord with those of others, some appear not to be. Previous studies reported correlations between SIB-S, SIB and MMSE that range .68-.99 [62,106]. In the original SIB-S development study subjects, stratified by MMSE 0-4, 5-7, and >7 exhibited a range of scores on the SIB-S, which suggests that were no important ceiling or floor effects on the SIB-S [62]. That study selected an 8 factor model accounting for 59.1% of common variance in the original 51 SIB items (US patient sample) and a 4 factor model accounting for 54.2% of variance (French patient sample) [62]. A second order factor analysis of the 8 factor model was not performed. In a pilot study (n=48) of SIB subscales scores a 4 factor model was selected [101]. A secondary analysis using SIB data from a clinical trial examining the effects of memantine, showed a very strong first factor (eigenvalue > 20) [105]. However, all of these studies assessed patients with the original SIB 51 items version and no patient was independently assessed with the SIB-S. In this study patients were assessed with the SIB-S and a 3 factor model of SIB-S items was selected.

Score variance accounted for was 67.4%, which indicates good model fit. The first factor explained more than half of the score variance. Also, the first factor eigenvalue accounted for more than 3.5 times the common variance of the second factor eigenvalue, which all in all strongly suggests that the SIB-S is a unidimensional measure of cognition. Others, using similar dementia screening tests found 2-4 latent structures underlying scale items [108-112] It is of interest to note that few factors are found when subtest scores are used as indicators, e.g. all questions pertaining to orientation are bundled and result in a single subscale score, while more factors are found when all individual items receive scores, e.g. 'which day is it' or 'which year', etc. [113] Using subscales or creating item bundles is in effect conducting a second order factor analysis. When interpreting our results in the light of previous studies, it should be acknowledged that differences in testing procedures such as the number of test items used in regular or short scale form or fatigue resulting from lengthy test sessions, may lead to diverging factor analysis results. Strengths of this study are the sufficiently large number of included patients, rigorous assessment procedures, classification of dementia severity, and use of the actual SIB-S scale.

Semantic memory loss is typically present in the later stage of dementia and by and large this is what the SIB-S measures. There is ample evidence from neuropathological and imaging studies suggesting that medial temporal lobe (MTL) atrophy is an early sign of Alzheimer's disease, that the lesions are associated with episodic memory deficits, and that the neuropathological changes spread out to other regions of the brain later [114-120]. Though the MTL is activated by semantic verbal memory processing [121], semantic memory loss is eminent when regions outside the MTL become affected [122,123]. Mildly impaired patients find it increasingly difficult to remember recent conversations or to recapture what they did the day before. When patients reach the later stages of dementia, not only do they have episodic memory problems, but general knowledge about the world is lost too. They may find it increasingly difficult naming familiar objects correctly, they may no longer be able to recognize objects or know how to use them. In the later stages of dementia patients may lose all ability for learning new material and episodic memory tests will show floor effects. Factor analysis of SIB-S scale items and correlational analysis with specific MMSE items suggests that most SIB-S scale items tap semantic memory processes and few items measure episodic memory. These findings underline content validity of a scale that was constructed to be used in moderate to severe dementia.

SIB-S scale construction is based on classic test theory principles. Future studies might want to use a modern approach, e.g., Item Response Theory (IRT). This type of analysis would be ideal to understand the value of each item of the SIB-S and how it contributed to understanding the individual's impairment. Further, IRT can be used to improve a test. IRT is based on the analysis of a continuum and is well suited for understanding how tests and their items perform on a compilation of items. Given that the factor analysis has already been done, IRT is a simple next step.

No gold standard exists for neurocognitive testing in clinical settings. Though many clinical trials including dementia patients use measures like the ADAS-cog or SIB, psychologists working with nursing home patients choose to use many different cognitive tests and neuropsychological batteries. Such lack of standardization hampers comparability of

clinical data, e.g. when individual patients are transferred from one institution to another and it does not facilitate data pooling in nursing home research projects. Therefore, we recommend using the SIB-S as the standard, brief, neuropsychological examination in moderate to severe dementia.

Weaknesses of the study are the cross-sectional design. Longitudinal SIB data are available [124], but as yet none are for the SIB-S. Future studies may want to focus on the SIB-S as a measure sensitive to change, so that it can be used in clinical trials and in studies monitoring cognitive decline.

Efficient scales are needed to evaluate cognitive functioning and cognitive change beyond the mild stages of dementia. The short version of the SIB proved to be a valid and unidimensional scale associated with dementia severity and ADL dependency. Item content and brevity of the SIB-S strongly suggest that this is a test suitable for assessing severely impaired patients, who are no longer able to complete lengthier and more difficult neuropsychological tests.

Chapter 5

Determinants of Quality of Life in Nursing Home Residents with Dementia

R Wetzels S Zuidema J de Jonghe F Verhey R Koopmans

Eerst verantwoordelijk verzorgende:

"…De cliënt waarom het gaat kon het ene moment heel aardig zijn, en je kusjes geven en het andere moment kon ze krabben en slaan en spugen.
Dit kon elk moment van de dag zijn, maar meestal gebeurde dit bij de ochtendzorg. Mw wilde gewassen worden en ik ging haar dan wassen en uit het niets kon ze dan in een keer krabben, slaan en spugen, en je uitmaken voor rotte vis. Mijn gevoel daarbij was machteloosheid want je kunt niets doen. Ook woorden van gerustelling haalde dan niets uit. Het beste was dan weglopen en een andere collega het overlaten nemen. Of mw. met twee personen helpen zodat je het van elkaar dan over kan nemen.
Maar het gevoel niets te kunnen doen als mw. zo was is een raar gevoel want je staat dan machteloos…"

Abstract

Aims*:* The goal of this study is to assess the relationship between quality of life (QoL), neuropsychiatric symptoms (NPS), psychotropic drug use (PDU) and patient characteristics in a large group of nursing home residents with dementia.

Methods: This cross-sectional observational study included 288 individuals with dementia who reside in fourteen special care units in nine nursing homes. The following measures were used: the Qualidem scale to assess QoL, the Neuropsychiatric Inventory-Nursing Home version (NPI-NH), the Global Deterioration Scale (GDS), the Severe Impairment Battery-short version (SIB-s), an Activities of Daily Living scale and PDU. Associations between QoL and NPS were examined using multivariate linear regression models with corrections for potential covariates.

Results: The average age of the residents was 84 years (SD±7). Agitation, depression, psychosis, psychomotor agitation, and psychotropic drugs were independently associated with poor QoL. In patients with mild to moderately severe dementia (GDS4-6), NPS, PDU and cognitive impairment explained almost half of the variance in QoL scores. Agitation and depression were particularly strong predictors of poor QoL. In patients with severe dementia (GDS7), agitation, depression, psychosis and cognitive impairment were associated with poor QoL.

Conclusions: NPS, cognition and PDU independently impair QoL for patients in both the moderate and advanced stages of dementia. These results challenge existing pharmacological intervention strategies and highlight the need for psychosocial interventions in the treatment of NPS.

Introduction

"Quality of life" (QoL) is a complex, multidimensional construct [125,126] that has been increasingly recognized as an important study outcome in cases of dementia. In recent years, research examining the factors that contribute to QoL has broadened our understanding of quality of care for community-dwelling patients with dementia. Previous studies have identified several disease-related determinants that influence QoL in patients with dementia; these include the presence of neuropsychiatric symptoms (NPS) [67,127-129], activities of daily living [37,129,130], cognition [129,130], and co-morbid psychosocial symptoms [131]. Of the determinants studied, NPS present a major challenge for clinicians since they occur frequently [66,132], are distressing for individuals with dementia and their partners, commonly place the patient and others at risk, and are a risk factor for early institutionalization. Of the NPS studied, depression has consistently been found to be negatively correlated with patient-reported QoL [37,67,127,128,131,133,134]. An equally strong correlation was found between apathy and QoL, although apathy has been studied less frequently [135]. Anxiety [133] and agitation [127,131] have been less consistently reported to affect a patient's QoL. In order to enhance QoL in patients with dementia, NPS are treated with psychotropic medications. However, concerns are growing over the limited efficacy of these treatments and the possibility of serious adverse outcomes [136] like stroke (which can further lower QoL) and even death [137]. Consequently, while NPS influence QoL, the prescription of psychotropic medication does as well [35,37]; the impact of treatment for NPS on QoL should be a key consideration [35]. Indeed, it has been stated that the use of psychotropic medication influences QoL more than NPS [33]. Finally, the type of dementia a patient has can influence his or her QoL; patients with diffuse Lewy-body disease report a lower QoL than patients with Alzheimer's disease [138,139].

In general, nursing home residents with dementia have a lower QoL than community-dwelling patients with dementia [37-39]. The factors contributing to these findings are largely unknown, but, as we hypothesize, may be related to advanced disease severity, a high prevalence and/or severity of NPS [12,13], and/or psychotropic drug use (PDU) [13,68]. Insight into the determinants of QoL, especially the roles of NPS and PDU, can further enhance care for nursing home residents with dementia. We studied the determinants of QoL in a large population of nursing home residents with dementia in order to establish the association between residents' demographics, NPS, psychotropic medication use, and QoL.

Methods

This was a cross-sectional observational study examining the correlates of poor QoL in nursing home residents with dementia. Residents with dementia from special care units (SCUs) in nine nursing homes in the Netherlands were invited to participate in the study; elderly care physicians systematically screened all residents for inclusion. Residents were considered for inclusion if they: (1) suffered from memory impairment and at least one of the following symptoms: aphasia, apraxia, agnosia, disturbances in executive functioning, impairment in social and occupational functioning, a decline from a previously higher level of functioning, or the dementia criteria listed in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [44]; (2) had no history of life-threatening disease at the time of inclusion; and (3) had to reside in the nursing home for at least four weeks.

Participants' characteristics

Data on age, gender, marital status, and length of stay in the nursing home SCU were recorded. An etiological diagnosis was established by the elderly care physicians using international accepted criteria for AD, VaD, mixed AD/VaD [46,47], frontotemporal lobar degeneration [48] and dementia with Lewy bodies [49]. The first author (RBW) independently checked the eligibility and diagnosis of all residents by examining the patient's clinical notes. When disagreement arose, consensus meetings were organized to ensure the inclusion of all residents who met the aforementioned criteria.

Assessment of quality of life

Quality of life (QoL) was assessed with the Qualidem questionnaire, which is specifically designed for institutionalized residents with dementia and is rated by professional caregivers [58,59]. This multidimensional scale includes 37 indicative and contra-indicative items with four possible responses (never, rarely, sometimes, and frequently). In addition to a total QoL score, responses to these items determine nine homogeneous subscales: "Care relationship," "Positive affect," "Negative affect," "Restless, tense behavior," "Positive self image," "Social relations," "Social isolation," "Feeling at home," and "Something to do." The reliability, internal structure, and validity of this instrument are satisfactory [58,59]. The authors of the Qualidem questionnaire state that in cases of severe dementia (GDS7) six subscales can be applied using approximately half the items (18/37 items); the reliability of this approach is moderately sufficient [60]. The analyses were therefore performed separately for patients in GDS7 and those in GDS4-6. To ensure independent ratings, QoL was rated by two licensed vocational nurses (LVN); NPS were evaluated by one LVN.

Assessment of neuropsychiatric symptoms

All of the licensed vocational nurses who had been assigned to individual residents were trained and instructed to observe symptoms during regular care giving over a two-week observation period before the assessment interview by RBW or research assistant. NPS were assessed with the Neuropsychiatric Inventory–Nursing Home version (NPI-NH) [50,51]. The NPI-NH is developed to be used by professional caregivers in institutions and is valid and reliable when administered by trained nursing staff [52]. The NPI-NH is a structured interview that includes 12 NPS: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime disturbances and appetite/eating changes. Both the frequency (F) and severity (S) of each symptom are rated on a four-point (1–4) and three-point (1–3) Likert scale, respectively. A separate score can be calculated for each symptom by multiplying the frequency and severity scores (to obtain the FxS score); resulting values range from zero to 12 for each symptom. The addition of FxS scores reveals a total score that ranges from zero to 144. The NPI-NH has been translated and validated in the Dutch setting [53]. In order to reduce the number of predictor variables, we used five NPI-NH factor scores based on the findings of previous studies [15,54]. The following factors were included: (1) agitation consisting of agitation/aggression, euphoria, disinhibition and irritability; (2) depression consisting of depression and anxiety; (3) psychosis consisting of hallucinations and delusions; (4) psychomotor agitation consisting of aberrant motor behavior and nighttime behavior; and (5) apathy consisting of apathy and eating disorders [15].

Assessment of psychotropic drug use (PDU)

Data on PDU on the day of assessment were retrieved from the patients' medical and pharmacist files. Drugs were classified using the Anatomical Therapeutic Chemical

classification (ATC) [43] and grouped into antipsychotics, anxiolytics, hypnotics, antidepressants, antiepileptics, anti-dementia drugs, and any psychotropic medication. Dichotomous categories of either "present" or "absent" were used to quantify PDU; prescriptions for incidental use were discarded.

Assessment of cognition and dementia severity

Cognitive functioning was assessed with the Mini Mental State Examination (MMSE) [63] and Severe Impairment Battery-short version (SIB-s) [62]. The SIB-s is a cognitive assessment instrument able to test cognition in individuals in the later stages of dementia. Scores range from 0 to 50 and higher scores denote better cognition. The SIB-s has been translated and validated in a large group of Dutch nursing home residents with dementia [140]. Severity of dementia was rated with the Global Deterioration Scale (GDS), which ranges from normal cognition (GDS stage one) to very severe cognitive decline (GDS stage seven) [61]. Stages four and higher are considered to represent subsequent dementia stages.

Assessment of activities of daily living (ADL)

ADL were assessed using section G of the InterRAI Long Term Care Facility scale (2005, version 07). This observational scale measures resident self-involvement in personal ADL. A hierarchical ADL-Scale includes four of the ADL items from the InterRAI with six response categories for each item. The scale is scored according to a decision tree with eight categories that ranging from 0 (independent) to 6 (totally dependent) and 8 (activity not seen). When the scale was first introduced, its reported psychometric properties were good to excellent (inter-rater reliability) and its internal consistency (Cronbach's alpha) was 0.90 [64]. The validity and reliability of the ADL scale have been established in a study of Dutch nursing home residents with dementia [65].

Data analysis

Differences between mean values or percentages for two groups were analyzed using the Student's *t*-test, Mann-Whitney U (MWU) test, or χ^2 test. Bivariate correlations were calculated to determine which variables were associated with QoL. Analysis of variance was used to determine the relationship between the type of dementia and QoL. Multivariate linear regression models were developed to analyze the relationship between the QoL total score and the following independent variables: age, gender, dementia stage, nosologic diagnosis, ADL, SIB-s total score, five NPI factors (NPI FxS cluster score), and PDU. PDU was entered in the regression model either as a group or an individual category. Several diagnostic steps were completed to ensure that the variables used met the statistical assumptions of linear regression. Normality was evaluated by comparing the expected normal distribution to the histogram of the residuals for the dependent variable. Linearity and equality of variance were evaluated by plotting residuals against the predicted values for the dependant variable. Collinearity was evaluated by examining tolerance, the variance inflation factor, eigenvalues of the scaled, uncentered cross-products matrix, the condition index, and the variance proportions for each variable. The Durbin-Watson test was used to evaluate the assumption of independent errors. All variables in the final model met these assumptions.

In cases of SIB-s scores with no more than 10% missing values, imputation was used with the modal test item scores. From the maximum of 9117 responses (207 times 37 and 81 times 18) Qualidem items, only 11 responses (0.1%) were missing. The missing responses were distributed across ten respondents with a maximum of five missing responses per item. This was considered sufficient support for these responses to be missing completely at random (Little's MCAR test: Chi-Square=47,138, df=280, Sig.=1,000). The missing

responses were imputed, using the estimation maximization algorithm. Statistical analyses were performed using SPSS version 16 for Windows.

Ethical Considerations

This study was approved by the regional research ethics committee. The participants and/or their relatives and legal guardians were informed about the study and gave their written consent.

Results

A total of 290 residents were eligible to participate in the study and 288 completed the study protocol. Table I lists the demographic and clinical characteristics of the study population. Most of the patients were female and the average age was 84 years; most patients had a low educational attainment and half of the residents were widowed. Most residents were diagnosed with Alzheimer's dementia (AD), though a small portion had vascular dementia (VaD) or a combination of both AD and VaD. However, in 40% of cases the type of dementia was classified as "not otherwise specified."

Table I
Demographic and clinical characteristics (*n=288*)

	GDS4-6 (n=207)	GDS7(n=81)	t(*df*) or χ^2(*df*)
Age, years (mean, SD, range)	83.4 (6.8; 59-98)	84.6 (8.0; 66-102)	NS
Female %	72.5	86.4	$\chi^2(1)=6.287^{*}$
Length of stay NH, yrs (mn, SD, rg)	2.4 (2.0; 0.1-10.3)	4.4 (3.1; 0-18)	$t(106.8)=-5.27^{***}$
Length of stay SCU, yrs (mn, SD, rg)	2.1 (1.9; 0-10.3)	4.2 (3.1; 0-18)	$t(104.4)=-5.66^{***}$
Marital status %			
- married	25.6	22.2	NS
- widow	51.2	54.3	NS
- divorced	3.9	3.7	NS
- unmarried	9.7	4.9	NS
- missing values	9.7	14.8	NS
GDS%			
4/5	41.1		
6	58.9		
Diagnosis (%)			
-Alzheimer	36.2	45.7	NS
-Vascular	11.6	7.4	NS
-Alz/vas	7.2	3.7	NS
-+	44.9	43.2	NS
MMSE (mean, SD, range)	9.5 (6.0; 0-25)	0.7 (1.6, 0-7)	$t(253.1)=-18.8^{***}$
SIB-s (mean, SD, range)	33.9(12.7; 0-50)	5.3(8.1, 0-32)	$t(206.2)=-21.8^{***}$
Education (%)			
- primary	25.1	34.6	
- low vocational secondary	19.3	17.3	
- mid vocational secondary	8.2	9.9	
- high vocational secondary	3.4	0	
- university	.5	1.2	
- missing values	43.5	37	
ADL (according to Morris 1999, %)			
-totally dependent	4.8	55.6	$\chi^2(6)=114.5^{***}$
-dependent	14.6	25.9	
-extensive 1	5.8	7.4	
-extensive 2	35.7	11.1	

-limited	8.7	0
-supervision	14.0	0
-independent	6.3	0

*<.05 ***<.000 NS= not significant

N=number yrs=years mn=mean rg=range ADL=activity of daily living MMSE=mini mental state examination SIB-s=severe impairment battery-short version SD=standard deviation GDS=global deterioration scale NH=nursing home SCU=special care unit

The residents had QoL subscales scores ranging from 1.98 (on the "something to do" subscale) to 15.59 (on the "care relationship" subscale). Interestingly, although their total scores did not significantly differ, men showed significantly higher scores than women on two subscales: negative affect (MWU z=-2.483, p=.013) and positive self image (MWU z=-2.241, p=.025). Behavior scores ranged from 1.57 (NPI-NH factor depression) to 6.34 (NPI-NH factor agitation) (see Table II) Residents in GDS7 had statistically significant lower scores for psychosis and statistically significant higher scores for apathy. About 60% of residents had been prescribed at least one psychotropic drug; most of these prescriptions were for antipsychotics (31.4%) or antidepressants (27.0%) for those in GDS4-6 and for antipsychotics (35.8%) and anxiolytics (23.5%) for those in GDS7.

Table II

NPI-NH Qualidem score and psychotropic drug use (*n=288*)

	GDS4-6(*n=207*)	GDS7(*n=81*)	t(*df*) or χ^2(*df*)
Qualidem sub scores[a] (mean; range)			
-Care relationship	15.59 (0-21)	6.26 (0-9)	
-Positive affect	13.40 (0-18)	6.94 (0-12)	
-Negative affect	6.40 (0-9)	4.57 (0-6)	
-Restless tense behaviour	5.40 (0-9)	4.62 (0-9)	
-Positive self image	7.47 (0-9)		
-Social relations	11.02 (0-18)	3.83 (0-9)	
-Social isolation	6.78 (0-9)	6.81 (0-9)	
-Feeling at home	9.76 (0-12)		
-Something to do	1.98 (0-6)		
-Total score	77.81 (0-111)	33.02 (0-54)	
NPI (FxS score mean; range)			
-NPI total	17.16 (0-48)	17.62 (0-48)	.800 NS
-NPI factor agitation	6.34 (0-24)	4.78 (0-24)	.153 NS
-NPI factor depression	2.87 (0-24)	2.12 (0-24)	.185 NS
-NPI factor psychosis	1.57 (0-24)	.84 (0-24)	t(286)=2.352*
-NPI factor psychomotor agitation	3.34 (0-24)	3.06 (0-24)	.672 NS
-NPI factor apathy	3.04 (0-24)	6.81 (0-24)	t(117)=-4.926***
Psychotropic drug use (%)			
-antipsychotic drugs	31.4	35.8	.474 NS
-antidepressant drugs	27.0	18.5	.112 NS
-anxiolytic drugs	15.9	23.5	.136 NS
-hypnotics/sedatives	13.5	12.3	.790 NS
-antiepileptic drugs	4.8	7.4	.391 NS
-antidementia drugs	5.3	2.5	.296 NS
-any drug	61.4	59.3	.744 NS

*<.05 ***<.000

[a] higher (sub) scores indicate higher QoL.

N=number NS not significant GDS=global deterioration scale NPI=neuropsychiatric inventory FxS=frequency times severity

QoL was particularly poor in residents with co-morbid NPS, more severe dementia (as indicated by cognition, GDS, or ADL dysfunction) and in those on psychotropic drugs (see Table III).

Table III
Bivariate Pearson's/Spearman's correlation of QUALIDEM total score

	GDS4-6(*n=207*)	GDS7(*n=81*)
Gender	.64	.122
Age	.006	.002
GDS(4/5 v. 6)	-.200*	
Antipsychotic drugs	-.241**	-.186 (p=.096)
Antidepressant drugs	-.187*	-.155
Anxiolytic drugs	-.291**	-.277*
Hypnotics/sedatives	-.134	-.101
Antiepileptic drugs	-.099	-.077
Antidementia drugs	-.004	.082
Psychotropic drug use	-.330**	-.131
ADL[a]	.187*	.133
SIB-s total score[b]	.234**	.194 (p=.099)
NPI factor agitation (FxS score) (Sp)	-.569**	-.414**
NPI factor depression (FxS score) (Sp)	-.407**	-.339**
NPI factor psychosis (FxS score) (Sp)	-.341**	-.291
NPI factor psychomotor agitation (FxS score) (Sp)	-.311**	-.190
NPI factor apathy (FxS score) (Sp)	-.215**	-.100

*<.05 **<.003 NS= not significant
[a]Higher ADL score indication higher dependency [b]Higher SIB-s score indicating higher cognition
Correlations are Pearson's unless specified Spearman's (Sp) QoL=Quality of Life ADL=activities of daily living SIB-s=severe impairment battery-short version NPI= Neuropsychiatric Invertory FXS=frequency times severity n=number GDS=global Deterioration Scale

Multivariate linear regression models were performed; analyses of patients in GDS4-6 and GDS7 are displayed in Tables IV and V, respectively. Due to multicollinearity, ADL was removed from the model. The multivariate regression analysis revealed that the type of dementia was not associated with QoL, given comparable total scores. In patients with mild to moderately severe dementia, a statistically significant association was found between QoL and agitation, depression, psychosis, psychomotor agitation, cognitive impairment and PDU; these factors explained 49% of the variance in QoL (see Table IV). Agitation and depression were the strongest predictors of QoL. Table V shows that agitation, depression, psychosis, and cognitive impairment were independent predictors of QoL in patients with severe dementia, explaining 34% of the variance.

Table IV
Multivariate linear regression models with significant correlates of QoL (GDS4-6; *n=207*)

		B	Se B	Beta
Model I	Gender	-.321	2.253	-.008
	Age	-.207	.145	-.083
	Marital status	1.880	1.186	.097
	Nosologic dementia diagnosis	-.737	.700	-.061
	ADL	.737	.613	.073
	Psychotropic drug use	-6.371	1.984	-.184**
	SIB-s total score	.190	.081	.145*
	NPI factor agitation	-.576	.120	-.293***
	NPI factor depression	-1.067	.229	-.306***
	NPI factor psychosis	-.726	.295	-.154*
	NPI factor psychomotor agitation	-.554	.192	-.175**
	NPI factor apathy	-.019	.213	-.005
Model II	Psychotropic drug use	-5.539	1.850	-.162**
	SIB-s total score	.182	.069	.139*
	NPI factor agitation	-.627	.113	-.321***
	NPI factor depression	-1.036	.209	-.292***
	NPI factor psychosis	-.665	.286	-.136*
	NPI factor psychomotor agitation	-.437	.177	-.135*

Model I: adj R^2.501 Model II: adj R^2.493
*<.05 **<.005 ***<.000
QoL=Quality of Life ADL=activities of daily living SIB-s=severe impairment battery-short version NPI= Neuropsychiatric Invertory FxS=frequency times severity n=number GDS=global Deterioration Scale

Table V
Multivariate linear regression models with significant correlates of QoL (GDS7; *n=81*)

		B	Se B	Beta
Model I	Gender	-4.549	3.415	-.159
	Age	.011	.142	.009
	Marital status	-2.473	1.439	-.203
	Nosologic dementia diagnosis	.233	.718	.036
	ADL	-.548	1.097	-.062
	Psychotropic drug use	-1.466	2.075	-.078
	SIB-s total score	.366	.123	.342*
	NPI factor agitation	-.577	.163	-.452**
	NPI factor depression	-.433	.253	-.177
	NPI factor psychosis	-1.029	.556	-.227
	NPI factor psychomotor agitation	-.229	.204	-.121
	NPI factor apathy	.037	.157	.026
Model II	SIB-s total score	.302	.106	.276*
	NPI factor agitation	-.382	.127	-.314**
	NPI factor depression	-.595	.233	-.248*
	NPI factor psychosis	-1.284	.502	-.270*

Model I: adj R^2.400 Model II: adj R^2.344
*<.05 **<.005
QoL: Quality of Life ADL: activities of daily living SIB-s: severe impairment battery-short version
NPI: Neuropsychiatric Invertory n=number GDS=global Deterioration Scale

QoL was only associated with the use of any psychotropic medication and was not associated with the six individual psychotropic medication ATC-groups.

Discussion

This is the first large study to report the influence of NPS, simultaneously assessed with cognition and PDU, on the QoL of a relatively homogenous sample of nursing home residents with dementia. Almost 50% of QoL in dementia patients is related to eminent NPS, PDU, and cognitive decline. Agitation and depression were particularly strong predictors of poor QoL. These associations were stronger in patients with mild to moderately severe dementia than those with severe dementia.

Our results correspond somewhat to those of previous studies. Samus et al. [128] found that agitation, depression, apathy and irritability predicted and explained 29% of the QoL score variance in dementia patients in assisted living facilities [128]. On one hand, as in our study, Samus et al. found that agitation and depression were particularly strong predictors of QoL. Sloane et al., on the other hand, used an aggregate of several different QoL instruments and found cognition and ADL function to be strong predictors of QoL [130]. Depression and agitation were also found to predict QoL, although less strongly. Indeed, these four predictors combined explained 27% of the variance in QoL. In our study, although ADL was also found to be correlated with QoL, it was dropped from the multivariate analysis due to multicollinearity since both ADL and cognition may reflect the severity of the disease. Banarjee et al. [67] also found that NPS accounted for more than half of the 35% model variation in QoL. Hoe et al. explained 43% of the variance in QoL with only a scale assessing behavioral problems and functional ability in residential care homes [133]. Although small differences exist in the amount of variance explained in these studies, our results confirm that NPS particularly impairs QoL in patients in the mild/moderate and severe stages of dementia. Since dementia-related agitation can result into early institutionalization and agitation is a strong predictor of poor QoL, these results may in part explain the lower QoL in institutionalized residents with dementia compared to community-dwelling patients with dementia.

Contrary to our results, Banarjee et al., using MMSE, found that cognition was not related to QoL, even after patients were placed in mild/moderate and severe dementia groups [67]. Hoe et al. [141] and Sloane et al. [130] identified an interaction between cognition and QoL. In contrast, Ballard et al. did not find any relationship between NPS and QoL but did show an association between QoL and psychotropic drugs [33]. Differences between study participants (i.e., setting, age, and dementia stage) and assessment instruments (patient-rated versus proxy-rated questionnaires and MMSE versus SIB-s) might account for these differences. Our study supports Ballard's claim that PDU impairs QoL in patients with dementia. In this study, cognition was found to be a predictor of QoL, even though a few residents scored a zero on the MMSE and SIB-s.

Qualidem scores were similar across dementia types. This finding seems to contradict those of previous studies [138,139]. Apparently, dementia etiology in older nursing home residents does not affect QoL. This might indicate that different etiological entities produce similar clinical manifestations due to increasing age and disease progressing in patients in the advanced stages of dementia. In addition, many residents were diagnosed with "dementia not otherwise specified," which indicates that multiple brain pathologies may have been present.

Some QoL aspects appeared to be associated with gender. Male residents scored higher on the Qualidem "negative affect" and "positive self image" sub-scores. These findings point to the need for further research in this area.

This is the first large study of nursing home residents with dementia to report the influence of NPS on QoL when simultaneously assessed with cognition and PDU. The strengths of this study include the use of homogenous nursing home resident sample, the use

of validated and well-known measures of QoL, NPS, and cognition, the use of multivariate analyses of different predictors and the efforts made to reduce inter-rater score variation.

This study has some limitations that need to be discussed. These relate to the observational nature of the study, the method of measuring psychotropic medications, and the content validity of the predictor variables used. As this is a cross-sectional study, no conclusions on causality can be made. In addition, the coding for psychotropic drug use was simple and straightforward and potentially important information (such as duration of usage and actual dose) was not measured. Pain, which is highly prevalent among nursing home residents [142,143] and is associated with the expression of agitation and aggression [144] or depression and anxiety [142], was not included as an independent variable. Pain can also have a direct influence on QoL variables [145]. Co-morbidity (recuperation from an acute illness) can also influence QoL and was not considered as an independent variable. Additionally, although NPI-NH factors were believed to be independent from each other, some of the explained variance might be due to a moderate correlation between them. Notably, correlations between the Qualidem subscales and NPI factors could have influenced the explained variance to some degree. Lastly, other possible factors contributing to the 50% unexplained variance might relate to the nursing home environment itself (such as physical surroundings, crowdedness, nurses' attitudes, and privacy); these factors have not been studied.

Considering the negative influence of PDU on QoL, nursing home residents may best benefit from multidimensional treatment strategies that include psychosocial interventions [146]. Resident management should also include adjustments in the resident's physical surroundings [147] and the well-being of nursing staff [148]. One article supports the idea that surroundings influence QoL [35]. Interestingly, the attitudes of nurse assistants towards residents with dementia explain additional variance in residents' QoL [129]. Education for certified nurse assistants should be a primary goal to enhance care giving to residents with dementia [149]. In addition, future longitudinal studies of the relationship between NPS/psychotropic medication and QoL can offer better insight into the underlying causal relationships. Specifically, studies of the influence on QoL of subsets of residents who started taking or who discontinued PDU are currently being conducted.

Almost 50% of QoL in patients with dementia is related to eminent NPS, PDU, and cognitive decline. For the first time, risk factors for poor QoL were studied simultaneously in a relatively homogenous sample of nursing home residents with dementia. NPS independently impair QoL in patients in both the moderate and advanced stages of dementia. The same holds true for cognition and PDU. These results underline the growing awareness that NPS have a major impact on QoL. We should make serious efforts to systematically monitor PDU in our residents, to re-evaluate pharmacological strategy interventions, and to focus more attention on psychosocial interventions.

Chapter 6

Course of Neuropsychiatric Symptoms in Residents with Dementia in Nursing Homes over two-year Period

R Wetzels S Zuidema J de Jonghe F Verhey R Koopmans

Eerst verantwoordelijke verzorgende:

"…Bij een gedragsverandering van een bewoner, bijvoorbeeld bij agressie, voel ik op dat moment mee met de bewoner. Ik krijg dan een gevoel van frustratie, omdat je op dat moment niets kan doen.
Ik vind dat een bewoner juist zijn/haar gedrag mag tonen of uiten, zodat de bewoner zelf daarna de innerlijke rust kan krijgen.
Als je dit gedrag zelf ook hebt, wil je jezelf ook tonen en uiten en voel je jezelf daarna zelf opgelucht…"

Abstract

Objectives: To determine the course of neuropsychiatric symptoms (NPS) in nursing home residents with dementia, and to determine their variability across diagnosis.

Design: Prospective cohort study over two-years.

Setting: Fourteen dementia special care units in nine nursing homes in the Netherlands

Participants: One hundred seventeen residents with dementia.

Measurements: NPS were measured using the Neuropsychiatric Inventory-Nursing Home version.

Results: The majority of residents had moderately severe to severe dementia. All but a few residents (97%) showed any NPS, co-occurrence of NPS was high. Agitation, irritability and aberrant motor behaviour were the most two-year prevalent. Depression and anxiety as well NPI-total score decreased over time, whereas apathy tended to increase. Agitation and aberrant motor behaviour were the most persistent symptoms. In asymptomatic residents, highest incidence rates were found for apathy, aggression/agitation, irritability and aberrant motor behaviour. Anxiety and apathy were more prevalent in Alzheimer's disease (AD) compared to vascular disease (VaD); vice versa aggression and depression were more prevalent in VaD. Differences in change over time between AD and VaD were found for irritability and disinhibition.

Conclusions: This is the first study examining the two-year course of NPS in a large group of nursing home residents with dementia. Virtually all residents demonstrated and/or developed NPS. While affective symptoms decreased, apathy tended to increase. Agitated behaviours were particularly persistent. Our data may contribute to improve mental health care for demented nursing home residents.

Objectives

Dementia is a major cause of suffering and disability in the elderly. Besides cognitive symptoms, behavioral and psychological problems, also referred to as neuropsychiatric symptoms (NPS), significantly contribute to this suffering, and are increasingly recognized as important research outcome measures [3,4]. NPS, like agitation/aggression, depression, psychosis and apathy, occur in up to half of community-dwelling patients with dementia [8,66] and up to 80% in nursing homes residents with dementia [12,13]. NPS are frequently treated with psychotropic drug, which only have a modest beneficial effect in short-term treatment but limited benefit in longer-term therapy. Their use is furthermore limited due to inefficacy and side-effects. Altogether, NPS have a negative impact on QoL [127,150], thus presenting a major challenge for clinicians.

As the rate and type of cognitive symptoms tend to vary across dementia etiology, so do NPS. Whereas irritability is often observed in mild Alzheimer's dementia (AD), disinhibition may be an early sign of frontotemporal dementia, and hallucinations are core symptoms of Lewy Body Dementia. In more advanced stages of dementia, prevalence rates of NPS also vary across dementia etiology as well [16-18]. According to several cross-sectional studies, sleep disturbances are encountered more frequent in vascular dementia (VaD) compared to AD [16], VaD is associated with less clinical relevant-NPS [17] and sleep disturbances, appetite changes and aberrant motor behaviour are seen more prevalent and more severe in AD [18]. For more and detailed insight into the course of NPS, however, additional longitudinal prospective studies are needed.

Longitudinal studies that included community-dwelling patients with dementia show that most NPS tend to be relatively persistent, that some symptoms are intermittent, and that there is considerable variation between subjects [9,25,151-153]. However, a considerable large group of patients with dementia resides in nursing homes or other long-term care facilities, and, although scarce, longitudinal studies including nursing home residents with dementia indicate similar patterns [81,86]. Selbæk et al. [81] studied NPS over one-year in residents with a diagnosis of dementia based on a standardized interview with the primary caregiver. Overall, persistence of NPS was high, but on the other hand, individual symptoms frequently resolved. Wancata et al. [86] studied the six-months natural course of NPS in a subgroup of residents with dementia and found affective and behavioral symptoms most prevalent. However, most studies examining the course of NPS in institutionalized residents with dementia are characterized by relatively small sample sizes, short follow-up periods, and limited assessments nor differentiated across dementia type [83,84,86,154]. With the expected rise in dementia prevalence and limited funds for institutionalized residents with dementia, insight into the course of NPS can provide best practice for treating NPS, increase residents' quality of life, and increase effective planning of staff allotment against reasonable costs. Consequently, there is a need to follow a large population of well-diagnosed residents with dementia over a long period. We hypothesize that NPS show different courses over two-year period and across subtype of dementia. We, therefore, studied the two-year course of NPS in nursing home residents with dementia across different dementia types.

Methods

This was a prospective cohort study in which residents were enrolled from fourteen dementia special care units (SCU) from nine nursing homes in the Netherlands. Resident's elderly care physicians systematically screened all residents for inclusion. Residents were considered for inclusion provided they: (1) met the Diagnostic and Statistical Manual of Mental Disorders fourth edition criteria for dementia [155]; (2) had no history of life-threatening disease at the time of inclusion; and (3) had to reside in the nursing home for at least four weeks. Residents had a two year follow-up, with five biannual assessments.

Participant's characteristics

Age, gender, marital status, length of stay at the nursing home were registered. Etiological diagnosis was established by the elderly care physicians using international accepted criteria [46,47] and the Dutch consensus guidelines [45] for AD, VaD, mixed AD/VaD or other diagnosis (including 'dementia not otherwise specified'). Independently from the elderly care physicians, the first author (RBW) checked eligibility and diagnosis of all residents against the patient's clinical notes. In cases of doubt, consensus meetings were subsequently organized to insure inclusion of residents who met the inclusion criteria.

Assessment of neuropsychiatric symptoms

NPS were assessed with the Neuropsychiatric Inventory Nursing Home version (NPI-NH) [50,51]. The nursing home version was developed for the use of professional caregivers within institutions and proved to be valid and reliable for trained nursing staff [52] and has been translated into Dutch [53]. The NPI-NH is a structured interview that includes 12 NPS: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, nighttime disturbances and appetite/eating change. Both the frequency (F) and severity (S) of each symptom are rated on a four- (1–4) and three-point (1–3) Likert scale, respectively. A separate score can be calculated for each symptom by multiplying the frequency and severity scores (FxS score), resulting values ranging from zero to 12 for each symptom. Summing FxS scores reveals a total score that ranges from 0–144. All licensed vocational nurses, who have been specifically assigned to individual residents, observed symptoms during a 2-week period prior to assessment, were interviewed by RBW or a research assistant.

Assessment of dementia severity and cognition

Severity of dementia was assessed with the Global Deterioration Scale (GDS) which ranges from normal cognition (stage one) to very severe cognitive decline (stage seven) [61]. Cognitive functioning was assessed with the Severe Impairment Battery-short version (SIB-s). The SIB-s is a cognitive assessment instrument able to test cognition into the later stages of dementia [62]. The SIB-s has been translated into Dutch and has been validated in a large group of Dutch nursing home residents with dementia [140]. At baseline, the MMSE was also used to assess cognitive functioning [63].

Assessment of activities of daily living (ADL)

ADL was assessed with the InterRAI Long Term Care Facility (LTCF) section G (2005, version 07). An hierarchy ADL-Scale includes 4 of the ADL items of the InterRAI LTCF, each with 6 response categories, and is scored according to a decision tree with 8 scale categories, ranging from 0 (independent) to 6 (totally dependent) and 8 (activity not seen). When first introduced, its reported psychometric properties were good to excellent (inter-rater reliability) and an internal consistency (Cronbach's alpha) of .90 [64]. Validity and reliability of the ADL scale are established in a study including Dutch nursing home residents with dementia [65].

Psychotropic drug use (PDU)

PDU was retrieved from the resident's medical- and pharmacist file on the day of the assessments. PDU was classified using the Anatomical Therapeutical Chemical - classification [43] and grouped into antipsychotics, antidepressants, hypnotics, anxiolytics, antiepileptics, antidementia medication, and any psychotropic drug. Dichotomous

categorization into either present or absent was used to quantify PDU; prescription for incidental use was discarded.

Analysis

Similar to Aalten et al. [9], the main outcome measures were frequency parameters and NPI-severity scores. We calculated the following frequency parameters: prevalence, resolution, persistence, and incidence of NPS. Clinically relevant NPS (NPS-CR) measured with the NPI-NH were defined by a FxS score for each individual symptom ≥4. Point prevalence was defined as the proportion of residents with specific CR-symptoms at each assessment. The cumulative two-year prevalence was defined as the proportion of residents developing a specific CR-symptom on at least one assessment over the two-year period. Resolution was defined as the proportion of residents who showed a specific CR-symptom at one assessment but not at the next assessment and was calculated for each two successive assessments. A CR-symptom was persistent if it was present on at least two subsequent assessments, and was calculated for any three and four consecutive assessments as well. Incidence was rated as the proportion of residents who developed a specific CR-symptom at one assessment but showed no CR-symptom on the preceding assessment. The cumulative incidence was rated as the proportion of residents who were symptom free at baseline, but developed the specific CR-symptom at next assessments. Prevalences were presented as percentages of total group. Frequency parameters are presented as percentages on subgroup level; by definition, persistence and resolution add up to 100%. NPI-severity scores (FxS≥0) over time were analysed using Friedman test for individual NPI items and total NPI score. Difference in change between AD and VaD in severity scores (FxS) over time were analyzed using MANOVA for repeated measurements.

Statistical analysis was performed using the SPSS software, version 16 (SPSS 16.0.1 for Windows; SPSS Inc., Chicago, IL). Frequency parameters were calculated using SPSS macro syntax. The analyses were performed in the cohort that ultimately survived two-years of follow-up. To assess any possible bias due to loss-to-follow-up, differences at baseline between completers and non-completers were evaluated using Student's *t*-test or χ^2-test.

Ethical Considerations

Approval of the regional research ethics committee was obtained. Relatives or legal guardians of all residents gave fully informed written consent.

Results

Residents

Two hundred and ninety residents were included in this study, of whom 117 (40%) residents completed the two-year follow-up period. Resident characteristics are shown in Table 1. The number of residents in this study declined through successive assessments to n= 223, 191, 153 and 117 at 6, 12, 18 and 24 months respectively due to death (n=159) or transfer to another SCU (n=14). The non-completers were more females, significantly older, and more ADL dependant at baseline. Non-completers showed higher severity scores for apathy and NPI-NH total score as well as higher prevalence of any NPI (see Table 1). At baseline, 11.1% of the completers had GDS4, 26.5% GDS5, 33.3% GDS 6, and 29.1% GDS7. At 24-months, percentages changed: GDS4: 6.4% GDS5: 13.6% GDS6: 40% GDS7: 40%, indicating significant increase in dementia stage ($\chi^2(9)=78.138$ $p<.0001$). Resident NPI-symptomatology and PDU are shown in Table 2.

Table 1 Demographic and clinical characteristics at baseline

	Residents with complete follow-up(*n=117*)	Residents with incomplete follow-up(*n=173*)	t(*df*) or χ^2(*df*)
Age mean (SD)	81.7 (7.4)	85.0 (6.7)	t(288)=3.943***
Female %	71.7	82.9	χ^2(1)=4.854*
Length of stay NH (yrs)	3.09 (2.7)	2.88 (2.4)	NS
Length of stay NH-SCU	2.77 (2.7)	2.62 (2.3)	NS
Diagnosis %			
- Alzheimer	35.0	41.3	NS
- Vascular	11.1	9.9	
- Mixed Alz/vas	1.7	2.3	
- Other	52.1	46.5	
Education %			
- primary	25.1	34.6	NS
- low vocational secondary	19.3	17.3	
- mid vocational secondary	8.2	9.9	
- high vocational secondary	3.4	0	
- university	.5	1.2	
- missing values	43.5	37	
ADL (%)			
-totally dependent	4.8	55.6	χ^2(6)=114.5***
-dependent	14.6	25.9	
-extensive 1	5.8	7.4	
-extensive 2	35.7	11.1	
-limited	8.7	0	
-supervision	14.0	0	
-independent	6.3	0	
MMSE (SD)	7.6 (7.1)	6.8 (6.1)	NS
SIB-s (SD)	27.1 (18.2)	25.1 (16.7)	NS
GDS %			
4	11.1	2.9	χ^2(3)=12.19*
5	26.5	21.1	
6	33.3	48.5	
7	29.1	27.5	

*<.05 ***<.0001 NS=none significant t= Student's t test χ^2= chi square test
n=number yrs=years rg=range ADL=activity of daily living MMSE=mini mental state examination SIB-s=severe impairment battery-short version SD=standard deviation GDS=global deterioration scale NH=nursing home SCU=special care unit

Residents in our study sample were of high age, mostly female, had in general low levels of educational attainment and many had advanced dementia. In addition, many residents were diagnosed with "dementia not otherwise specified," which indicates that multiple brain pathologies may have been present.

Table 2 NPS and PDU at baseline

	Residents with complete follow-up (*n=117*)	Residents with incomplete follow-up (*n=173*)	t(*df*) or χ^2(*df*)
NPI-symptoms (SD)			
Delusion	.67 (2.0)	1.02 (2.5)	NS
Hallucination	.35 (1.1)	.56 (1.6)	NS
Agitation/aggression	1.79 (3.0)	2.36 (3.6)	NS
Depression	.97 (2.0)	1.39 (2.7)	NS
Anxiety	1.33 (2.6)	1.51 (3.0)	NS
Elation/euphoria	.34 (1.3)	.33 (1.5)	NS
Apathy/indifference	1.90 (3.6)	3.29 (4.5)	2.939(280)**
Disinhibition	1.03 (2.7)	1.21 (2.9)	NS
Irritability/lability	2.42 (3.4)	2.23 (3.5)	NS
Aberrant motor behaviour	2.07 (3.7)	2.38 (4.0)	NS
Nighttime behaviour	.69 (2.2)	1.22 (2.7)	NS
Eating change	1.04 (2.4)	1.66 (3.4)	NS
NPI total	14.61 (13.6)	19.16 (16.5)	2.564(277)*
Prevalence any NPI-item (FxS≥4)	67.5%	79.8%	5.558(1)*
Psychoactive drug use (%)			
antipsychotic	28.2%	35.3%	NS
antidepressant	18.8%	28.9%	NS
anxiolytic	18.8%	17.3%	NS
hypnotic	6.8%	16.8%	6.177(1)*
antiepileptic	5.1%	5.8%	NS
antidementia	3.4%	5.2%	NS
any medication	57.3%	62.4%	NS

*<.05 **<.005 NS=none significant t= Student's t test χ^2= chi square test
NPS=neuropsychiatric symptoms PDU=psychotropic drugs use NPI=Neuropsychiatric symptoms FxS=frequency times severity n=number

Neuropsychiatric symptoms

Severity scores

Initially, nursing home residents with dementia were much disturbed behaviourally as was shown for agitation, irritability and aberrant motor behaviour, but also for affective symptoms apathy and anxiety. Over time, however, overall level of NPS decreased, as NPI-total score decreased. Additionally, specific decreases were also observed for affective symptoms as evidenced by depression and anxiety, see Table 3 and Figure 1.

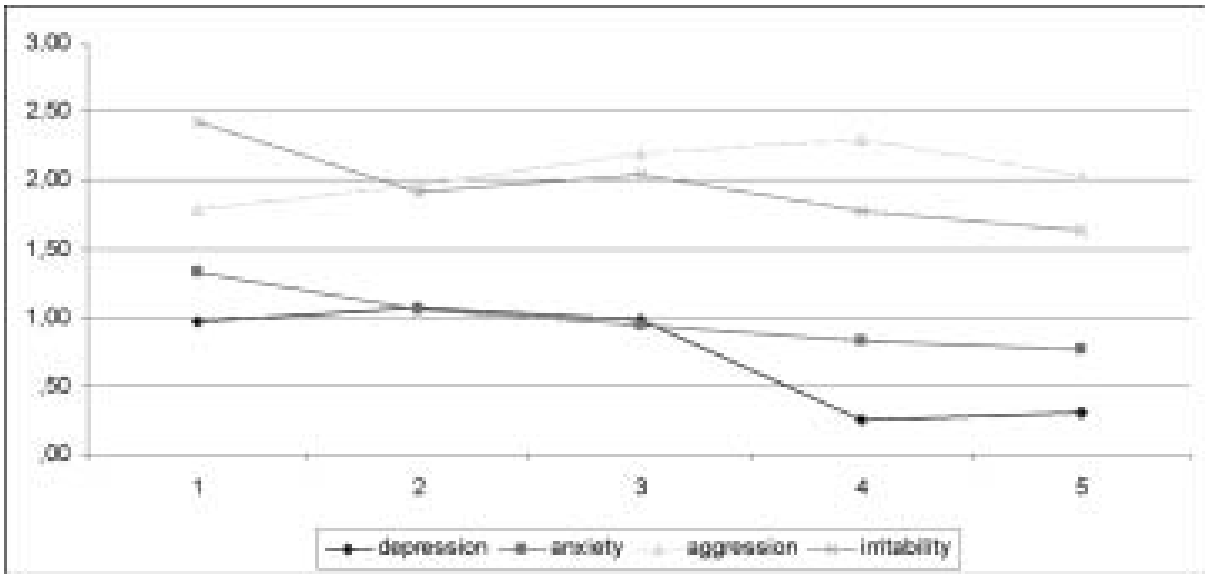
Table 3 Mean severity scores NPI-items (FxE≥0 at baseline) at successive assessments (T0-T4; *n=117*)

	T_0	T_1	T_2	T_3	T_4	P
Symptoms						
Delusion	.67	.66	.59	.38	.46	NS
Hallucination	.35	.34	.20	.24	.44	NS
Agitation/aggression	1.79	1.97	2.20	2.30	2.03	NS
Depression	.97	1.07	.98	.26	.31	.000***
Anxiety	1.33	1.06	.95	.83	.77	.043*
Elation/euphoria	.34	.49	.46	.31	.33	NS
Apathy/indifference	1.90	1.83	2.03	2.98	1.82	NS
Disinhibition	1.03	.81	.72	.51	.54	NS
Irritability/lability	2.42	1.91	2.04	1.78	1.64	NS

Aberrant motor behaviour	2.07	2.14	2.15	1.5	1.45	NS
Nighttime behaviour	.69	.58	.68	.32	.62	NS
Eating change	1.01	.85	1.08	.85	.53	NS
Total	14.61	13.7	14.08	12.25	10.94	.018*

*<.05 ***<.0001 Friedman test
NPI=Neuropsychiatric symptoms FxS=frequency times severity n=number T_0-T_4=successive assessment

FIGURE 1. Mean Severity Scores of NPI Items at Successive Assessments (T0–T4; n = 117)



Frequency parameters (see Table 4)

Agitation

Agitation/aggression was among the most prevalent NPS ranging from 20.5% to 29.1%. Consistent higher persistence (range: 52.9-62.4%) over resolution (range: 37.6-47.1%) combined with considerable incidence rate (range: 10.9-18.2%) increased its prevalence over time. More than one out of two residents developed agitation/aggression (53.8%).

Disinhibition, on the other hand, showed a consistent higher resolution (range: 63.2-90.4) over persistence (range: 9.6-33.6) combined with low incidence rate (range: 4.9-7.4%), prevalence (12.8-7.7%) declined. Irritability was most prevalent (range: 21.4-28.2%), showed the highest cumulative two-year prevalence (58.1%) and high cumulative incidence (41.7%). Its fluctuating point prevalence was indicated by different resolution (range: 43.9-62.4%) and persistence (range: 37.6-56.1%) percentages. Aberrant motor behaviour point prevalences fluctuated (range: 18.8-26.5%) and showed intermittent course over time due to different resolution (range: 36.8-58.1%) and persistence (range: 41.9-62.8%). One out of two residents developed aberrant motor behaviour (50.4%).

In this agitation cluster, aggression/agitation and irritability showed high cumulative incidence (41.9% resp. 41.7%) indicating that both NPS developed frequently in previously non-symptomatic residents.

Psychosis

Hallucinations and delusions were among the least prevalent NPS found (range: 1.7-5.1% resp. 4.3-9.4%). In fact, as were its cumulative prevalence (10.3%) and incidence (7.1%), hallucinations were the least prevalent on most assessments. As its point prevalence

remained in a narrow range (1.7-5.1%), and resolution and persistence were comparable at successive assessments at 50%, hallucinations showed the most consistency of all NPS studied. As the point prevalence ranged from 4.3-9.4%, delusions were slightly more prevalent. In addition, its resolution was higher (range: 63.8-88.2%) than persistence (range: 13.2-36.2%) indicating a variable and intermittent course, as was further evidenced by its cumulative two-year prevalence (21.4%) and incidence (13.2%).

Mood disorders

Depression point prevalence showed a gradual decline towards 3.4% due to increasing resolution up to 100% during successive intervals. However, more than one out of four residents developed depression as indicated by its cumulative two-year prevalence (26.5%).
Since resolution (range: 56.7-75.2%) was higher than persistence (range: 17.6-39.5%) at all intervals, anxiety point prevalence also declined gradually (17.1-3.4%). More than one out of three residents ultimately developed anxiety during the two-year period (37.6%).
Apathy was one of the two gradually increasing NPS (18.8-32.5%) but showed a variable course indicated by alternating different resolution (range: 45.2-64.0%) and persistence (36.0-54.8%) and by its incidence rate (range: 8.9-27.2%). More than one out of two residents developed apathy (53%). Apathy showed the highest cumulative incidence (42.1%) indicating that apathy developed frequently in previously non-apathic residents.

Euphoria was the second least prevalent NPS (range: 3.4-5.1%) as indicated by its low cumulative two-year prevalence (13.7%) and incidence (9.8%) due to its consistent higher resolution (range: 60.5-84.3%) over persistence (range: 17.6-39.5%) combined with low incidence rate (range: 2.7-4.5%).

Nighttime behaviour and eating changes

Nighttime behaviour showed a fluctuating course (prevalence range: 4.3-8.5%) and almost one out of four residents developed nighttime behaviour (23.1%). Eating change declined (range: 9.4-13.7%) as its resolution (range: 50-85.8%) remained higher than or equalled its persistence (range: 14.2-50.0%) even though the incidence rate was considerable (range: 2.9-11.8%).

Overall NPS

Point prevalence of any-NPS at the successive assessment remained considerable (range: 59.8-73.5%). Resolution (range: 67.5-80.3%) of any-NPS remained high as did persistence (range: 51.2-74.7%) combined with a considerable incidence (range: 37.6-57.5%) resulted in very high cumulative two-year prevalence (96.6%) and cumulative incidence (82.9%). Moreover, the presence of more than one CR-NPS was found on average in one out of four residents along the five assessments (range: 20.5-29.1%). These frequency parameters indicate high co-occurrence of NPS. When any two consecutive assessments were considered, agitation showed the highest persistence (29.1%) before apathy (28.2%), irritability (27.4%), and aberrant motor behaviour (25.6%). Persistence for any three consecutive assessments, agitation, irritability, and aberrant motor behaviour equalled at 14.5%. For any four consecutive assessments, agitation and aberrant motor behaviour persistence equalled at 8.5%. Asymptomatic residents typically showed new onset of apathy (42.1%), aggression/agitation (41.9%), irritability (41.7%), and aberrant motor behaviour (35.6%) at any successive assessment. Once present at baseline, two-year persistence for individual NPS is as follows: delusions 9%; irritability 9%; anxiety 10%; aberrant motor behaviour 11%; disinhibition 13%; agitation 17% and hallucination 25%.

Table 4 Frequency parameters of NPI symptoms (FxS≥4) in nursing home patients with dementia at successive assessments (T0-T4; prevalences on total group level; resolution, persistence, and incidence on subgroup level; *n=117*).

Symptoms	T_0	First interval			T_1	Second interval			T_2	Third interval			T_3	Fourth interval			T_4	Cum prev	Cum inci*
		Resolution[a]	Persistence[b]	Incidence[c]		Resolution[a]	Persistence[b]	Incidence[c]		Resolution[a]	Persistence[b]	Incidence[c]		Resolution[a]	Persistence[b]	Incidence[c]			
Delusions	**9.4**	63.8	36.2	2.9	**6.0**	71.7	28.3	5.4	**6.8**	87.5	12.5	5.5	**6.0**	71.7	28.3	2.8	**4.3**	21.4	13.2
Hallucination	**3.4**	50.0	50.0	1.8	**3.4**	75.0	25.0	2.7	**3.4**	50.0	50.0	0.0	**1.7**	50.0	50.0	4.3	**5.1**	10.3	7.1
Agitation	**20.5**	45.9	54.1	17.2	**24.8**	44.8	55.2	18.2	**27.4**	37.6	62.4	16.5	**29.1**	47.1	52.9	10.9	**23.1**	53.8	41.9
Depression	**8.5**	30.0	70.0	8.4	**13.7**	62.5	37.5	9.8	**13.7**	87.6	12.4	3.0	**4.3**	100	0.0	3.6	**3.4**	26.5	19.6
Anxiety	**17.1**	60.2	39.8	6.2	**12.0**	57.1	42.9	9.7	**13.7**	75.2	24.8	11.9	**13.7**	68.6	31.4	5.0	**8.5**	37.6	24.7
Euphoria	**4.3**	60.5	39.5	3.6	**5.1**	84.3	17.6	4.5	**5.1**	66.7	33.3	2.7	**4.3**	79.1	20.9	2.7	**3.4**	13.7	9.8
Apathy	**18.8**	45.2	54.8	13.7	**21.4**	64.0	36.0	17.4	**21.4**	48.1	51.9	27.2	**32.5**	60.6	39.4	8.9	**18.8**	53.0	42.1
Disinhibition	**12.8**	66.4	33.6	4.9	**8.5**	70.0	30.0	7.4	**9.4**	90.4	9.6	6.6	**6.8**	62.5	37.5	5.5	**7.7**	27.4	16.7
Irritability	**28.2**	48.6	51.4	9.5	**21.4**	48.1	51.9	20.6	**27.4**	62.4	37.6	15.3	**21.4**	43.9	56.1	14.1	**23.1**	58.1	41.7
Aberrant motor behaviour	**23.1**	37.0	63.0	15.6	**26.5**	41.9	58.1	15.1	**26.5**	58.1	41.9	10.5	**18.8**	41.0	59.0	9.5	**18.8**	50.4	35.6
Nighttime behaviour	**6.0**	43.3	56.7	1.8	**5.1**	50.0	50.0	6.3	**8.5**	100	0.0	4.7	**4.3**	79.1	20.9	8.0	**8.5**	23.1	18.2
Eating change	**13.7**	75.2	24.8	10.9	**12.8**	73.4	26.6	11.8	**13.7**	50.0	50.0	5.9	**12.0**	85.8	14.2	8.8	**9.4**	36.8	26.7
Any symptom	**67.5**	71.0	74.7	47.9	**68.4**	67.5	61.3	54.7	**70.1**	74.3	57.5	56.4	**73.5**	80.3	51.2	37.6	**59.8**	96.6	82.9

[a] The ratio of residents without CR-NPS at follow-up to residents with CR-NPS at previous assessment
[b] The ratio of residents with CR-NPS at follow-up to residents with CR-NPS at previous assessment.
[c] The ratio of residents with CR-NPS at follow-up to residents without CR-NPS at previous assessment
*: cumulative incidence: baseline: FxE<4 and any follow-up assessment: FxE≥4
NPI=Neuropsychiatric symptoms FxS=frequency times severity n=number CR=clinically relevant NPS=neuropsychiatric symptoms cum prev=cumulative prevalence cum inci=cumulative incidence T_0-T_4=successive assessment

Association between NPS and nosologic diagnosis

Point prevalence of any-NPS at successive assessments remained considerable for AD (range: 51.2-78.0%) as for VaD (range: 38.5-76.9%), see Table 5. Looking at individual NPS, slight differences in prevalences between AD and VaD occurred in mood disorders: for depression, a decrease in prevalences was observed in AD (12.2 to 2.4%) compared to a more constant course in VaD. On average, depression occurred more often in VaD, whereas anxiety and apathy occurred more often in AD. On the other hand, agitation, irritability and disinhibition were more frequent in VaD whereas aberrant motor behaviour was more frequent in AD. Similar results emerged from the analysis of severity scores (FxS≥0): disinhibition and irritability showed a significant difference in development over time between VaD and AD, see figure 2. On the other hand, total severity scores did not change significantly over time between AD and VaD.

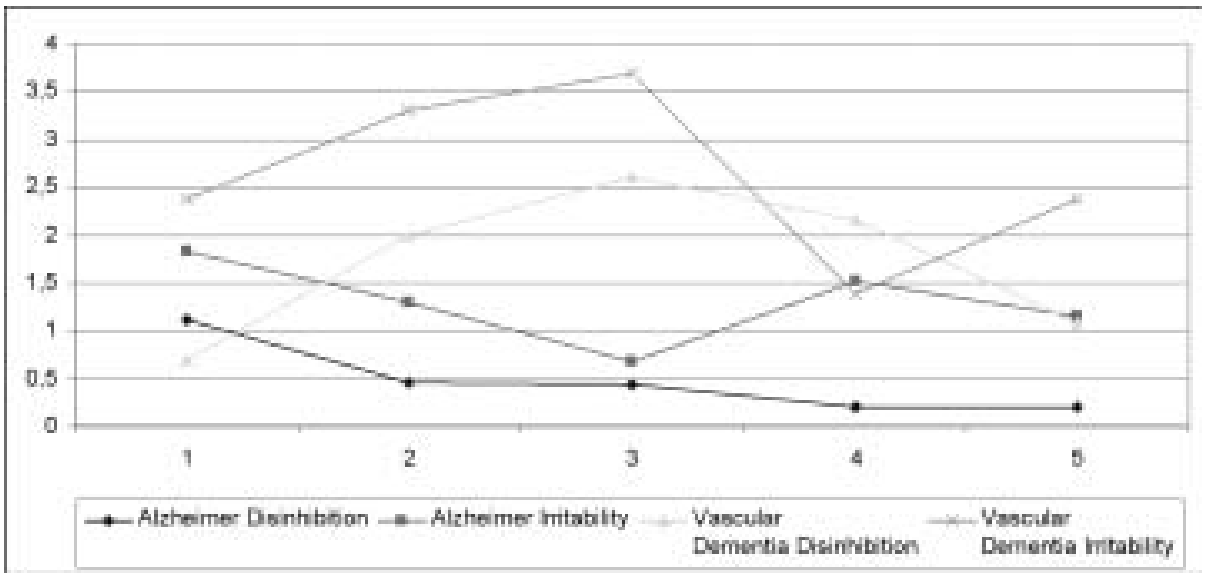
Table 5 Prevalences of NPI symptoms and severity scores at successive assessments (T0-T4) between AD and VaD.

Symptoms	**Prevalences NPI symptoms** (FxS≥4)										**Severity Scores** (FxS≥0; MANOVA for repeated measurements)										F
	Alzheimer's disease (*n=41*)					**Vascular dementia** (*n=13*)					**Alzheimer's disease** (*n=41*)					**Vascular dementia** (*n=13*)					
	T_0	**T_1**	**T_2**	**T_3**	**T_4**	**T_0**	**T_1**	**T_2**	**T_3**	**T_4**	**T_0**	**T_1**	**T_2**	**T_3**	**T_4**	**T_0**	**T_1**	**T_2**	**T_3**	**T_4**	
Delusions	7.3	4.9	9.8	4.9	4.9	0.0	7.7	0.0	7.7	7.7	.49	.49	.66	.29	.41	.00	.62	.08	.31	.69	NS
Hallucination	2.4	2.4	0.0	0.0	2.4	0.0	0.0	0.0	0.0	15.4	.24	.22	.00	.02	.22	.00	.08	.00	.23	1.15	NS
Agitation	9.8	14.6	17.1	19.5	9.8	23.1	38.5	38.5	23.1	46.2	1.07	1.05	1.20	1.54	1.02	1.38	3.23	3.46	2.15	3.46	NS
Depression	12.2	17.1	9.8	2.4	2.4	0.0	7.7	23.1	7.7	7.7	1.22	1.15	.80	.17	.20	.54	.69	1.69	.46	.54	NS
Anxiety	26.8	12.2	22.0	14.6	9.8	7.7	15.4	15.4	7.7	7.7	2.05	1.10	1.32	.93	.80	.62	1.46	1.23	.38	.92	NS
Euphoria	2.4	2.4	4.9	0.0	4.9	7.7	7.7	7.7	15.4	7.7	.20	.32	.37	.00	.34	.69	.69	.92	1.08	.77	NS
Apathy	22.0	19.5	24.4	29.3	9.8	7.7	23.1	15.4	15.4	7.7	1.95	1.78	2.46	2.73	1.15	1.15	1.31	1.23	.92	.92	NS
Disinhibition	14.6	2.4	2.4	2.4	2.4	7.7	23.1	30.8	30.8	15.4	1.12	.46	.44	.20	.20	.69	2.00	2.62	2.15	1.08	4.126 .006*
Irritability	24.4	12.2	9.8	17.1	14.6	23.1	38.5	46.2	15.4	30.8	1.83	1.29	.68	1.51	1.15	2.38	3.31	3.69	1.38	2.38	3.615 .012*
Aberrant motor behaviour	26.8	29.3	36.6	24.4	24.4	15.4	30.8	23.1	23.1	7.7	3.02	2.59	2.80	1.93	1.95	1.38	1.85	1.77	1.77	.92	NS
Nighttime behaviour	7.3	4.9	7.3	2.4	9.8	7.7	7.7	7.7	7.7	7.7	.83	.51	.56	.27	.71	1.00	1.15	.46	.46	.77	NS
Eating change	9.8	12.2	22.0	4.9	2.4	15.4	7.7	7.7	15.4	0.0	.90	1.02	1.54	.34	.15	1.38	.46	.62	1.38	.00	NS
Any symptom	73.2	70.7	78.0	70.7	51.2	38.5	61.5	69.2	76.9	53.8	14.93	11.98	12.83	9.93	8.29	11.23	16.85	17.77	12.69	13.62	NS

*<.05 NS= not significant MANOVA= repeated measures ANOVA using the multivariate approach

NPI=Neuropsychiatric symptoms AD=Alzheimer disease VaD=vascular dementia FxS=frequency times severity n=number T_0-T_4=successive assessment

FIGURE 2. Mean Severity Scores of NPI Items at Successive Assessments Between AD and VaD (T0–T4; AD: n = 41; VaD: n = 13)



Discussion

In this first study that examined the course of NPS in a large sample of nursing home residents with dementia over a two-year period, nearly all residents (96.6%) developed one of more clinically relevant NPS during the two-year follow-up period. Moreover, high co-occurrence of NPS was seen since any-NPS showed high persistence, resolution and incidence, and one out of four residents showed more than one NPS at any given assessment. Individual NPS showed specific frequency parameters with a high persistence for aggression and aberrant motor behaviour, and high resolution for depression. Residents without CR-NPS on baseline typically showed signs and symptoms of apathy, aggression/agitation, irritability, or aberrant motor behaviour during the two-years following their initial assessment. Residents with VaD showed more depression and agitated behaviours, whereas anxiety and apathy were more common in residents with AD. In addition, although their severity scores developed in similar patterns, VaD and AD showed a difference in development over time for irritability and disinhibition.

Depression initially showed the highest persistence of all NPS as has been seen in other studies [26,156]. Depression prevalence as well as severity scores, however, decreased subsequently over time, as found previously [84,152,157,158]. In line with other studies, aggression tended to increase in time [152,159]. If analyzing all assessments, on the other hand, aggression together with aberrant motor behaviour showed highest persistence, as is seen in an outpatient study [151]. In addition, Selbæk et al. also found highest persistence for agitation/aggression and irritability in residents with dementia in nursing homes [81]. Apathy two-year prevalences and severity scores showed an increase, although it did not reach statistical significance. Other studies have also found an increase in apathy prevalence in outpatients with dementia over time [9,160]. The divergent courses of depression and apathy contribute to the notion that these symptoms represent different entities. Overall, our longitudinal results contribute to a

growing body of results, indicating the emergence of, as dementia progresses, a preponderance of specific NPS at subsequent dementia stages [12,13,66].

In this study, attrition was high (55%) as might be expected in this very frail population, and comparable to previous findings [161]. This study sample, however, is typical of nursing home residents with dementia and the results found are believed to represent the course of NPS of treated and untreated residents.

Our results contribute to the notion that different types of dementia show different neuropsychiatric profiles; moreover, we have shown different courses of individual NPS across dementia type. AD and VaD have been found to have different levels in awareness [162], that can account for the differences found in our study. Higher levels of unawareness, which is related to apathy, is found in AD ; whereas higher level of awareness, related to depression, has been found in VaD [163]. These results, if confirmed in a larger resident sample, can have implications for current treatment options.

Recent new insights into the treatment of aggression/agitation challenge the widely used pharmacological interventions [30,164]. Since persistence of aggression/agitation is universally found, one might consider this to be an indication of irreversible changes in brain morphology or neurophysiology of residents with dementia. The emergence of aggression is influenced by complex hierarchical regulatory mechanisms involving diverse brain regions from primitive parts of the brain involved in the more basic aggressive drives to higher level regulators in specific brain structures, like amygdala, temporolimbic and prefrontal cortices involved in cognitive and affective components [165]. In advanced stages of dementia, the temporolimbic and prefrontal cortices are largely affected [166] and can result in disinhibition of aggression through diminished cognitive and/or affective control [165]. One can wonder if indeed pharmacological intervention can be regarded the best treatment option for persistent aggressive symptomatology given the limited benefit in longer-term therapy, potential side effects, and its negative impact on QoL [150]. Instead, as a first-line management strategy for agitation, psychological interventions, some of which have lasting effects in terms of months, and staff-training programs are increasingly recommended [30,164].

Strengths of this study are the long follow-up period, large resident's population, vigorous dementia diagnosis screening according to international accepted criteria, and the systematic assessment of NPS at five points in time. In addition, this prospective longitudinal study provides evidence for individual development of specific NPS.

This study has several critical points that limit generalisability. First, variations in course between two successive assessments is unknown and pertains to differences between discrete-time analysis v. continuous-time analysis [73]. Second, a gradual decrease in symptom severity can be due to the Hawthorne effect, as previously mentioned by Selbæk et al., since a limited intervention like our scheduled visits and interviews can influence the course of NPS in a positive way [81]. Indeed, to overcome an influential effect of the introduction of an assessment instrument, it is suggested that a stabilization phase for measurements prior to a planned trial should be installed [88], which was not included is this study. Third, no co morbidity or pain were considered in these analyses that could have triggered NPS [164] e.g. differentiating between foreground and background pattern of NPS.

Fourth, the analyses were performed in the cohort that ultimately survived two-years of follow-up. Results might have been biased due to loss-to-follow-up. In addition, due to multiple testing, an inflated type I error has occurred. Interpretation of results must be seen in light of this inflated type I error. Finally, psychotropic drug use (PDU) was not considered in the analysis. In this study, more than half of residents received any-PDU, possibly influencing the course or severity of NPS differently compared to the non-PDU group. On the other hand, previous studies question the influence of PDU on the actual course of NPS [81,83,167].

Our results, concluding, indicate the omnipresence of NPS in residents with dementia in nursing homes over time. Co-occurrence of NPS is high but individual NPS show specific courses and across dementia type. The insight of high cumulative incidences of several NPS can increase awareness and vigilance of the nursing staff for early recognition and diagnosis, and subsequent treatment. These results help clinicians to better understand the clinical course of NPS and in making treatment decisions of NPS. Data from longitudinal studies on NPS in residents with dementia, therefore, can contribute to and increase best principles of care e.g. support, delay of functional decline and of disability, control of symptoms, and maximization of quality of life [6]. In particular, our results will provide continuous support to and inform patient and caregiver on prognosis based on frequency parameters of individual NPS and patient's characteristics, and will further increase nursing staff vigilance. Moreover, these data can provide the individual resident with dementia with an individually tailored treatment approach. Future prospective studies, however, should observe for longer periods that cover the progression of dementia to the final stages.

Response to Volicer Letter. Wetzels RB, Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT Editor:

The letter by Dr. Volicer points toward an important shortcoming in the use of the NPI-NH, that "rejection of care" probing questions as part of the NPI "agitation/aggression" are mislabeled since agitation and rejection of care are probably different entities, since rejection of care could also be present in patients who are depressed. Although this does not seem to affect the construct validity of the NPI "agitation" cluster of symptoms like agitation, disinhibition, and irritability,1 or our results,2 we acknowledge the shortcoming as pointed out by Dr. Volicer and to start a discussion on this shortcoming is worthwhile and should be supported by researchers. Especially when studying the course of neuropsychiatric symptoms over time, the assessment instrument should be sensitive to change over time and the definitions used should be clearcut and unequivocal.3 This is important not only for researchers but also for clinicians to translate research into practice. We, therefore, greatly acknowledge this initiative and would like to broaden this discussion so rightly initiated by Dr. Volicer by pointing out that more neuropsychiatric symptoms in the NPI are mislabeled; for example, the definition of depression used by the NPI is also applicable when a resident is only crying. Or, eating change can be differentiated into an excessive eating (because of disinhibition) or a devoid of eating as can be seen with advanced stages of dementia. These two different clinical entities are falsely labeled under one and the same heading. This labeling of depression and eating change is questionable and merits further research into more applicable labeling of symptoms. Importantly, differences exist between the descriptive and explanatory level of labeling: hitting is hitting (descriptive), the reason why a person hits (explanatory) is something different. Rejection of care is a social/psychological explanation of overt behavior. Agitation, on the other hand, denotes both levels of labeling. Also important is that concepts used to describe psychiatric patients may not be equally useful in patients with dementia. So, in short, we greatly welcome the initiative by Dr. Volicer to start a discussion of the concepts used to describe neuropsychiatric symptoms in dementia, but more finetuning is required before a change in definition and a sure application of clinical research findings can be achieved.

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Am J Geriatr Psychiatry. 2011 Aug 27.
[Epub ahead of print]

Chapter 7

Prescribing pattern of psychotropic drugs in Nursing Homes Residents with Dementia

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Eerst verantwoordelijke verzorgende:

Probleem gedrag.

"….Moeilijk te zeggen wat ik probleem gedrag vind. Wanneer is het een probleem voor de cliënt?

Een cliënt blijkt met enige regelmaat 's avonds agressief te zijn tegen personeel en medecliënten. Zelf heb ik hier geen last van, wat het wel moeilijk maakt om mij in te leven in de situatie. Is het dan een probleem voor dhr. of zijn omgeving? Er is voldoende gedaan om benadering van dhr. duidelijk op papier te zetten,advies hoe met dhr. om te gaan en adviezen om in een bepaalde situatie te handelen. Toch blijkt dat dhr. af en toe nogal eens boos/agressief kan reageren. Nu is dit voor mij niet zo zeer probleem met de cliënt zijn probleemgedrag maar meer frustratie waarom blijft dit gebeuren.

Wat doet probleem gedrag met mij?

Voorbeeld: Dhr. X communiceert bijna niet met de verzorging, hij kijkt je aan maar zegt niets. Alleen aan zijn gezichtsuitdrukking maak ik op dat er iets moet zijn, maar ja wat????????

*Soms vind ik het dan moeilijk om erachter te komen wat er in zijn hoofd omgaat,vraag wel door in de hoop nog een antwoord te krijgen. Vaak verloopt de communicatie dan op dezelfde wijze: ik praat en stel vragen en krijg met een gebaar een kort ja of nee antwoord. Dit vind ik soms best moeilijk en zou wat meer verbaal contact willen, maar weet ook dat het er niet inzit bij dhr. Maar wanneer ik dan een glimlach of zelfs hartelijke lach krijg denk ik ,"*wat is nu eigenlijk het probleem *?" …"*

Abstract

Background: The goal of this study is to determine patterns of psychotropic drugs use (PDU), the association with neuropsychiatric symptoms (NPS), and the variability across dementia types in nursing home residents with dementia. In addition, PDU was analyzed across multiple indications.

Methods: Prospective cohort study over a two-year period from 2006 until 2008. Fourteen dementia special care units in nine nursing homes residing one hundred seventeen residents with dementia, of which 35% suffered from Alzheimer's dementia (AD); 11% of vascular dementia (VaD). PDU was classified according to anatomical therapeutic chemical-classification categorized as either "present" or "absent".

Results: The majority of residents had moderately severe to severe dementia. At all successive assessments, almost two-thirds of residents received any-PD and almost one-third continued to receive any-PD. Of all psychotropic drugs (PD), antipsychotics (AP) were prescribed most frequently. Fewer residents started with antidepressants, but continued to receive antidepressants at higher percentages. Anxiolytics showed an intermittent course, but a subgroup of 9% showed two-year continuation. Once started PD at baseline, residents continued to use PD at a high percentages: three-quarters continued to receive AP for at least six months. Half of residents received at least one PD; one-fifth received at least two PD's simultaneously. Residents with AD received more hypnotics and antidementia drugs; residents with VaD received more antipsychotics, antidepressants, anxiolytics and anticonvulsants.

Conclusions: PD differs among themselves with respect to utilization patterns, but overall, consistent high continuation rates were found. These results warrant scrutiny into the continuous use of PD.

Introduction

Neuropsychiatric symptoms (NPS) in dementia are highly prevalent in long-term care institutions [12,13], and have important clinical consequences such as lowered patients' quality of life, increased demands on staff resources, increase of job related stress, burnout and staff turnover. Furthermore, NPS can result in the application of physical restraints and in injury to staff, other patients and/or the patient self. There are five main clusters of NPS: agitation, psychosis, mood disorders, psychomotor agitation and apathy [15], of which agitation most frequently results in distress to patient and staff, often requiring intervention [168]. A clear need exists to treat NPS, either by psychosocial or by pharmacological interventions.

The pharmacological treatment of NPS consists of various psychotropic drugs (PD) [27,169-173], of which antipsychotics (AP) are the most frequently prescribed [13,27,68,174]. Other PD's such as antidepressants (ADP), anxiolytics (ANX), hypnotics (HYP), anticonvulsants (AC), and antidementia medication (ADM) drugs are also prescribed. Several studies, however, have shown that AP are often prescribed inappropriately [175] and, in the absence of approved agents, many physicians have turned to off-label use [13,68,174,176]. In addition, PD are prescribed as long-term treatment to a majority of nursing home residents, even beyond one-year duration [32,177] and, once started, frequently inadequately reviewed [28], contributing to over use of PD. Recent evidence has indicated that AP have a limited benefit in long-term therapy, and severe side effects such as stroke and increased mortality [30]. The US Food and Drug Administration [31] and the UK Committee for Safety of Medicine [178], therefore, issued serious safety warnings for the use of AP in elderly patients with dementia. Furthermore, a recent meta-analysis shows that the use of sedatives and HYP, ADP, and benzodiazepines demonstrate a significant association with falls in elderly individuals [179].

In the light of these recent safety and efficacy data, there is an urgent need to examine the nature, extent and patterns of psychotropic drug use (PDU) in nursing home residents with dementia. Insight into the use of PD may provide valuable information, and may further reflect to what extent clinicians actually apply guidelines [180]. After the recent safety warnings on PDU in nursing home residents with dementia, however, very few prospective longitudinal studies have been published [81,181-183], with mixed results. In addition, AP can be prescribed for psychosis but for several forms of agitation as well, e.g. multiple indications. Hence, additional studies are required to quantify PDU in nursing home residents with dementia. This study examined PDU in nursing home residents with dementia over a two-year period, the association with neuropsychiatric symptoms (NPS), and the variability across dementia types in nursing home residents with dementia and we hypothesized that PD show different patterns over time and across dementia subtypes, with high rates of 50% of persistence.

Methods

In this prospective closed cohort study, residents were enrolled from fourteen dementia special care units (SCU) from nine nursing homes in the Netherlands, which represent an average nursing home population. Residents' elderly care physicians, who are involved in the daily care of residents, systematically screened all residents for inclusion. Residents were considered for inclusion provided they: (1) met the Diagnostic and Statistical Manual of Mental Disorders fourth edition criteria for dementia [44]; (2) had no history of life-

threatening disease at the time of inclusion; and (3) had to reside in the nursing home for at least four weeks. Baseline data were collected in 2006. Residents had a two-year follow-up and all assessments were administered at baseline and subsequently during four biannual follow up visits.

Residents' characteristics

Data on age, gender, length of stay in the special care unit were recorded. An etiological diagnosis was established by the elderly care physicians using international accepted criteria [46,47] and the Dutch consensus guidelines [45] for AD, VaD, mixed AD/VaD or other diagnosis (including dementia not otherwise specified). The first author (RBW) independently checked the eligibility and diagnosis of all residents by examining the patient's clinical notes. When disagreement arose, consensus meetings were organized to ensure the inclusion of all residents who met the aforementioned criteria.

Assessment of psychotropic drug use (PDU)

Data on PDU on the day of assessment were retrieved from the patients' medical and pharmacist files. Drugs were classified using the Anatomical Therapeutic Chemical classification (ATC) [43] and grouped into antipsychotics (AP No5A…) anxiolytics (ANX N05B…), hypnotics (HYP N05C…), antidepressants (ADP N06A…), anticonvulsants (AC No3A…), anti-dementia drugs (ADM N06A…), and any psychotropic drugs. Dichotomous categories of either "present" or "absent" were used to quantify PDU; prescriptions for incidental use were discarded.

Assessment of cognition and dementia severity

Cognitive functioning was assessed with the Mini Mental State Examination (MMSE) [63] and the Severe Impairment Battery-short version (SIB-s) [62]. The SIB-s is a cognitive assessment instrument able to test cognition in individuals in the later stages of dementia. Scores range from 0 to 50 and higher scores denote better cognition. The SIB-s has been translated and validated in a large group of Dutch nursing home residents with dementia [184]. Severity of dementia was rated with the Global Deterioration Scale (GDS), which ranges from normal cognition (GDS stage one) to very severe cognitive decline (GDS stage seven) [61].

Assessment of NPS

NPS were assessed with the Neuropsychiatric Inventory–Nursing Home version (NPI-NH) [50,51]. The NPI-NH is developed to be used by professional caregivers in institutions and is valid and reliable when administered by trained nursing staff [52]. The NPI-NH is a structured interview that includes 12 NPS: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime disturbances and appetite/eating changes. Both the frequency (F) and severity (S) of each symptom are rated on a four-point (1–4) and three-point (1–3) Likert scale, respectively. A separate score can be calculated for each symptom by multiplying the frequency and severity scores (to obtain the FxS score); resulting values range from zero to 12 for each symptom. The addition of FxS scores reveals a total score that ranges from zero to 144. The NPI-NH has been translated and validated in the Dutch setting [53]. RBW or a research assistant interviewed all licensed vocational nurses, who have been specifically assigned to individual residents and observed symptoms during a two-week period prior to assessment.

Analysis

The outcome measures were frequency parameters: point prevalence (baseline, follow-up, and cumulative), discontinuation, continuation, and (cumulative) new onset of PDU specified as users and non-users of the ATC-groups. Clinically relevant NPS (CR-NPS) measured with the NPI-NH were defined by Frequency (F) x Severity (S) ≥4 score for each individual symptom. Subclinical NPS (SC-NPS) was defined as FxS≤3. Prevalence was defined as the proportion of residents with PDU at each assessment. The two-year cumulative prevalence was defined as the proportion of residents with PDU on at least one assessment over the two-year period. Discontinuation was defined as the proportion of residents who used PD at one assessment but not at the next assessment. PDU was defined as 'continuous' if it was present on at least two subsequent assessments. New use of PD was rated as the proportion of residents using PD at one assessment but not on the preceding assessment. The cumulative rate of new onset PDU was rated as the proportion of residents who did not use PD at baseline, but at any of the next assessments. Prevalences were presented as percentages of total group. Frequency parameters are presented as percentages on subgroup level. By definition, continuation and discontinuation add up to 100%. Utilization patterns of PD at successive assessments were calculated per dichotomized (0:SC-NPS or 1:CR-NPS) NPI symptom, e.g. 0: FxS≤3 and 1: FxS≥4. Multiple indications for AP were delusion, hallucinations, agitation, disinhibition, irritability and/or aberrant motor behaviour symptom. Multiple indications for ADP were depression and/or anxiety symptom. Combined indications for ANX were anxiety and/or agitation.

Statistical analysis was performed using the SPSS software, version 16 (SPSS 16.0.1 for Windows; SPSS Inc., Chicago, IL). Frequency parameters were calculated using SPSS macro syntax. The analysis was performed in the cohort that ultimately survived two-years of follow-up. To assess any possible bias due to loss-to-follow-up, differences between completers and non-completers were evaluated using Student's *t*-test or χ^2 test.

Ethical Considerations

This study was approved by the regional research ethics committee. The participants and/or their relatives and legal guardians were informed about the study and gave their written consent.

Results

Residents

Two hundred and ninety residents (99% of all eligible residents) were included in this prospective cohort study, of which 117 (40%) residents completed the two-year follow-up period (see Table I for participant's description). Residents in our study sample were of advanced age, mostly female, had in general low levels of educational attainment and 62% had advanced dementia (GDS 6 and 7). Thirty-five % of residents were diagnosed with Alzheimer's dementia (AD), only 11% had vascular dementia (VaD) and 1.7% with mixed AD/VaD. However, in 40% of cases the type of dementia was classified as "not otherwise specified", which indicated that multiple brain pathologies might have been present. The number of residents in this study declined through successive assessments to n= 223, 191, 153 and 117 at 6, 12, 18 and 24 months respectively due to death (n=159) or transfer to another SCU (n=14). Non-completers were, compared to completers, significantly more often females and were older at baseline, had higher NPI-NH total scores, higher apathy severity scores, and were prescribed hypnotics more often (see Table I). At baseline, 11.1% of the completers had

GDS4, 26.5% GDS5, 33.3% GDS 6, and 29.1% GDS7. At 24-months, percentages changed: GDS4: 6.4% GDS5: 13.6% GDS6: 40% GDS7: 40%, indicating significant progression in dementia stage ($\chi^2(9)=78.138$ p<.0001).

Table I Demographic and Clinical Characteristics at Baseline

	Residents with complete follow-up (*n*=117)	Residents with incomplete follow-up (*n*=173)	P
Age mean (SD)	81.7 (7.4)	85.0 (6.7)	0.001**
Female %	71.7	82.9	0.028*
Length of stay NH-SCU (SD)	2.77 (2.7)	2.62 (2.3)	0.607
Diagnosis %			
Alzheimer	35.0	45.7	
Vascular	11.1	7.4	
Mixed AD/VaD	1.7	3.7	
Other (including 'not otherwise specified')	52.1	43.2	
MMSE mn (SD)	7.6 (7.1)	6.8 (6.1)	0.333
SIB-s mn (SD)	27.1 (18.2)	25.1 (16.7)	0.372
GDS %			
4	11.1	2.9	0.007**
5	26.5	21.1	
6	33.3	48.5	
7	29.1	27.5	
NPI-symptoms			
Delusion	0.67	1.02	0.186
Hallucination	0.35	0.56	0.188
Agitation/aggression	1.79	2.36	0.145
Depression	0.97	1.39	0.134
Anxiety	1.33	1.51	0.595
Elation/euphoria	0.34	0.33	0.941
Apathy/indifference	1.90	3.29	0.004**
Disinhibition	1.03	1.21	0.580
Irritability/lability	2.42	2.23	0.642
Aberrant motor behaviour	2.07	2.38	0.512
Nighttime behaviour	.69	1.22	0.065
Eating change	1.04	1.66	0.069
NPI total	14.61	19.16	0.011*
Psychotropic drug use (%)			
antipsychotic	28.2%	35.3%	0.208
antidepressant	18.8%	28.9%	0.051
anxiolytic	18.8%	17.3%	0.750
hypnotic	6.8%	16.8%	0.013*
anticonvulsants	5.1%	5.8%	0.811
antidementia	3.4%	5.2%	0.471
any medication	57.3%	62.4%	0.378
Education %			
- primary	25.1	34.6	
- low vocational secondary	19.3	17.3	
- mid vocational secondary	8.2	9.9	
- high vocational secondary	3.4	0	
- university	0.5	1.2	
- missing values	43.5	37	

*<.05 **<.005 t= Student's t test χ^2= chi square test n=number yrs=years mn=mean rg=range MMSE=mini mental state examination (range: 0-30) SIB-s=severe impairment battery-short version (range: 0-50) SD=standard deviation GDS=global deterioration scale NH=nursing home NPI=neuropsychiatric inventory (range: 0-144) FxS=frequency times severity (range: 0-12).

Psychotropic drug use

Overall PDU

During the two-year follow-up, nearly two-thirds (66%) of residents were treated with any PD and almost one-third (31%) continued this treatment for two years (see Tables II and III). In addition, of all PD naive residents at baseline, about one-third (32%) started treatment during follow-up. Notably, more than half of the residents who were on PD at baseline continued to be so all along the follow-up. Half of the residents received at least one PD (range: 48-56%), whereas one-fifth (range: 18-24%) received at least two PD's.

Antipsychotics

AP were most often prescribed, with prevalences of 26-31% during consecutive assessments. Overall, 42% of residents received AP at baseline or during follow-up. One out of eight residents (12%) was treated with an AP during the entire follow-up. About one out of five AP-naive residents at baseline started AP treatment during follow-up. Of all residents entering the study who were on AP, 43% persisted to use AP during the whole follow-up.

Antidepressants

Twenty four percent of the residents were treated with ADP, and one out of eight continued to receive ADP through all four follow-up assessments, indicating that fewer residents started ADP compared to AP, but were treated more continuously (persistence range: 82-92%). Indeed, of all residents who used ADP at baseline, two-thirds continued usage during follow-up. Of ADP-naive residents at baseline, just one-sixteenth (6%) started treatment during follow-up.

Hypnotics

About one out of six residents (16%) were treated with HYP and only 3% continued these throughout the follow-up. Nevertheless, once prescribed at baseline, half the residents continued to receive HYP during follow-up. Ten percent of HYP-naive residents were treated at follow-up.

Anxiolytics

Residents received ANX slightly more frequent (range: 15-19%) than ADP but less persistently (range: 72-95%), indicating a slightly intermittent use. At the same time, 9% of residents continued to receive ANX through follow-up suggesting a subgroup of persistent users. Indeed, half the residents receiving ANX at baseline, continued to receive them along follow-up. Altogether, nearly three out of ten residents received ANX (30%). One-seventh (15%) of residents who were ANX-free at baseline, received new-onset ANX at follow-up.

Anticonvulsants

AC were seldom prescribed (3-5 %, cumulative use 6 % and cumulative new onset 0.9%). Those residents using AC at baseline continued often to do so, with a continuation rate of 67-100%. Indeed, two-thirds of residents receiving AC at baseline continued to receive them at all assessments.

Antidementia medication

ADM were rarely prescribed (range: 0-3%) or started (range: 0-2%) as can also be concluded from its cumulative use (4%) and cumulative new onset (1%). Residents remained for only a short period on ADM as discontinuation (range: 50-100%) was equal or higher than continuation (range: 0-50%).

Insert TABLES II

Table III PDU Continuation in Nursing Home Residents with Dementia over all Assessments (percentage on group level; *n=117*).

Medication	Continuation 24-months	Cumulative use	Cumulative new onset
Antipsychotic	12	41.9	19.0
Antidepressant	12.8	23.9	6.3
Hypnotic	3.4	16.2	10.1
Anxiolytic	9.4	29.9	14.6
Anticonvulsants	3.4	6.0	0.9
Antidementia	0.0	4.3	0.9
Any-psychotropic drug	30.8	65.8	31.6

N=number PDU=psychotropic drug use

Association between PDU and combined indications

Table IV shows utilization patterns of PD per dichotomized NPS. In addition, since PD can be prescribed for multiple indications, table IV shows PDU for multiple indications. This table indicates that a number of residents who show CR-NPS receive no PD, whereas a number of residents showing SC-NPS are treated with PD, please see the table IV.

Table IV PDU per multiple NPS at baseline (NPI-NH-scores FxS; *n=117*).

Psychotropic Drug Use for Neuropsychiatric Symptoms*		
Antipsychotic[1]	**nonuser**	**user**
0	77%	23%
1	67%	33%
Antidepressant[2]		
0	85%	15%
1	76%	24%
Anxiolytic[3]		
0	87%	13%
1	69%	31%

*0: FxS≤3 1: FxS≥4; percentages per dichotomy add up to 100% n=number PDU=psychotropic drug use NPS=neuropsychiatric symptom NPI-NH=neuropsychiatric inventory-nursing home edition FxS=frequency times severity

[1] symptom: either delusion, hallucinations, agitation, disinhibition, irritability and/or aberrant motor behaviour
[2] symptom: either depression, anxiety, delusion, hallucinations, and/or agitation,
[3] symptom: either anxiety and/or agitation

Association between PDU and etiological diagnosis

On average, residents with AD were prescribed more HYP and ADM, whereas residents with VaD received relatively more frequent AP, ADP, ANX and AC, see Table V. In addition, for any-PD, almost a different utilization pattern was found between: VaD receiving more PD than AD ($\chi^2(1)=3.713$ $p=.054$), see Table V.

Table V PDU per dementia subtype at successive assessments (prevalences on group level).

	Psychotropic drug use									
Psychotropic drug	**Alzheimer's disease** (*n=41*)					**Vascular dementia** (*n=13*)				
	T_0	**T_1**	**T_2**	**T_3**	**T_4**	**T_0**	**T_1**	**T_2**	**T_3**	**T_4**
Antipsychotic	29.3	26.8	22.0	31.7	24.4	30.8	30.8	38.5	38.5	38.5
Antidepressant	17.1	17.1	17.1	22.0	19.5	38.5	46.2	46.2	38.5	38.5
Hypnotic	2.4	4.9	12.2	12.2	9.8	0.0	7.7	0.0	0.0	0.0
Anxiolytic	14.6	17.1	12.2	12.2	14.6	30.8	23.1	23.1	30.8	30.8
Anticonvulsants	2.4	0.0	0.0	0.0	0.0	15.4	7.7	7.7	15.4	15.4
Antidementia	4.9	2.4	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0
Any-psychotropic drug	53.7	48.8	39.0	46.3	41.5	76.9	69.2	69.2	76.9	76.9

PDU=psychotropic drug use n=number

Discussion

This study examined the use of psychoactive medications in a large sample of nursing home residents with dementia after the FDA warnings for AP use in elderly people. We found that on average, PDU was highly prevalent and persistent in our study. No less than two out of every three residents were treated with PD at some stage during the two-year follow-up. Approximately one out of three residents was treated with any PD for 24-months continuously. Remarkably, the majority of residents with moderate to severe neuropsychiatric symptoms did not receive antipsychotic medications. This finding may suggest that residents were treated otherwise or did not receive treatment at all. Similarly, depressed residents were often not on antidepressants, indicating under treatment, vice versa, non-depressed residents were treated with ADP, possibly indicting over use. Different PDU was found across dementia diagnosis. Strengths of this study are the two-year follow-up period, homogeneous large resident sample, thorough dementia diagnosis used, and the systematic biannual assessments.

Our results are in line with previous reports. The high PDU at baseline was also found in other studies [12,32,170,173,185]. Kim et al. recruited residents for their study who were prone to exhibit NPS and found that ADP were prescribed most frequently followed by AP . Kamble et al. found AP prescribed in 33% of residents [27]. Pitkala et al. found that PDU and individual PD were prescribed in 42% of residents with heterogeneous cognitive disorders admitted to acute geriatric wards [172]. In this study, treatment with AP was discontinued in 20% of residents and some were on AP for two years. In Selbaek's study, discontinuation during one-year follow-up was 25% [81]. Notably, international guidelines state that an attempt should be made to discontinue or taper AP in nursing home residents with dementia with NPS [180]. Though depression prevalence and severity scores declined over time [186], no discontinuation of ADP was observed. This could be caused by the reason that ADP are prescribed not only

for depression but for other indications as well, e.g. for aggression or psychosis [187]. In this study, a dissociation between symptoms and ADP prescriptions remained even after we adjusted for multiple indications (Table 5), suggesting ADP over use. Even though anxiety prevalence and severity scores decline over time [186], ANX remained frequently prescribed. Dutch guidelines on NPS in nursing home residents with dementia state that ANX should only be prescribed for a short period [188]. In contrast to our results, Selbæk et al. [81] found higher percentages for ADM. His study, however, involved a substantial number of residents with mild dementia, who might respond better to cognitive enhancers than our sample of resident with more advanced dementia. Recent studies, however, found a positive impact of memantine on NPS in moderately severe to severe dementia [189]. As has been stated in an earlier study, ADM are not prescribed frequently in Dutch nursing homes [190], unawareness of recent effect studies on ADM and NPS might account for this discrepancy. At the same time, according to our study, NPS show both under and over use of PDU, as has been found in a previous study [28]. In their review, Furniss et al. concluded that nursing home residents with dementia are prescribed more PD than patients living at home [28], suggesting that nursing home residents are prone to PD over use. These results suggest that efforts to screen residents for inadequate PDU should be undertaken.

In this study, as has been seen in an earlier study [191], different prescription patterns were observed for AD and VaD. This can be explained by different NPS profiles between AD and VaD; since residents with VaD show more depression and agitation and patients with AD more anxiety and apathy [191]. The use of AC in VaD might be related to emergence of post-stroke epilepsy. Even though a large proportion of residents had a diagnosis dementia not otherwise specified, these results contributes to the growing evidence that different types of dementia are associated with different profiles of psychotropic drug use.

Prolonged treatment with PD was highly prevalent. Regardless of recent safety warnings, PDU remains high [183]. Some debate exists on which factors are associated with PD prescription. PDU is associated with NPS [13,68,174]. Another explanation is that nursing staff or physicians inadequately review medication on a regular basis and therefore are unaware of the ongoing pharmacological treatment [28]. Intriguingly, the presence of NPS has not been found to be an independent predictor for PDU [170]. Indeed, that study showed a negative relationship between nursing staffing and PDU, suggesting that PDU was used as a substitute for the nursing staff. Furthermore, Kamble et al. found that larger facility bed capacity was significantly associated with less use of atypical AP [27], and Chen et al. found, after adjusting for potential clinical indications, a culture of prescribing of AP to be more related to the nursing home instead of related to the resident with dementia [192]. Indeed, one study suggests that residents were treated for the sake of nursing staff [174]. Recent insight into motivational and attitudinal commitment of nursing staff into working with residents with AD and agitation might contribute to the aforementioned arguments [193,194]. Staff has little motivation [194], report a sense of helplessness or report a preference towards not working with residents with AD and agitation [193]. Moreover, staff can be in disagreement with the views of evidence based practices for the management of Alzheimer's disease and agitation [193] or even be unaware of recent thinking about dementia care [194]. As reported by nursing home physicians, the use of nonpharmacological methods is limited due to staff requests for medication and insufficient resources [195]. Overall, our results suggest that PD are often used in the absence of NPS, that many residents with CR-NPS do not get pharmacological treatment, and that many others are treated with these medications for 6 months or up to two-years. The emerging picture from all this is alarming and has far-reaching implications that warrant replication.

Some limitations of this study need to be discussed. First, biannual assessments do not measure what happens in between, thereby possibly biasing results. Our study, however, extends current knowledge with the use of biannual assessments. Secondly, no medication dosages were used, or 'as needed' medications were registered. In addition, several potentially relevant drugs were not monitored in this study, e.g. beta-adrenergic receptor blockers can be used for the treatment of agitation [196]. Neither does it take into account a combination of drugs from the same group. However, our study examined six subgroups of PDU illustrating high persistence and over use as well as under use. In addition, no multivariate analysis was performed to examine factors associated with psychotropic, antipsychotic, or antidepressant use to account for the level of NPS, gender or etiology. Also, future studies should involve an analysis of PDU per SCU corrected for confounders (level of NPS, dementia diagnosis). Finally, the analyses were performed in the cohort that ultimately survived two-years of follow-up. Results might have been biased due to loss-to-follow-up.

Previous studies suggest that antipsychotics are effective in the short term as are antidepressants, anxiolytics, and anti-dementia medications. The effect size is small but real. This must be taken into account in the risk benefit discussion of initiating and continuing therapy. However, great efforts should be taken to carefully monitor pharmacological interventions in nursing home residents with dementia, especially in long-term treatment. PD do not change the course of NPS [81,83], combined with our results of high persistent PDU seriously stress (re)evaluation of pharmacological intervention. A first-line management strategy for agitation, psychological interventions and staff-training programs are increasingly recommended, some of which are efficacious [197]. When nonpharmacologic approaches have failed to adequately control NPS, prudent PDU can be considered and should involve carefully targeted prescribing, given for short periods of time (up to three months), and reserved for severe and distressing symptoms [169]. In addition, constant monitoring should be applied toward dose reduction or discontinuation, and for drug-drug interactions. Due to the multicausality origin of NPS, a multidisciplinary approach (e.g. geriatric psychologist, occupational therapist and well trained and well educated, specialized nursing staff) can help optimize care and symptom management. To increase the quality of prescribing and lower potential serious side effects, it has also been suggested to periodically involve pharmacists in the management of PDU in elderly residents; they can improve resident care and be cost-effective [28].

In conclusion, our study is the first examining the two-year utilization pattern of PDU in nursing home residents with dementia after the safety warnings. Efficacious drugs with potential harmful side effects were often prescribed for prolonged periods to those who are considered amongst the frailest of elderly persons. Importantly, physicians working in nursing homes should understand that residents, family and nursing staff are advised about the best treatment strategies available. Notably, they should put a great effort in regular monitoring the use of these drugs in residents with dementia, to discontinue drugs whenever possible; ultimately, in order to provide high-quality of care and improve mental health care for demented nursing home residents. Our results warrant more research to understand why these medications are prescribed and continued.

Table II PDU in Nursing Home Residents with Dementia (prevalences on total group level; discontinuation, continuation, and new onset on subgroup level; *n=117*).

Medication	T_0	First interval			T_1	Second interval			T_2	Third interval			T_3	Fourth interval			T_4
		Dis Continuation[a]	Continuation[b]	New onset[c]		Dis continuation[a]	Continuation[b]	New onset[c]		Dis continuation[a]	Continuation[b]	New onset[c]		Dis continuation[a]	Continuation[b]	New onset[c]	
Antipsychotic	**28.2**	15.2	84.8	7.1	**29.1**	17.6	82.4	2.4	**25.6**	20.0	80.0	9.1	**30.8**	22.2	77.8	3.8	**26.5**
Antidepressant	**18.8**	9.0	91.0	3.2	**19.7**	17.4	82.6	1.1	**17.1**	9.9	90.1	5.2	**20.5**	8.3	91.7	1.1	**19.7**
Hypnotic	**6.8**	25.0	75.0	2.8	**7.7**	11.7	88.3	4.7	**11.1**	15.3	84.7	1.9	**11.1**	38.7	61.3	1.9	**8.5**
Anxiolytic	**18.8**	22.7	77.3	3.2	**17.1**	25.1	74.9	3.1	**15.4**	27.9	72.1	7.1	**17.1**	5.3	94.7	2.1	**17.9**
Anticonvulsants	**5.1**	33.3	66.7	0.0	**3.4**	0.0	100	2.7	**3.4**	0.0	100	0.9	**4.3**	0.0	100	0.0	**4.3**
Antidementia	**3.4**	50.0	50.0	0.0	**1.7**	100	0.0	0.0	**0.0**	0.0	0.0	0.9	**0.9**	100	0.0	1.7	**1.7**
Any-PD	**57.3**	25.7	81.9	29.4	**53.8**	25.5	84.2	20.3	**47.9**	21.5	91	37.8	**53.0**	20.9	90.4	14.5	**52.1**

T0-T4: successive assessments

[a] The ratio of residents without PDU at follow-up to residents with PDU at previous assessment.

[b] The ratio of residents with PDU at follow-up to residents with PDU at previous assessment.

[c] The ratio of residents with PDU at follow-up to residents without PDU at previous assessment.

N=number PDU=psychotropic drug use PD=psychotropic drug

General discussion

Introduction

This chapter summarizes the main findings of this thesis by addressing the research questions. Some methodological issues of the Waalbed-II study are discussed, followed by implications for daily clinical practice. This chapter ends with suggestions for future reseach and a general conclusion.

Summary of main findings.

1. *What is the course of NPS people with dementia residing in long-term care facilities?*

In this two-year observational study, it is found that the course of NPS is heterogenous (chapter 7) but some general conclusions can be delineated. Individual symptoms show more or less characteristic courses. Over time, prevalence of overall-NPS remained considerable and constant (59,8-73,5%) across T_0-T_4-assessments; the cumulative prevalence over 2-year is nearly 97%, indicating that NPS are ubiquitous and probably universal for every patient at some point during the course of the disease. Prevalence of more than one NPS-symptom in one patient was also high (20,5-29,1%). In terms of severity scores (NPI-NH FXS), the total NPS-symptomatology showed a decrease over time (chapter 7), and for depression and anxiety specifically. Affective symptoms show a tendency to decrease over time (chapter 3 and 7), whereas agitation/aggression did show a course of constant prevalence-rate or tended to increase over time in terms of severity scores. Rates of psychosis remained stable over time, prevalences showed a stable tendency indicating a constant level of psychosis symptomatology with similar rates of resolutions and new onset. The most persistent over the 2-year observation period were agitation and hallucinations, although less prevalent. Differences between AD and VaD have been found; apathy and anxiety were more prevalent in AD, whereas depression and aggression were more prevalent in VaD. These data contribute to the notion that biological factors (e.g. different types of dementia) are the cause of different patterns of NPS.

Our review is the first systematic review on the longitudinal course of NPS in residents with dementia in long-term care institutions. Of the 18 included studies in this review, after extracting frequency parameters, prevalences were found for a broad range of NPS. We found that aberrant motor behaviour, depression, anxiety, and euphoria showed decline over time, but psychosis remained constant, as in our study. Although the prevalences can differ slightly, the courses over time somewhat show a similar picture: behavioural symptoms, especially agitation and aggression, remain constant or increase, affective symptoms decrease, and psychosis tend to persist. However, different definition, classification and assessments instruments make comparison between studies difficult (chapter 3).

2. *What is the validity of Severe Impairment Battery-short version in a sample of nursing home residents with dementia?*

Using the baseline, crosse-sectional data of both the MMSE and the SIB-s, low scores on total SIB-S were associated with cognitive impairment as measured with the MMSE (Spearman rho = .91, p<.001) and with functional dependency as measured with total ADL scale (Spearman rho = -.61, P<.001). Cognitive impairment was associated with dementia severity as evidenced by lower SIB-s scores in GDS stage 7 compared to GDS 6, and in GDS 6 compared to GDS 4-5. Diagnostic accuracy of SIB-S as measured with the Receiver

Operating Characteristic-curve was modest for mild to moderate stages of dementia, and it increased importantly for moderate to very severe stages. SIB-s total scores differentiated between dementia severity as measured with the GDS (F=164.6 df: 3,260, P<.001). These data provide evidence to the concept of concurrent validity. Three principal components were found that explained 67.4% of score variance: first factor which was called 'Aphasia-Agnosia'; the second factor called 'Apraxia', and the third factor was called 'Episodic memory'. Notably, the first factor explains more than half of common variance. Internal consistency of the SIB-s was very high (Cronbach's alpha=.97). These data provide evidence to the concept of construct validity.
Overall these data indicate that the SIB-s is a homogeneous, unidimensional and valid measure of cognitive impairment, particularly semantic memory loss. This short scale is easy to administer and can be used to assess moderate to severely residents with dementia who may find it difficult to complete the traditional, lengthier neuropsychological tests.

3. *What are determinants of Quality of Life in residents with dementia in nursing homes?*

In this study, using multivariate linear regression models, NPS, cognition and PDU were found to be significant contributors to QoL in residents with dementia in nursing homes and explained almost 50% of the total variance. Instead of individual symptoms, NPS were studied as part of the factor structure previously found and the factors agitation and depression explained particularly a large proportions of the variance of poor QoL. These associations were stronger in residents with mild to moderately severe dementia than in those with severe dementia. In the latter residents, NPS psychosis is also a strong predictor.

4. *What are prescriptions patterns of psychotropic drugs over 2-year period?*

At all successive assessments, almost two-thirds of residents received any-PD and almost one-third continued to receive any-PD over 2-year period. Of all psychotropic drugs (PD), antipsychotics (AP) were prescribed most frequently and 1 out 8 residents continued to receive AP over 2-year period. Fewer residents started with antidepressants, but continued to receive antidepressants at higher percentages. Anxiolytics showed an intermittent course, but a subgroup of 9% showed two-year continuation. Once started PD at baseline, residents continued to use PD at a high percentages: three-quarters continued to receive AP for at least six months. Half of residents received at least one PD; one-fifth received at least two PD's simultaneously. Similarly, depressed residents were often not on antidepressants, indicating under treatment, vice versa, non-depressed residents were treated with ADP, possibly indicting over use. Though depression prevalence and severity scores declined over time, no discontinuation of ADP was observed. This could be caused by the reason that ADP are prescribed not only for depression but for other indications as well, e.g. for aggression or psychosis. In this study, dissociation between symptoms and ADP prescriptions remained even after adjusting for multiple indications, suggesting ADP over use. Even though anxiety prevalence and severity scores decline over time, ANX remained frequently prescribed also possibly indicating overuse. Residents with AD received more hypnotics and antidementia drugs; residents with VaD received more antipsychotics, antidepressants, anxiolytics and anticonvulsants.

Methodological issues

Assessment instruments

This study used many assessments instruments that have been used before in previous research, but several comments can be made. First, to insure a valid interview using the NPI-NH and to overcome interpretation differences, we first engaged in an introduction period on one SCU to ensure familiarity of the researchers with the use of the NPI-NH. After this introduction period, it was found that certified nursing assistant (CNA) can easily work with this instrument in an interview setting. However, it is mandatory in a longitudinal study to interview the same CNA at each assessment to secure the least variance, since it has been established that the reliability of NPI-NH is only modest [198]. This raises serious questions about the sensitivity to measure change of assessments instruments used in prospective studies on the course of NPS. In our studies, efforts were taken to ensure the same CNA to be interviewed on each assessment. This was, however, not practically feasible and might have contributed to less reliable results. Second, the NPI-NH is a broad neuropsychiatric assessment instrument. The advantage of the NPI-NH is just this broad range of NPS studied. A disadvantage of the NP-NH is that it assesses not all potential NPS: sexual problems [199] are not assessed nor selfinjurious behaviour [200], nor loneliness or boredom. Moreover, individual NPS like depressive symptoms can be observed in a patient when he only cries occasionally. Possibly, the prevalence of depressive symptoms is overestimated. Eating change, as another example, can denote two different underlying subsyndromes: the anorexia induced in a final phase of dementia versus the disinhibited eating changes seen in for example frontotemporal dementia. In addition, agitation/aggression can be misinterpreted when in fact resisteance to care evoked the behaviour. It is obvious that different NPS should be demarcated from eachother although concepts might be similar, as has been studied in wandering and physically non-aggressive behaviour [201]. Additionally, another aspect needs to be discussed in the use of the NPI-NH. In the literature, a cutoff score of FXS $\geq$4 is used almost universally indicating clinically significant behaviour [52,173]. This cutoff point favors frequency (Likert scale 1-4) and severity (Likert scale 1-3) not equally possibly giving raise to skewed clinically relevant behaviour.

A need therefore exists to further delineate and redefine behaviours sharply and gain international consensus in order to provide a pivotal platform on which researchers from all over the world can draw upon.

QUALIDEM is a dementia specific QoL questionnaire rated by professional caregivers in residential settings. During the development of this questionnaire, a solid theoretical framework (the adaptation-coping model) was chosen to use as a background upon which the 40-items were defined, resulting in the "evaluation of the multidimensions of the person-environment system of the individual, in terms of adaptation to the perceived consequences of dementia" [58,202]. The QUALIDEM requires residents with advanced stages of dementia (GDS7) are observed on only 18 items instead of the 40 items. This lowers the pratical use of the QUALIDEM. There is only one interview sheet for all residents with dementia and all items can be rated by the CNA and lead to confusion. Also, during data-analysis, this split rating system causes residents with advanced stages of dementia to be analysed separately.

During the interview with certified nursing assistant, it remained difficult to rate residents in the advanced stage of dementia on some of the remaining 18 items. This might have contributed to less reliable answers, QoL profiles and QoL total scores. The QUALIDEM found similar QOL scores among different types of dementia. Our study population was either too small to find differences, or the QUALIDEM is indeed not able to assess difference in QoL between different types of dementia.

Implications for researchers

Assessment of cognitive function

In most dementia studies, cognitive function is assessed with the MMSE including in drug trials dealing with patients in more advanced stage of dementia. With the results of our study, showing that the SIB-s is a valid and reliable assessment instrument to tap cognitive function into more advanced stages of dementia with less floor effects than the MMSE, more avenues to assess cognition in dementia patients are available to researchers. Particularly, the SIB-s does not exclude the use of the MMSE but rather complete the spectrum of cognitive assessments instruments capable of tapping cognitive function along all stages of dementia. Nonetheless, further studies with longitudinal data should evaluate the validity and reliability of SIB-s changes scores.

Biopsychosocial nature of NPS

According to the biopsychosocial model [203], all aspects of personal living of nursing home residents with dementia can be taken into account in the emergence of disease, like NPS. So far, several symptoms have been unraveled, like depression, psychosis and sleep disturbances in AD, in which neurobiological correlates have been found [204]. And there is preliminary data suggesting an association between morning cortisol and NPS in patients in nursing home residents with dementia, potentially indicating a possible neuroendocrine basis involving the hypthalamuspituaryadrenal-axis dysregulation [205]. Our data contribute to the biopsychosocial nature of NPS. The differences found between AD and VaD, not only the symptomatology profile but also the different courses over time of several symptoms, give raise to this idea.
Topics not covered in this study, but still relevant are: weight loss [206], diet (vit. D [207,208], omega-FFA [209], apple juice [210]), genetic polymorphism (Apo-E [211], of 5-HHT/glutamate [212]), premorbid personality [213,214], melatonine shortage and light exposure [147], sensory impairment/deprivation (hearing [215], seeing, expression), pain [216,217] (osteoporosis, oral hygiene [218]), physical activities/involvement and environment [194]. This summary is still incomplete but points toward the complex nature of NPS.
In addition, pain and NPS, especially depression and anxiety, are closely related [219]. Apart from the impact of pain on NPS, one can also imagine that itch, dizziness of dental hygiene can evoke NPS. Still, there is a lot of work to be done when it comes to the course of NPS regarding definition, assessment, reliable and valid interpretation of differences, interplay with patients' characteristics like severity of dementia, comorbidity and interplay with the patients' surroudings.

Implications of elderly care physicians

The main goal of the treatment initiated by the elderly care physician is to reduce suffering and disability in order to increase quality of life and quality of care. In the assessment of NPS, the elderly care physicians should examine the resident thoroughly and exclude for example delirium [188], and recommendations on the use of different assessments intruments for a comprehensive assessment of depression and behavioural problems have been formulated [220]. Individual symptoms show heterogeneous course and some NPS, like agitated behaviours are particularly persistent. A clear need exists to treat these behaviours and the

elderly care physicians should make an individually tailored approach, weighing all interventions options given the unique aspects of the individual residents and their situations.
NPS, especially agitation and depression, lower QoL. This finding alone urges the elderly care physician to treat NPS and, if possible, with non-pharmacological interventions. Pharmacological treatment, on the other hand, should only be reserved for severe cases when an immediate interventions is required [169].
PDU is high and persistent. These results suggest that efforts to screen residents for inadequate PDU should be undertaken. In addition, constant monitoring should be applied toward dose reduction and/or discontinuation, and for drug-drug interactions. As has been proven in the DART-AD study, psychotropic medications can be stopped without increasing NPS [137]. Once started, AP should only be prescribed for a maximum of up to 12 weeks [69].
Intriguenly, the low prescriptions rates of ADM can indicate ignorance about the additional pharmacological treatment options to treat NPS. Our study is the second study to find the impact of PDU on QoL. This impact was, however, a group effect and was not found for individual psychotropic drugs. These findings additionally warrant continuous scrutiny into lower or stopping of psychotropic medications.
In contrast to previous studies, QoL was equall among different types of dementia. Additional studies are needed to these results. Moreover, longitudinal data will provide more details information on the development of QoL among different types of dementia.
Non-pharmacological interventions, like psychosocial interventions, should be the first step of treatment [30]. The spectrum of psychosocial interventions is broad and evidence of their efficacy is lacking although some interventions are effective in reducing NPS [146,197,221]. These interventions, however, are time consuming, and require implementation and commitment of the staff to change opinions and consequent personal behaviour. Recent studies, however, on staff motivation report a sense of helplessness [194] or a preference for not working with residents with AD and agitation [193] or disagree with the views of evidence-based practices for the management of AD and agitation [193] or even be unaware of recent thinking about dementia care. Moreover, as reported by nursing home physicians, the use of non-pharmacological methods is limited due to staff requests for medication and insufficient resources [195]. These aspects hamper unequivocal introduction of the psychosocial interventions, although these interventions emerge as a useful, versatile and potentially cost-effective approach to improve outcomes and QoL for both patient with dementia and its caregiver [222]. Consequently, the management staff and/or policy makers is/are to take efforts into promoting the implementation of psychosocial interventions.
Owing to the the aforementioned arguments, and the multi-causal biopsychosocial origins of NPS, a multidisciplinary approach (e.g. geriatric psychologist, occupational therapist and well-trained and well-educated, specialized nursing staff) need to evaluate NPS and help optimize care and symptom management.
Overall, elderly care is complex. But with a multidisciplinary team approach to treatment, vigilance toward lowering or stopping of PDU, implementation of psychosocial interventions, better mental health care can be obtained for our elderly residents in nursing homes.

Implications for nursing staff

Nursing a person with dementia in a ward setting can be stressful and a challenge for staff and patients alike. Caregivers do play an important role in the onset of aggression with the quality of the patient-caregiver relationship ("mutuality" [223]), including the frequency of communication, positive engaging interactions, attachment, and emotional support. Therefore, a key role in the interplay between NPS and treatment is reserved for the nursing staff. For example, communication with patients with dementia can be challenging and it has been

shown that nursing staff can improve their communication with residents with dementia and possiby improve the quality of care [224]. In addition, attitudes towards the resident with dementia and NPS can have great influence on hope and person-centred attitudes [225]. Motivational and attitudinal commitment of nursing staff into working with residents with AD and agitation have been studied [193,194]. Staff has little motivation [194], report a sense of helplessness or report a preference towards not working with residents with AD and agitation [193]. Moreover, staff can be in disagreement with the views of evidence based practices for the management of AD and agitation [193] or even be unaware of recent thinking about dementia care [194]. As reported by eldely care physician, the use of nonpharmacological methods is limited due to staff requests for medication and insufficient resources [195]. Instead of pharmacological intervention, nonpharmacological intervention should be used as first-line treatment and should be tailored targeted toward the resident with agitation [164,169]. Some psychosocial intervention, like behavioural management techniques, cognitive stimulation and physical exercise have been proven to be effective in reducing NPS and is recommended to use care plans to improve quality of care and quality of life [221]. Knowledge translation has been mentioned as a bridge for the gap between knowledge obtained in dementia research and the practical use of it [226]. Indeed, nursing staff are identified as requiring a specific training program, since they form part of the front-line workforce and yet have the least access to training but often most contact with residents [227]. Person-centred care and dementia-care mapping are examples of interventions that proved to be valuable in the reduction of aggression [228]. The results of DCM can change the way the person with dementia experiences care and support, while also assessing the staff who deliver that care and identifying staff training needs.

A need, herefore, exists to approach the resident with NPS using a spectrum of interventions in which the nursing staff plays a pivotal role. These interventions should involve a multidisciplinairy team including eldely care physician, geriatric psychologist, occupational therapist and well trained and well educated, specialized nursing staff. Basically, this multidisciplinairy approach can help expert symptom management and optimize care, and increase family satisfaction with care.

Implications for geriatric psychologists

A major role is expected from the geriatric psychologist. As a member of the multidisciplinairy team, the geriatric psychologist should take the lead in assessing and evaluating the nature of the NPS, the interaction of nursing staff with the resident and advise the elderly care physician and the nursing staff on how to proceed and give support and guidance.

The assessment should be thorough and should include an assessment the patients' psychosocial environment, the interaction of the nursing staff as well an assessment of the resident's premorbid personality. In the literature, a positive relationship was found between pre-morbid personality and behaviour [213,229,230]. Indeed, testing of the premorbid personality should be normal routine if NPS are persistent of difficult to manage. Furthermore, family members should also be considered to participate in the evaluation of NPS, since the patients is best known by these familiy members.

The geriatric psychologist is the first to engage psychosocial intervention after the assessment what is the best intervention for resident at hand. The geriatric psychologist should take into account the theories formulated for the explanation of behaviour in dementia, like the adaptation-coping model [202], the unmet needs model [231], the progressive lowered stress model [232] and the comprehensive process model of engagement of persons with dementia [233].

Implications for nursing home management

In light of the increasing costs of institutionalized residents with dementia, an urgent need exists to develop best practises. A clear ambition, therefore, exists to educate personnel involved in the management of NPS. Furthermore, better organization of workprocesses can help manage NPS. A multidisciplinary team approach should take the lead in the treatment of NPS. This requires commitment from the management staff to provide funds and time [226].
Apart from increased psychosocial interventions as mentioned earlier, education on drug efficacy and safety [234-236] and medication review [237,238] are also effective strategies to lower psychotropic drug prescription in long-term care. The implementation of education on drug efficacy and medication review are part of organization of workprocesses.
Besides well-educated personnel, the management staff should also provide adequate housing for residents with dementia. Recent findings indicate that physical surroundings also influence the emergence of NPS and that buildings are not constructed for residents with dementia [194]. This should include specific design features including high levels of visual access, highly visible and signed toilet doors, increased lighting, age appropriate fixtures and fittings, and individualized personal space. Design guidelines for long term environments for people with dementia are formulated based on sufficient evidence [239]. Of particular interest, is the recent discussion on small-scale housing for residents with dementia. Policy makers believe that this sort of housing is a panacea for NPS. Recent results, however, show no particular benefit [42].

Suggestions for future research

There is still a lot of research to be done on neuropsychiatric symptoms. First, the definition, classification and conceptual issues of NPS can be evaluated further and consensus established. Furthermore, factors in the emergence of NPS should be further clarified. The differences found in course of NPS and prescription pattern in psychotropic drugs in different types in dementia in this thesis should be confirmed in (larger) studies. Also, differences were found in this thesis between AD and VaD, but other types of dementia should also be investigated (e.g. mix AD/VaD, frontotemporal dementia, Parkinson's disease dementia and Lewy Body Dementia). The challenge now is to delineate further the contribution of individual factors in the emergence of NPS, not only patient characteristics' but psychological (types of nursing styles) and social (environmental) factors as well. In addition, factors that are related to persistence of NPS need to be studied. The interplay between NPS, QoL, PDU and cognition can contribute on this interplay. The complex interaction of the factors of the biopsychosocial warrents further research in residents with dementia in nursing homes. Factors that influence this interaction are further studied in a longitudinal randomized trial on the factors associated with the prescription of psychotropic drugs ('Priority medicine-study'), currently conducted in Nijmegen, the Netherlands. Apart from the factors influencing the emergence of NPS, the interaction needs to be established of cognition, PDU, NPS and QoL over time. Since these factors influence each other, studies aimed at the interplay of these factors might contribute to the causal effect question and direct treatment options more at the causal factor.

General conclusion

NPS are omniprescent in residents with dementia in nusing homes, are treated with (persistent) psychotropic drugs and have a major impact on residents' quality of life. In this

thesis, type of dementia has been found to influence the pattern of NPS. The findings of the WAALBED-II study point toward the biopsychosocial model as explanation of the origin of neuropsychiatric symptoms.

Referenties

1. Wimo A, Jonsson L, Winblad B: An estimate of the worldwide prevalence and direct costs of dementia in 2003. *Dementia and Geriatric Cognitive Disorders.*21,175-181 (2006).
2. AlzheimerNederland **(**2011**)**: http://www.alzheimer-nederland.nl/informatie/wat-is-dementie/dementie.aspx.
3. Tariot PN: Neuropsychiatric Features of Dementia: What is the Big Picture? *American Journal of Geriatric Psychiatry.*14,557-560 (2006).
4. Burns A: Another nail in the coffin of the cognitive paradigm of dementia. *Br J Psychiatry.*194,199-200 (2009).
5. Finkel SI, Costa e Silva J, Cohen G *et al.*: Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. *Int Psychogeriatr.*8 Suppl 3,497-500 (1996).
6. Lyketsos CG, Colenda CC, Beck C *et al.*: Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. *American Journal of Geriatric Psychiatry.*14,561-572 (2006).
7. Lyketsos C, Lopez O, Jones B *et al.*: Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA.*288,1475-1483 (2002).
8. Savva GM, Zaccai J, Matthews FE *et al.*: Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *British Journal of Psychiatry.*194,212-219 (2009).
9. Aalten P, de Vugt M, Jaspers N *et al.*: The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *International Journal of Geriatric Psychiatry.*20,523-530 (2005).
10. de Vugt ME, Stevens F, Aalten P *et al.*: A prospective study of the effects of behavioral symptoms on the institutionalization of patients with dementia. *International Psychogeriatrics.*17,577-589 (2005).
11. Gilley DW, Bienias JL, Wilson RS *et al.*: Influence of behavioral symptoms on rates of institutionalization for persons with Alzheimer's disease. *Psychological Medicine.*34,1129-1135 (2004).
12. Zuidema SU, Derksen E, Verhey FR *et al.*: Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. *International Journal of Geriatric Psychiatry.*22,632-638 (2007).
13. Selbaek G, Kirkevold O, Engedal K: The prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes. *International Journal of Geriatric Psychiatry.*22,843-849 (2007).
14. Werner P, Cohen-Mansfield J, Braun J *et al.*: Physical restraints and agitation in nursing home residents. *Journal of the American Geriatrics Society.*37,1122-1126 (1989).
15. Zuidema SU, de Jonghe JF, Verhey FR *et al.*: Neuropsychiatric Symptoms in Nursing Home Patients: Factor Structure Invariance of the Dutch Nursing Home Version of the Neuropsychiatric Inventory in Different Stages of Dementia. *Dementia and Geriatric Cognitive Disorders.*24,169-176 (2007).
16. Fuh JL, Wang SJ, Cummings JL: Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. *J Neurol Neurosurg Psychiatry.*76,1337-1341 (2005).
17. Caputo M, Monastero R, Mariani E *et al.*: Neuropsychiatric symptoms in 921 elderly subjects with dementia: a comparison between vascular and neurodegenerative types. *Acta Psychiatrica Scandinavia.*117,455-464 (2008).
18. Fernandez-Martinez M, Castro J, Molano A *et al.*: Prevalence of neuropsychiatric symptoms in Alzheimer's disease and vascular dementia. *Current Alzheimer Research.*5,61-69 (2008).
19. Zuidema SU, de Jonghe JF, Verhey FR *et al.*: Predictors of neuropsychiatric symptoms in nursing home patients: influence of gender and dementia severity. *Int J Geriatr Psychiatry.*24,1079-1086 (2009).
20. Zuidema SU, de Jonghe JF, Verhey FR *et al.*: Environmental correlates of neuropsychiatric symptoms in nursing home patients with dementia. *Int J Geriatr Psychiatry.*25,14-22 (2009).
21. Engel GL: The need for a new medical model: a challenge for biomedicine. *Science.*196,129-136 (1977).
22. Spector A, Orrell M: Using a biopsychosocial model of dementia as a tool to guide clinical practice. *Int Psychogeriatr.*22,957-965 (2010).
23. Zuidema S **(**2008**)** Neuropsychiatric symptoms in Dutch nursing home patients with dementia. Nijmegen: Radboud University Nijmegen.
24. Marin DB, Green CR, Schmeidler J *et al.*: Noncognitive disturbances in Alzheimer's disease: frequency, longitudinal course, and relationship to cognitive symptoms. *Journal of the American Geriatrics Society.*45,1331-1338 (1997).
25. Devanand DP, Jacobs DM, Tang MX *et al.*: The course of psychopathologic features in mild to moderate Alzheimer disease. *Archives of General Psychiatry.*54,257-263 (1997).
26. Ryu SH, Katona C, Rive B *et al.*: Persistence of and changes in neuropsychiatric symptoms in Alzheimer disease over 6 months: the LASER-AD study. *American Journal of Geriatric Psychiatry.*13,976-983 (2005).
27. Kamble P, Chen H, Sherer JT *et al.*: Use of Antipsychotics among Elderly Nursing Home Residents with Dementia in the US: An Analysis of National Survey Data. *Drugs and Aging.*26,483-492 (2009).
28. Furniss L, Craig SK, Burns A: Medication use in nursing homes for elderly people. *International Journal of Geriatric Psychiatry.*13,433-439 (1998).
29. Bartels S, Horn S, Smout R *et al.*: Agitation and depression in frail nursing home elderly patients with dementia: treatment characteristics and service use. *American Journal of Geriatric Psychiatry.*11,231-238 (2003).
30. Ballard CG, Gauthier S, Cummings JL *et al.*: Management of agitation and aggression associated with Alzheimer disease. *Nature Reviews Neurology.*5,245-255 (2009).
31. FDA **(**2008**)** FDA Requests Boxed Warnings on Older Class of Antipsychotic Drugs. (ed http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116912.htm): FDA ALERT [6/16/2008].
32. Koopmans RT, van Rossum JM, van den Hoogen HJ *et al.*: Psychotropic drug use in a group of Dutch nursing home patients with dementia: many users, long-term use, but low doses. *Pharmarcy World & Science.*18,42-47 (1996).
33. Ballard C, O'Brien J, James I *et al.*: Quality of life for people with dementia living in residential and nursing home care: the impact of performance on activities of daily living, behavioral and psychological symptoms, language skills, and psychotropic drugs. *Int Psychogeriatr.*13,93-106 (2001).

34. Finnema E, Droes RM, Ettema T *et al.*: The effect of integrated emotion-oriented care versus usual care on elderly persons with dementia in the nursing home and on nursing assistants: a randomized clinical trial. *Int J Geriatr Psychiatry.*20,330-343 (2005).
35. Ballard C, Margallo-Lana M: The relationship between antipsychotic treatment and quality of life for patients with dementia living in residential and nursing home care facilities. *J Clin Psychiatry.*65,23-28 (2004).
36. Winblad B, Brodaty H, Gauthier S *et al.*: Pharmacotherapy of Alzheimer's disease: is there a need to redefine treatment success? *Int J Geriatr Psychiatry.*16,653-666 (2001).
37. Gonzalez-Salvador T, Lyketsos CG, Baker A *et al.*: Quality of life in dementia patients in long-term care. *Int J Geriatr Psychiatry.*15,181-189 (2000).
38. Zimmerman S, Sloane PD, Williams CS *et al.*: Dementia care and quality of life in assisted living and nursing homes. *Gerontologist.*45 Spec No 1,133-146 (2005).
39. Missotten P, Squelard G, Ylieff M *et al.*: Quality of life in older Belgian people: comparison between people with dementia, mild cognitive impairment, and controls. *Int J Geriatr Psychiatry.*23,1103-1109 (2008).
40. Koopmans RT, Lavrijsen JC, Zuidema SU: The physician's role in nursing homes: the Dutch solution. *Arch Intern Med.*170,1406; author reply 1406-1407 (2010).
41. Koopmans RT, Lavrijsen JC, Hoek JF *et al.*: Dutch elderly care physician: a new generation of nursing home physician specialists. *J Am Geriatr Soc.*58,1807-1809 (2010).
42. Verbeek H, Zwakhalen SM, van Rossum E *et al.*: Dementia care redesigned: Effects of small-scale living facilities on residents, their family caregivers, and staff. *J Am Med Dir Assoc.*11,662-670
43. Classification NCoMGfA: Guidelines for ATC Classification. WHO collaborating Center for Drugs Statistics Methodology. (1990).
44. Diagnostic and Statistical Manual of Mental Disorders. Association AP American Psychiatric Association: Washington, DC. (ed^(eds, 1994
45. CBO: Guideline diagnosis and pharmacological treatment of dementia. http://www.cbo.nl/Downloads/387/rl_dement_2005.pdf (accessed January 2010). (2005).
46. Roman GC, Tatemichi TK, Erkinjuntti T *et al.*: Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology.*43,250-260 (1993).
47. McKhann G, Drachman D, Folstein M *et al.*: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.*34,939-944 (1984).
48. Neary D, Snowden JS, Gustafson L *et al.*: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology.*51,1546-1554 (1998).
49. McKeith IG, Dickson DW, Lowe J *et al.*: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.*65,1863-1872 (2005).
50. Cummings J, Mega M, Gray K *et al.*: The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology.*44,2308-2314. (1994).
51. Cummings J: The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology.*48,S10-16 (1997).
52. Wood S, Cummings J, Hsu M *et al.*: The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. *American Journal of Geriatric Psychiatry.*8,75-83 (2000).
53. Kat MG, de Jonghe JF, Aalten P *et al.*: [Neuropsychiatric symptoms of dementia: psychometric aspects of the Dutch Neuropsychiatric Inventory (NPI)]. *Tijdschrift voor Gerontologie en Geriatrie.*33,150-155 (2002).
54. Aalten P, Verhey FR, Boziki M *et al.*: Consistency of neuropsychiatric syndromes across dementias: results from the European Alzheimer Disease Consortium. Part II. *Dement Geriatr Cogn Disord.*25,1-8 (2008).
55. Cohen-Mansfield J, Billig N: Agitated behaviors in the elderly. I. A conceptual review. *J Am Geriatr Soc.*34,711-721 (1986).
56. Miller RS, J. Vaughan, R.: The use of the Cohen-Mansfield Agitation Inventory in the assessment of behavioral disorders in nursing homes. *J Am Geriatr Soc.*43,546-549 (1995).
57. de Jonghe J, Kat M: Factor structure and validity of the Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI-D). *J Am Geriatr Soc.*44,888-889 (1996).
58. Ettema TP, Droes RM, de Lange J *et al.*: QUALIDEM: development and evaluation of a dementia specific quality of life instrument. Scalability, reliability and internal structure. *Int J Geriatr Psychiatry.*22,549-556 (2007).
59. Ettema TP, Droes RM, de Lange J *et al.*: QUALIDEM: development and evaluation of a dementia specific quality of life instrument--validation. *Int J Geriatr Psychiatry.*22,424-430 (2007).
60. Bouman AIE, Ettema TP, Wetzels RB *et al.*: QUALIDEM: Evaluation of a Dementia Specific Quality of Life Instrument for Persons with mild to very severe Dementia; scalability and reliability. (2009).
61. Reisberg B, Ferris S, de Leon M *et al.*: The Global Deterioration Scale for assessment of primary degenerative dementia. *American Journal of Psychiatry.*139,1136-1139 (1982).
62. Saxton J, Kastango KB, Hugonot-Diener L *et al.*: Development of a short form of the Severe Impairment Battery. *American Journal of Geriatric Psychiatry.*13,999-1005 (2005).
63. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research.*12,189-198 (1975).
64. Morris JN, Fries BE, Morris SA: Scaling ADLs within the MDS. *J Gerontol A Biol Sci Med Sci.*54,M546-553 (1999).
65. Gerritsen D, Ooms M, Steverink N *et al.*: [Three new observational scales for use in Dutch nursing homes: scales from the Resident Assessment Instrument for Activities of Daily Living, cognition and depression]. *Tijdschr Gerontol Geriatr.*35,55-64 (2004).

66. Lyketsos CG, Lopez O, Jones B *et al.*: Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *Jama.*288,1475-1483 (2002).
67. Banerjee S, Smith SC, Lamping DL *et al.*: Quality of life in dementia: more than just cognition. An analysis of associations with quality of life in dementia. *Journal of Neurology, Neurosurgery and Psychiatry.*77,146-148 (2006).
68. Nijk RM, Zuidema SU, Koopmans RT: Prevalence and correlates of psychotropic drug use in Dutch nursing-home patients with dementia. *International Psychogeriatrics.*21,485-493 (2009).
69. Schneider LS, Tariot PN, Dagerman KS *et al.*: Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *New England Journal of Medicine.*355,1525-1538 (2006).
70. Diagnostic and Statistical Manual of Mental Disorders. In DSM-IV APA American Psychiatric Association (ed^(eds, 1994
71. Vandenbroucke JP, von Elm E, Altman DG *et al.*: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Medicine.*4,e297 (2007).
72. de Lange AH, Taris TW, Kompier MA *et al.*: "The very best of the millennium": longitudinal research and the demand-control-(support) model. *Journal of Occupational Health Psychology.*8,282-305 (2003).
73. A primer in longitudinal data analysis. Taris TW Sage Publications (ed^(eds, 2000
74. Brodaty H, Ames D, Snowdon J *et al.*: A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *Journal of Clinical Psychiatry.*64,134-143 (2003).
75. Chappell NL, Reid RC: Dimensions of care for dementia sufferers in long-term care institutions: are they related to outcomes? *Journal of Gerontology Series B, Psychological Science and Social Science.*55,S234-244 (2000).
76. Frisoni G, Gozzetti A, Bignamini V *et al.*: Special care units for dementia in nursing homes: a controlled study of effectiveness. *Archives Gerontology and Geriatrics.*suppl.6,215-224 (1998).
77. Lawton MP, Van Haitsma K, Klapper J *et al.*: A stimulation-retreat special care unit for elders with dementing illness. *International Psychogeriatrics.*10,379-395 (1998).
78. Reimer MA, Slaughter S, Donaldson C *et al.*: Special care facility compared with traditional environments for dementia care: a longitudinal study of quality of life. *Journal of the American Geriatrics Society.*52,1085-1092 (2004).
79. Rovner BW, Steele CD, Shmuely Y *et al.*: A randomized trial of dementia care in nursing homes. *Journal of the American Geriatrics Society.*44,7-13 (1996).
80. Sloane PD, Zimmerman S, Gruber-Baldini AL *et al.*: Health and functional outcomes and health care utilization of persons with dementia in residential care and assisted living facilities: comparison with nursing homes. *Gerontologist.*45 Spec No 1,124-132 (2005).
81. Selbaek G, Kirkevold O, Engedal K: The course of psychiatric and behavioral symptoms and the use of psychotropic medication in patients with dementia in Norwegian nursing homes--a 12-month follow-up study. *American Journal of Geriatric Psychiatry.*16,528-536 (2008).
82. Tariot PN, Cummings JL, Katz IR *et al.*: A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *Journal of the American Geriatrics Society.*49,1590-1599 (2001).
83. Ballard C, Margallo-Lana M, Fossey J *et al.*: A 1-year follow-up study of behavioral and psychological symptoms in dementia among people in care environments. *Journal of Clinical Psychiatry.*62,631-636. (2001).
84. Payne JL, Sheppard JM, Steinberg M *et al.*: Incidence, prevalence, and outcomes of depression in residents of a long-term care facility with dementia. *International Journal of Geriatric Psychiatry.*17,247-253 (2002).
85. Burton LC, Rovner BW, German PS *et al.*: Neuroleptic use and behavioral disturbance in nursing homes: a 1-year study. *International Psychogeriatrics.*7,535-545 (1995).
86. Wancata J, Benda N, Meise U *et al.*: Non-cognitive symptoms of dementia in nursing homes: frequency, course and consequences. *Social Psychiatry Psychiatric Epidemiology.*38,637-643 (2003).
87. Wagner AW, Teri L, Orr-Rainey N: Behavior problems among dementia residents in special care units: changes over time. *Journal of the American Geriatrics Society.*43,784-787 (1995).
88. Sival R, Albronda T, Haffmans P *et al.*: Is aggressive behaviour influenced by the use of a behaviour rating scale in patients in a psychogeriatric nursing home? *International Journal of Geriatric Psychiatry.*15,108-111 (2000).
89. Bland JM, Altman DG: Regression towards the mean. *British Medical Journal.*308,1499 (1994).
90. Demers L, Oremus M, Perrault A *et al.*: Review of outcome measurement instruments in Alzheimer's disease drug trials: introduction. *Journal of Geriatric Psychiatry and Neurology.*13,161-169 (2000).
91. Perrault A, Oremus M, Demers L *et al.*: Review of outcome measurement instruments in Alzheimer's disease drug trials: psychometric properties of behavior and mood scales. *Journal of Geriatric Psychiatry and Neurology.*13,181-196 (2000).
92. Panisset M, Roudier M, Saxton J *et al.*: Severe impairment battery. A neuropsychological test for severely demented patients. *Arch Neurol.*51,41-45 (1994).
93. Feldman H, Gauthier S, Hecker J *et al.*: A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology.*57,613-620 (2001).
94. Reisberg B, Doody R, Stoffler A *et al.*: Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med.*348,1333-1341 (2003).
95. Tariot PN, Farlow MR, Grossberg GT *et al.*: Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *Jama.*291,317-324 (2004).
96. Winblad B, Kilander L, Eriksson S *et al.*: Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet.*367,1057-1065 (2006).
97. Black SE, Doody R, Li H *et al.*: Donepezil preserves cognition and global function in patients with severe Alzheimer disease. *Neurology.*69,459-469 (2007).
98. Wajman JR, Bertolucci PH: Comparison between neuropsychological evaluation instruments for severe dementia. *Arq Neuropsiquiatr.*64,736-740 (2006).

99. Suh GH, Kang CJ: Validation of the Severe Impairment Battery for patients with Alzheimer's disease in Korea. *Int J Geriatr Psychiatry.*21,626-632 (2006).
100. Ahn IS, Kim JH, Ku HM *et al.*: Reliability and validity of the severe impairment battery (SIB) in Korean dementia patients. *J Korean Med Sci.*21,506-517 (2006).
101. Pelissier C, Roudier M, Boller F: Factorial validation of the Severe Impairment Battery for patients with Alzheimer's disease. A pilot study. *Dement Geriatr Cogn Disord.*13,95-100 (2002).
102. Wild KV, Kaye JA: The rate of progression of Alzheimer's disease in the later stages: evidence from the Severe Impairment Battery. *J Int Neuropsychol Soc.*4,512-516 (1998).
103. Schmitt FA, Ashford W, Ernesto C *et al.*: The severe impairment battery: concurrent validity and the assessment of longitudinal change in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord.*11 Suppl 2,S51-56 (1997).
104. Bergh S, Selbaek G, Engedal K: Reliability and validity of the Norwegian version of the Severe Impairment Battery (SIB). *Int J Geriatr Psychiatry.*23,896-902 (2008).
105. Gortelmeyer R, Schmitt F: Principal component analysis SIB Memantine study. Data on file. Merz Pharmaceuticals. Personal communication. (2006).
106. Ahn IS, Kim JH, Saxton J *et al.*: Reliability and validity of a short form of the Severe Impairment Battery in Korean Alzheimer's disease patients. *Int J Geriatr Psychiatry.*22,682-687 (2007).
107. The Severe Impairment Battery. Saxton J, McGonigle K, Swihart A *et al.* Thames Valley Test Company, www.hartcourtassessment.com (ed^(eds, 1993
108. Tinklenberg J, Brooks JO, 3rd, Tanke ED *et al.*: Factor analysis and preliminary validation of the mini-mental state examination from a longitudinal perspective. *Int Psychogeriatr.*2,123-134 (1990).
109. Talwalker S, Overall JE, Srirama MK *et al.*: Cardinal features of cognitive dysfunction in Alzheimer's disease: a factor-analytic study of the Alzheimer's Disease Assessment Scale. *J Geriatr Psychiatry Neurol.*9,39-46 (1996).
110. Pasqualetti P, Moffa F, Chiovenda P *et al.*: Mini-mental state examination and mental deterioration battery: analysis of the relationship and clinical implications. *J Am Geriatr Soc.*50,1577-1581 (2002).
111. Strauss ME, Fritsch T: Factor structure of the CERAD neuropsychological battery. *J Int Neuropsychol Soc.*10,559-565 (2004).
112. Noale M, Limongi F, Minicuci N: Identification of factorial structure of MMSE based on elderly cognitive destiny: the Italian Longitudinal Study on Aging. *Dement Geriatr Cogn Disord.*21,233-241 (2006).
113. Jones RN, Gallo JJ: Dimensions of the Mini-Mental State Examination among community dwelling older adults. *Psychol Med.*30,605-618 (2000).
114. Hyman BT, Van Hoesen GW, Damasio AR *et al.*: Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. *Science.*225,1168-1170 (1984).
115. Jobst KA, Smith AD, Szatmari M *et al.*: Detection in life of confirmed Alzheimer's disease using a simple measurement of medial temporal lobe atrophy by computed tomography. *Lancet.*340,1179-1183 (1992).
116. Haroutunian V, Perl DP, Purohit DP *et al.*: Regional distribution of neuritic plaques in the nondemented elderly and subjects with very mild Alzheimer disease. *Arch Neurol.*55,1185-1191 (1998).
117. Mitchell TW, Mufson EJ, Schneider JA *et al.*: Parahippocampal tau pathology in healthy aging, mild cognitive impairment, and early Alzheimer's disease. *Ann Neurol.*51,182-189 (2002).
118. Scahill RI, Schott JM, Stevens JM *et al.*: Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. *Proc Natl Acad Sci U S A.*99,4703-4707 (2002).
119. Nagy Z, Jobst KA, Esiri MM *et al.*: Hippocampal pathology reflects memory deficit and brain imaging measurements in Alzheimer's disease: clinicopathologic correlations using three sets of pathologic diagnostic criteria. *Dementia.*7,76-81 (1996).
120. Braak H, Braak E: Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol (Berl).*82,239-259 (1991).
121. Bartha L, Brenneis C, Schocke M *et al.*: Medial temporal lobe activation during semantic language processing: fMRI findings in healthy left- and right-handers. *Brain Res Cogn Brain Res.*17,339-346 (2003).
122. Hirono N, Mori E, Ishii K *et al.*: Neuronal substrates for semantic memory: a positron emission tomography study in Alzheimer's disease. *Dement Geriatr Cogn Disord.*12,15-21 (2001).
123. Zahn R, Juengling F, Bubrowski P *et al.*: Hemispheric asymmetries of hypometabolism associated with semantic memory impairment in Alzheimer's disease: a study using positron emission tomography with fluorodeoxyglucose-F18. *Psychiatry Res.*132,159-172 (2004).
124. Schmitt FA, Cragar D, Ashford JW *et al.*: Measuring cognition in advanced Alzheimer's disease for clinical trials. *J Neural Transm Suppl.*135-148 (2002).
125. Gerritsen DL, Ettema TP, Boelens E *et al.*: Quality of life in dementia: do professional caregivers focus on the significant domains? *Am J Alzheimers Dis Other Demen.*22,176-183 (2007).
126. Ettema TP, Droes RM, de Lange J *et al.*: The concept of quality of life in dementia in the different stages of the disease. *Int Psychogeriatr.*17,353-370 (2005).
127. Shin I, Carter M, Masterman D *et al.*: Neuropsychiatric Symptoms and Quality of Life in Alzheimer Disease. *American Journal of Geriatric Psychiatry.*13,469-474 (2005).
128. Samus QM, Rosenblatt A, Steele C *et al.*: The association of neuropsychiatric symptoms and environment with quality of life in assisted living residents with dementia. *Gerontologist.*45 Spec No 1,19-26 (2005).
129. Winzelberg GS, Williams CS, Preisser JS *et al.*: Factors associated with nursing assistant quality-of-life ratings for residents with dementia in long-term care facilities. *Gerontologist.*45 Spec No 1,106-114 (2005).
130. Sloane PD, Zimmerman S, Williams CS *et al.*: Evaluating the quality of life of long-term care residents with dementia. *Gerontologist.*45 Spec No 1,37-49 (2005).

131. Snow AL, Dani R, Souchek J *et al.*: Comorbid psychosocial symptoms and quality of life in patients with dementia. *American Journal of Geriatric Psychiatry.*13,393-401 (2005).
132. Tractenberg RE, Weiner MF, Thal LJ: Estimating the prevalence of agitation in community-dwelling persons with Alzheimer's disease. *J Neuropsychiatry Clin Neurosci.*14,11-18 (2002).
133. Hoe J, Hancock G, Livingston G *et al.*: Quality of life of people with dementia in residential care homes. *Br J Psychiatry.*188,460-464 (2006).
134. Fuh JL, Wang SJ: Assessing quality of life in Taiwanese patients with Alzheimer's disease. *Int J Geriatr Psychiatry.*21,103-107 (2006).
135. Yeager CA, Hyer L: Apathy in dementia: relations with depression, functional competence, and quality of life. *Psychol Rep.*102,718-722 (2008).
136. Zuidema SU, van Iersel MB, Koopmans RT *et al.*: [Efficacy and adverse reactions of antipsychotics for neuropsychiatric symptoms in dementia: a systematic review]. *Ned Tijdschr Geneeskd.*150,1565-1573 (2006).
137. Ballard C, Hanney ML, Theodoulou M *et al.*: The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurol.*(2009).
138. Bostrom F, Jonsson L, Minthon L *et al.*: Patients With Dementia With Lewy Bodies Have More Impaired Quality of Life Than Patients With Alzheimer Disease. *Alzheimer Dis Assoc Disord.*21,150-154 (2007).
139. Thomas P, Lalloue F, Preux PM *et al.*: Dementia patients caregivers quality of life: the PIXEL study. *Int J Geriatr Psychiatry.*21,50-56 (2006).
140. De Jonghe JFM, Wetzels RB, Mulders A *et al.*: Validity of the Severe Impairment Battery Short Version. *J neurol neurosurg psychiatry.*80,954-959 (2009).
141. Hoe J, Katona C, Roch B *et al.*: Use of the QOL-AD for measuring quality of life in people with severe dementia--the LASER-AD study. *Age Ageing.*34,130-135 (2005).
142. Smalbrugge M, Jongenelis LK, Pot AM *et al.*: Pain among nursing home patients in the Netherlands: prevalence, course, clinical correlates, recognition and analgesic treatment--an observational cohort study. *BMC Geriatr.*7,3 (2007).
143. Zwakhalen SM, Koopmans RT, Geels PJ *et al.*: The prevalence of pain in nursing home residents with dementia measured using an observational pain scale. *Eur J Pain.*13,89-93 (2009).
144. Buffum M, Miaskowski C, Sands L *et al.*: A pilot study of the relationship between discomfort and agitation in patients with dementia. *Geriatr Nurs.*22,80-85 (2001).
145. Cipher DJ, Clifford PA: Dementia, pain, depression, behavioral disturbances, and ADLs: toward a comprehensive conceptualization of quality of life in long-term care. *Int J Geriatr Psychiatry.*19,741-748 (2004).
146. Livingston G, Johnston K, Katona C *et al.*: Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. *Am J Psychiatry.*162,1996-2021 (2005).
147. Riemersma-van der Lek RF, Swaab DF, Twisk J *et al.*: Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *Jama.*299,2642-2655 (2008).
148. Edvardsson D, Sandman PO, Nay R *et al.*: Associations between the working characteristics of nursing staff and the prevalence of behavioral symptoms in people with dementia in residential care. *Int Psychogeriatr.*20,764-776 (2008).
149. Furaker C, Nilsson A: The competence of certified nurse assistants caring for persons with dementia diseases in residential facilities. *J Psychiatr Ment Health Nurs.*16,146-152 (2009).
150. Wetzels RB, Zuidema SU, de Jonghe JF *et al.*: Determinants of Quality of Life in Nursing Home Patients with Dementia. *Dement Geriatr Cogn Disord.*in press. (2010).
151. Haupt M, Kurz A, Janner M: A 2-year follow-up of behavioural and psychological symptoms in Alzheimer's disease. *Dement Geriatr Cogn Disord.*11,147-152 (2000).
152. Eustace A, Coen R, Walsh C *et al.*: A longitudinal evaluation of behavioural and psychological symptoms of probable Alzheimer's disease. *Int J Geriatr Psychiatry.*17,968-973 (2002).
153. Hope T, Keene J, Fairburn CG *et al.*: Natural history of behavioural changes and psychiatric symptoms in Alzheimer's disease. A longitudinal study. *Br J Psychiatry.*174,39-44 (1999).
154. Selbæk G, Kirkevold O, Engedal K: The course of psychiatric and behavioral symptoms and the use of psychotropic medication in patients with dementia in Norwegian nursing homes--a 12-month follow-up study. *Am J Geriatr Psychiatry.*16,528-536 (2008).
155. Diagnostic and Statistical Manual of Mental Disorders. In DSM-IV Association AP American Psychiatric Association (ed^(eds, 1994
156. Steinberg M, Tschanz JT, Corcoran C *et al.*: The persistence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry.*19,19-26 (2004).
157. Starkstein SE, Mizrahi R, Garau L: Specificity of symptoms of depression in Alzheimer disease: a longitudinal analysis. *American Journal of Geriatric Psychiatry.*13,802-807 (2005).
158. Smalbrugge M, Jongenelis L, Pot AM *et al.*: Incidence and outcome of depressive symptoms in nursing home patients in the Netherlands. *American Journal of Geriatric Psychiatry.*14,1069-1076 (2006).
159. Steinberg M, Shao H, Zandi P *et al.*: Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry.*23,170-177 (2008).
160. Starkstein SE, Jorge R, Mizrahi R *et al.*: A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry.*77,8-11 (2006).
161. Koopmans RT, Ekkerink JL, van den Hoogen HJ *et al.*: [Mortality in patients with dementia following admission to a nursing home; a 10-year analysis]. *Ned Tijdschr Geneeskd.*138,1169-1174 (1994).
162. Aalten P, van Valen E, Clare L *et al.*: Awareness in dementia: a review of clinical correlates. *Aging Ment Health.*9,414-422 (2005).

163. Aalten P, van Valen E, de Vugt ME *et al.*: Awareness and behavioral problems in dementia patients: a prospective study. *Int Psychogeriatr.*18,3-17 (2006).
164. Ballard C, Corbett A, Chitramohan R *et al.*: Management of agitation and aggression associated with Alzheimer's disease: controversies and possible solutions. *Curr Opin Psychiatry.*22,532-540 (2009).
165. Aggression. In Textbook of geriatric neuropsychiatry Lyketsos C American Psychiatric Press, Inc. (ed^(eds E. Coffey & J. Cummings), pp. 477-488.2000
166. Braak H, Braak E: Evolution of the neuropathology of Alzheimer's disease. *Acta Neurol Scand Suppl.*165,3-12 (1996).
167. Kleijer BC, van Marum RJ, Egberts AC *et al.*: The course of behavioral problems in elderly nursing home patients with dementia when treated with antipsychotics. *Int Psychogeriatr.*21,931-940 (2009).
168. Howard R, Ballard C, O'Brien J *et al.*: Guidelines for the management of agitation in dementia. *International Journal of Geriatric Psychiatry.*16,714-717 (2001).
169. Salzman C, Jeste DV, Meyer RE *et al.*: Elderly patients with dementia-related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. *Journal of Clinical Psychiatry.*69,889-898 (2008).
170. Kim H, Whall AL: Factors associated with psychotropic drug usage among nursing home residents with dementia. *Nursing Research.*55,252-258 (2006).
171. Lee P, Gill S, Freedman M *et al.*: Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. *British Medical Journal.*329,75 (2004).
172. Pitkala KH, Laurila JV, Strandberg TE *et al.*: Behavioral symptoms and the administration of psychotropic drugs to aged patients with dementia in nursing homes and in acute geriatric wards. *International Psychogeriatrics.*16,61-74 (2004).
173. Margallo-Lana M, Swann A, O'Brien J *et al.*: Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. *International Journal of Geriatric Psychiatry.*16,39-44 (2001).
174. Lovheim H, Sandman PO, Kallin K *et al.*: Relationship between antipsychotic drug use and behavioral and psychological symptoms of dementia in old people with cognitive impairment living in geriatric care. *International Psychogeriatrics.*18,713-726 (2006).
175. McGrath AM, Jackson GA: Survey of neuroleptic prescribing in residents of nursing homes in Glasgow. *British Medical Journal.*312,611-612 (1996).
176. Kamble P, Sherer J, Chen H *et al.*: Off-label use of second-generation antipsychotic agents among elderly nursing home residents. *Psychiatric Services.*61,130-136 (2010).
177. Ruths S, Straand J, Nygaard HA: Psychotropic drug use in nursing homes--diagnostic indications and variations between institutions. *European Journal of Clinical Pharmacology.*57,523-528 (2001).
178. CSM **(**2004**)** Atypical Antipsychotic Drugs And Stroke. (ed CEM/CMO/2004/1).
179. Woolcott JC, Richardson KJ, Wiens MO *et al.*: Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of Internal Medicine.*169,1952-1960 (2009).
180. AGS;AAGP: Consensus statement of improving the quality of mental health care in U.S. nursing homes: management of depression and behavioral symptoms associated with dementia. *Journal of the American Geriatric Society.* 51,1287-1298 (2003).
181. Sanfelix-Gimeno G, Cervera-Casino P, Peiro S *et al.*: Effectiveness of safety warnings in atypical antipsychotic drugs: an interrupted time-series analysis in Spain. *Drug Safety.*32,1075-1087 (2009).
182. Dorsey ER, Rabbani A, Gallagher SA *et al.*: Impact of FDA black box advisory on antipsychotic medication use. *Archives of Internal Medicine.*170,96-103 (2010).
183. Trifiro G, Sini G, Sturkenboom MC *et al.*: Prescribing pattern of antipsychotic drugs in the Italian general population 2000-2005: a focus on elderly with dementia. *International Clinical Psychopharmacology.*25,22-28 (2010).
184. de Jonghe JF, Wetzels RB, Mulders A *et al.*: Validity of the Severe Impairment Battery Short Version. *Journal Neurology Neurosurgery and Psychiatry.*80,954-959 (2009).
185. Eggermont LH, de Vries K, Scherder EJ: Psychotropic medication use and cognition in institutionalized older adults with mild to moderate dementia. *International Psychogeriatrics.*21,286-294 (2009).
186. Wetzels RB, Zuidema SU, de Jonghe JF *et al.*: Course of neuropsychiatric symptoms in residents with dementia in nursing homes over 2-year period. *American Journal of Geriatric Psychiatry.*18,1054-1065 (2010).
187. Pollock BG, Mulsant BH, Rosen J *et al.*: A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. *American Journal of Geriatric Psychiatry.*15,942-952 (2007).
188. Smalbrugge M, Boersma F, Kleijer B *et al.* **(**2008**)** Guideline problem behavior: NVVA.
189. Wilcock GK, Ballard CG, Cooper JA *et al.*: Memantine for Agitation/Aggression and Psychosis in Moderately Severe to Severe Alzheimer's Disease: A Pooled Analysis of 3 Studies. *Journal of Clinical Psychiatry.*e1-e8 (2008).
190. Zuidema SU, de Jonghe JF, Verhey FR *et al.*: Agitation in Dutch institutionalized patients with dementia: factor analysis of the Dutch version of the Cohen-Mansfield Agitation Inventory. *Dementia and Geriatric Cognitive Disorders.*23,35-41 (2007).
191. Kim JM, Lyons D, Shin IS *et al.*: Differences in the behavioral and psychological symptoms between Alzheimer's disease and vascular dementia: are the different pharmacologic treatment strategies justifiable? *Human Psychopharmacology.*18,215-220 (2003).
192. Chen Y, Briesacher BA, Field TS *et al.*: Unexplained variation across US nursing homes in antipsychotic prescribing rates. *Archives of Internal Medicine.*170,89-95 (2010).

193. Ayalon L, Arean P, Bornfeld H *et al.*: Long term care staff beliefs about evidence based practices for the management of dementia and agitation. *International Journal of Geriatric Psychiatry.*24,118-124 (2009).
194. Marshall M: The challenge of looking after people with dementia. *British Medical Journal.*323,410-411 (2001).
195. Cohen-Mansfield J, Jensen B: Nursing home physicians' knowledge of and attitudes toward nonpharmacological interventions for treatment of behavioral disturbances associated with dementia. *Journal of the American Medical Directors Association.*9,491-498 (2008).
196. Wang LY, Shofer JB, Rohde K *et al.*: Prazosin for the treatment of behavioral symptoms in patients with Alzheimer disease with agitation and aggression. *American Journal of Geriatric Psychiatry.*17,744-751 (2009).
197. Ayalon L, Gum AM, Feliciano L *et al.*: Effectiveness of nonpharmacological interventions for the management of neuropsychiatric symptoms in patients with dementia: a systematic review. *Archives of Internal Medicine.*166,2182-2188 (2006).
198. Zuidema SU, Buursema AL, Gerritsen MG *et al.*: Assessing neuropsychiatric symptoms in nursing home patients with dementia: reliability and Reliable Change Index of the Neuropsychiatric Inventory and the Cohen-Mansfield Agitation Inventory. *Int J Geriatr Psychiatry.*26,127-134 (2011).
199. Rosen T, Lachs MS, Bharucha AJ *et al.*: Resident-to-resident aggression in long-term care facilities: insights from focus groups of nursing home residents and staff. *J Am Geriatr Soc.*56,1398-1408 (2008).
200. de Jonghe-Rouleau A, Pot A, de Jonghe J: Self-Injurious Behaviour in nursing home residents with dementia. *Int J Geriatr Psychiatry.*20,651-657 (2005).
201. Algase DL, Antonakos C, Yao L *et al.*: Are wandering and physically nonaggressive agitation equivalent? *American Journal of Geriatric Psychiatry.*16,293-299 (2008).
202. Droes RM **(**1991**)** In beweging: over psychosociale hulpverlening aan demente ouderen. [In movement;on psychosocial care for elderly with dementia]. Amsterdam: Vrije Universiteit.
203. Engel GL: The clinical application of the biopsychosocial model. *Am J Psychiatry.*137,535-544 (1980).
204. Meeks TW, Ropacki SA, Jeste DV: The neurobiology of neuropsychiatric syndromes in dementia. *Curr Opin Psychiatry.*19,581-586 (2006).
205. Woods DL, Kim H, Yefimova M: Morning Cortisol in Relation to Behavioral Symptoms of Nursing Home Residents With Dementia. *Biol Res Nurs.*(2010).
206. White HK, McConnell ES, Bales CW *et al.*: A 6-month observational study of the relationship between weight loss and behavioral symptoms in institutionalized Alzheimer's disease subjects. *J Am Med Dir Assoc.*5,89-97 (2004).
207. Oudshoorn C, Mattace-Raso FU, van der Velde N *et al.*: Higher serum vitamin D3 levels are associated with better cognitive test performance in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord.*25,539-543 (2008).
208. Buell JS, Dawson-Hughes B, Scott TM *et al.*: 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. *Neurology.*(2009).
209. Freund-Levi Y, Basun H, Cederholm T *et al.*: Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. *Int J Geriatr Psychiatry.*23,161-169 (2008).
210. Remington R, Chan A, Lepore A *et al.*: Apple Juice Improved Behavioral But Not Cognitive Symptoms in Moderate-to-Late Stage Alzheimer's Disease in an Open-Label Pilot Study. *Am J Alzheimers Dis Other Demen.*
211. Del Prete M, Spaccavento S, Craca A *et al.*: Neuropsychiatric symptoms and the APOE genotype in Alzheimer's disease. *Neurol Sci.*30,367-373 (2009).
212. Di Maria E, Bonvicini C, Bonomini C *et al.*: Genetic Variation in the G720/G30 Gene Locus (DAOA) Influences the Occurrence of Psychotic Symptoms in Patients with Alzheimer's Disease. *J Alzheimers Dis.*18,953-960 (2009).
213. Archer N, Brown RG, Reeves SJ *et al.*: Premorbid Personality and Behavioral and Psychological Symptoms in Probable Alzheimer Disease. *American Journal of Geriatric Psychiatry.*15,202-213 (2007).
214. Thissen AJC, Ekkerink JL, Mahler M *et al.*: Boos, bedreigd of impulsief? Een onderzoek naar premorbide persoonlijkheid en agressie bij psychogeriatrische verpleeghuisbewoners *Tijdschr Gerontol Geriatr.*(2010).
215. Burkhalter CL, Allen RS, Skaar DC *et al.*: Examining the effectiveness of traditional audiological assessments for nursing home residents with dementia-related behaviors. *J Am Acad Audiol.*20,529-538 (2009).
216. Geda YE, Rummans TA: Pain: cause of agitation in elderly individuals with dementia. *Am J Psychiatry.*156,1662-1663 (1999).
217. Cipher DJ, Clifford PA, Roper KD: Behavioral manifestations of pain in the demented elderly. *J Am Med Dir Assoc.*7,355-365 (2006).
218. Mancini M, Mancini M, Amenta F: Oral Health in Alzheimer's Disease: A Review. *Curr Alzheimer Res.*(2009).
219. Walid MS, Zaytseva N: Pain in nursing home residents and correlation with neuropsychiatric disorders. *Pain Physician.*12,877-880 (2009).
220. Koopmans RT, Zuidema SU, Leontjevas R *et al.*: Comprehensive assessment of depression and behavioral problems in long-term care. *Int Psychogeriatr.*22,1054-1062 (2010).
221. Vernooij-Dassen M, Vasse E, Zuidema S *et al.*: Psychosocial interventions for dementia patients in long-term care. *Int Psychogeriatr.*22,1121-1128 (2010).
222. Olazaran J, Reisberg B, Clare L *et al.*: Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. *Dement Geriatr Cogn Disord.*30,161-178 (2010).
223. Kunik ME, Snow AL, Davila JA *et al.*: Causes of aggressive behavior in patients with dementia. *J Clin Psychiatry.*71,1145-1152 (2010).
224. Vasse E, Vernooij-Dassen M, Spijker A *et al.*: A systematic review of communication strategies for people with dementia in residential and nursing homes. *Int Psychogeriatr.*22,189-200 (2010).
225. Kada S, Nygaard HA, Mukesh BN *et al.*: Staff attitudes towards institutionalised dementia residents. *J Clin Nurs.*18,2383-2392 (2009).

226. Draper B, Low LF, Withall A *et al.*: Translating dementia research into practice. *Int Psychogeriatr.*21 Suppl 1,S72-80 (2009).
227. Chapman A, Law S: Bridging the gap: an innovative dementia learning program for healthcare assistants in hospital wards using facilitator-led discussions. *Int Psychogeriatr.*21 Suppl 1,S58-63 (2009).
228. Chenoweth L, King MT, Jeon YH *et al.*: Caring for Aged Dementia Care Resident Study (CADRES) of person-centred care, dementia-care mapping, and usual care in dementia: a cluster-randomised trial. *Lancet Neurol.*(2009).
229. Osborne H, Simpson J, Stokes G: The relationship between pre-morbid personality and challenging behaviour in people with dementia: A systematic review. *Aging Ment Health.*14,503-515 (2010).
230. Thissen AJ, Ekkerink JL, Mahler MM *et al.*: [Premorbid personality and aggressive behavior: a study with residents of psychogeriatric nursing homes]. *Tijdschr Gerontol Geriatr.*41,116-125 (2010).
231. Cohen-Mansfield J: Nonpharmacologic interventions for inappropriate behaviors in dementia: a review, summary, and critique. *American Journal of Geriatric Psychiatry.*9,361-381 (2001).
232. Hall GR, Buchwalter KC: Progressively Lowered Stress Threshold model for care of adults with Alzheimer's disease. *Archives of psychiatric nursing.*6,399-406 (1987).
233. Cohen-Mansfield J, Dakheel-Ali M, Marx MS: Engagement in persons with dementia: the concept and its measurement. *American Journal of Geriatric Psychiatry.*17,299-307 (2009).
234. Avorn J, Soumerai SB, Everitt DE *et al.*: A randomized trial of a program to reduce the use of psychoactive drugs in nursing homes. *N Engl J Med.*327,168-173 (1992).
235. Fossey J, Ballard C, Juszczak E *et al.*: Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. *BMJ.*332,756-761 (2006).
236. Crotty M, Halbert J, Rowett D *et al.*: An outreach geriatric medication advisory service in residential aged care: a randomised controlled trial of case conferencing. *Age Ageing.*33,612-617 (2004).
237. Westbury J, Jackson S, Gee P *et al.*: An effective approach to decrease antipsychotic and benzodiazepine use in nursing homes: the RedUSe project. *Int Psychogeriatr.*22,26-36 (2010).
238. Verrue CL, Petrovic M, Mehuys E *et al.*: Pharmacists' interventions for optimization of medication use in nursing homes : a systematic review. *Drugs Aging.*26,37-49 (2009).
239. Fleming R, Purandare N: Long-term care for people with dementia: environmental design guidelines. *Int Psychogeriatr.*22,1084-1096 (2010).

Samenvatting

Introductie

Dit hoofdstuk geeft de bevindingen van deze dissertatie weer van de resultaten van het onderzoek naar aanleiding van de onderzoeksvragen.

Samenvatting van de voornaamste bevindingen.

2. *Wat is het beloop van neuropsychiatrische symptomen bij dementiepatiënten in het verpleeghuis?*

In deze twee jaar durende observationele studie, is vastgesteld dat het beloop van NPS heterogeen is (hoofdstuk 7), maar enkele algemene en specifieke conclusies kunnen worden getrokken. Individuele symptomen vertonen min of meer karakteristieke belopen. Na verloop van tijd, blijft prevalentie van overall-NPS aanzienlijk en constant (59,8-73,5%) over T0-T4-assessments; de 2-jaarscumulatieve prevalentie is bijna 97%. Dit geeft aan dat NPS zeer veel voorkmen en waarschijnlijk universeel tijdens het verloop van de ziekte zijn. Prevalentie van het hebben van meer dan èèn NPS-symptoom was ook hoog (20,5-29,1%). In termen van ernstscores (NPI-NH FXS), vertoonde de totale NPS-symptomatologie een daling in de tijd (hoofdstuk 7), en voor depressie en angst in het bijzonder. Affectieve symptomen vertonen de neiging om na verloop van tijd (hoofdstuk 3 en 7), terwijl agitatie / agressie heeft een cursus van constante prevalentie-rate tonen of de neiging om na verloop van tijd te verhogen in termen van ernst scores. De tarieven van de psychose stabiel is gebleven in de tijd, prevalenties toonde een stabiele tendens wijst op een constant niveau van psychose symptomatologie met vergelijkbare percentages van resoluties en nieuwe ontstaan. De meest hardnekkige over de 2-jaar observatieperiode waren agitatie en hallucinaties, hoewel minder vaak voor. Verschillen tussen AD en VaD zijn gevonden: apathie en angst werden vaker gezien bij Alzheimer, terwijl depressie en agressie vaker voorkomen bij VaD. Deze gegevens dragen bij aan het idee dat biologische factoren (bv. verschillende vormen van dementie) de oorzaak van verschillende patronen van NPS kunnen zijn. Ons review is het eerste systematische onderzoek naar het longitudinale bloop van NPS bij bewoners met dementie in de langdurige zorginstellingen. Van de 18 opgenomen studies in deze review, na het overnemen en/of berekenen van frequentieparameters werden prevalenties gevonden van een breed scala aan NPS. Wij vonden dat afwijkend motorisch gedrag, depressie, angst en euforie een daling vertoonde na verloop van tijd, dat psychose constatn bleef, net zoals in onze studie. Hoewel de prevalenties kan enigszins afwijken, de cursussen na verloop van tijd een beetje laten een vergelijkbaar beeld: gedragsproblemen symptomen, vooral agitatie en agressie, constant blijven of toenemen, affectieve symptomen verminderen, en psychose hebben de neiging te blijven bestaan. Echter, andere definities, classificaties en assessments instrumenten maken eht vergelijken van studies moeilijk (hoofdstuk 3).

2. *Wat is de validiteit van de Severe Impairment Battery-short version in een groep verpleeghuispatienten met dementie?*

Met behulp van de data van de baseline, cross-sectionele meting, bleken zowel de MMSE en de SIB-s, lage scores op de totale SIB-S geassocieerd met cognitieve stoornissen zoals gemeten met de MMSE (Spearman rho = 0,91, p <0,001) en met functionele afhankelijkheid zoals gemeten met een totale ADL schaal (Spearman rho = -. 61, p <0,001). Cognitieve stoornis werd in verband gebracht met dementie ernst, zoals blijkt uit een lagere SIB-s scores in GDS fase 7 ten opzichte van GDS 6, en in het GDS 6 ten opzichte van GDS 4-5.

Diagnostische nauwkeurigheid van SIB-S zoals gemeten met de Receiver Operating Characteristic-curve was bescheiden voor milde tot gematigde dementie, en het meer belangrijk voor matige tot zeer ernstige stadia. SIB-s totaalscores onderscheid tussen dementie ernst zoals gemeten met de GDS (F = 164.6 df: 3.260, P <0.001). Deze gegevens leveren het bewijs van het concept van de concurrente validiteit. Drie belangrijkste componenten gevonden die verklaarde 67,4% van de score variantie: eerste factor die werd genoemd 'Afasie-agnosie', het tweede factor genaamd 'Apraxie', en de derde factor was de naam 'episodische geheugen'. Met name de eerste factor verklaart meer dan de helft van de gemeenschappelijke variantie. Interne consistentie van de SIB-s was zeer hoog (Cronbach's alpha =. 97). Deze gegevens dragen bij aan het concept van constructvaliditeit. Het algemeen komen deze gegevens blijkt dat de SIB-s is een homogeen, eendimensionale en valide meten van cognitieve stoornissen, in het bijzonder van semantisch geheugen. Dit korte meetinstrument is eenvoudig af te nemen en kan gebruikt worden voor het beoordelen patiënten met matige tot ernstige dementie, die de traditionele, langere neuropsychologische tests te moeilik vinden om te voltooien.

3. *Wat zijn determinanten van kwaliteit van leven voor verpleeghuisbewoners met dementie?*

Met behulp van multivariate lineaire regressie modellen, werden in deze studie, NPS, cognitie en PDU gevonden bij te dragen kwaliteit van leven bij bewoners met dementie in verpleeghuizen. Bovendien, deze determinanten verklaarde bijna 50% van de totale gevonden variantie. In plaats van afzonderlijke symptomen, werd de factorstructuur van NPS bestudeerd en bleken de factoren ‘agitatie’ en ‘depressie’ in het bijzonder bij te dragen aan een lagere kwaliteit van leven. Deze associaties waren sterker bij bewoners met milde tot matig ernstige dementie dan bij patiënten met ernstige dementie. In deze laatste groep, bleek de factor psychose ook een sterke voorspeller.

4. *Wat zijn voorschrijfpatronene van psychotrope medicatie over 2 jarige periode?*

Op alle opeenvolgende assessments, bijna tweederde van de inwoners ontvangen-PD en bijna een derde bleef any-PD ontvangen via periode van 2 jaar. Van alle psychofarmaca (PD), werden antipsychotica (AP) het meest voorgeschreven en 1 op de 8 bewoners bleven AP ontvangen over een periode van 2 jaar. Antidepressiva werd minder voorgeschreven, maar persisteerde in hogere percentages. Anxiolytica toonde een intermitterende beloop; een subgroep van 9% toonde een chronisch gebruik van tweejaar. Eenmaal begonnen PD bij aanvang van de bewoners bleef PD te gebruiken bij een hoge percentages: driekwart bleef AP ontvangen voor ten minste zes maanden. De helft van de bewoners ten minste een PD, een vijfde ten minste twee PD's tegelijk. Ook depressieve bewoners waren vaak niet op antidepressiva, wat aangeeft onder behandeling, vice versa, niet-depressieve bewoners werden behandeld met ADP, mogelijk aanklagen over het gebruik. Hoewel depressie prevalentie en ernst scores loop der tijd afgenomen, was er geen stoppen van ADP waargenomen. Dit kan worden veroorzaakt door de reden dat ADP zijn voorgeschreven, niet alleen voor depressies maar ook voor andere indicaties ook, bijvoorbeeld voor agressie of psychose. In deze studie, dissociatie tussen de symptomen en ADP voorschriften bleef, zelfs na correctie voor meerdere indicaties, wat erop wijst ADP over het gebruik. Hoewel angst prevalentie en ernst scores dalen na verloop van tijd, ANX bleef vaak ook voorgeschreven mogelijk met vermelding van overmatig gebruik. Bewoners met AD kreeg meer slaapmiddelen en middelen tegen dementie; bewoners met VaD ontvangen meer antipsychotica, antidepressiva, anxiolytica en anti-epileptica.

First, facts & figures:

4X365 dagen, vijf metingen, 974 patiënten en dito interviews, meer dan 4000km per auto, 16 multomappen met over 1300 artikelen, 14.4h/wk (op papier), 25h/wk (in werkelijkheid), niet-te-tellen-aantal computeruren en geheugenuitbreiding (∑>TB), vier versies van SPSS, vier cursussen + autodidactische typecursus, elf presentaties, drie buitenlandreizen, drie verhuizingen, twee nieuwe huizen, vijf artikelen en slechts èèn boekje -van wat is het?- 20 bij 15 bij 1 cm.

Kortom; naarmate de tijd voorschreed en het einde naderde werd het resultaat alsmaar kleiner en kleiner; wel met een compenserende toegenomen compactheid van importantie, (dat dan weer wel!)

Nu de emotie:

Moe, loom en stroef bewegend sta ik nu licht gebogen, als na zwaar, lichamelijke inspanning, en schuif mijn Stetson iets naar achteren om mijn bezwete voorhoofd te kunnen deppen en overzie, voldaan met een hand in de zij, mijn inspanningen.

Bloed, zweet en tranen wordt wel eens gezegd; Welk een onzin!

Het is eerder: **BZI**: **B**alen, **Z**uur en **I**nsomnia…

Een toenmalige promovendus in Rotterdam bemerkte: ”Promoveren is slechts *10%* inspiratie en *90%* transpiratie”. En inderdaad, af en toe moest ik mijzelf tot de orde roepen om door te werken onder het motto: „*I don’t have to sleep, I don’t have to eat; I have to study*” (citaat uit film “Soul Man”); òf, een stuk papier bevestigd aan het plafond met opschrift „*You should be working!*”; zoals te zien is in de film “Hollow man”.

Tot de oren toe enthousiast en vol energie, en dit gebleven tot het eind toe.

Maar, nu serieus:

Eigenlijk kan maar een groep het meest -en vooral als eerste- bedankt worden: de mensen van de negen verpleeghuizen. Allereerst de bewoners/vertegenwoordigers die zich bereid vonden mee te werken aan dit onderzoek. Hoe belangrijk deze positieve beslissing geweest is voor het onderzoek van de ouderengeneeskunde, was niet te overzien in het begin van 2006. Maar, meer dan alle lof en dank komen U toe.

In de tweede plaats: de verzorgenden van de veertien verpleegafdelingen die geïnterviewd zijn. Zoveel enthousiasme en nieuwsgierigheid en betrokkenheid! Zonder jullie hulp kwam dit onderzoek niet eens van de grond. Ik denk dat de bestuurders van de deelnemende verpleeghuizen (laat staan onze minister van VWS) niet weten dat ze goud in hun personeelsbestand hebben. DANK. En nog eens DANK.

Professor Koopmans, beste Raymond, bedankt voor jouw vertrouwen dat in je mij gaf en mij aanstelde als promovendus van het voor jou o-zo-belangrijke Waalbed-II project, nadat ik een paar schreden in onderzoeksland had gezet in 2004-5. Bedankt voor jouw snelle en enthousiasmerende inbreng; zeker in het begin van onze samenwerking toen jij richting aangaf. Jij verdient alle lof voor hoe jij jouw vakgebied/afdeling hebt weten om te toveren van een

voornamelijk opleidingsafdeling tot ook een onderzoeksafdeling! Bedankt voor je geduld; die artikelen zijn er gekomen, en hoe!
In het begin begon ik met zoveel enthousiasme en energie dat ik niet kon vermoeden hoe zwaar het zou worden. Je had het over buffelen; en, inderdaad dit werd het; mede door externe omstandigheden: drie keer verhuisd en toegenomen drukte in het verpleeghuis.

Ik zag analogie in een Tour-de-France etappe: in het begin zat ik een bungelend groepje achter het peloton; terwijl jij en Sytse in de kopgroep het tempo aangaven. Geleidelijk heb ik mij naar het peloton gewerkt en kon ik uiteindelijk aanhaken bij de kopgroep. Bovendien, promoveren is het beklimmen van de Alpe d'Heuz: in de Tour-de-France het pièce de résistance en moment suprême, de berg opklimmen, allèèn onderweg, zwoegen, de top bereiken en vervolgens in de rit naar beneden oogsten wat onderweg gezaaid is (heerlijk!). En, dit -zijnde een diesel- vergt veel vertrouwen, wat je gegeven hebt, dank.

Professor Verhey, beste Frans, meestal niet de spraakzaamste tijdens de begeleidingscommissie maar wel degene met de meeste richtinggevende ideeën.
En, volgens mij zit er veel jeugdig enthousiasme en humor in je.
Jij gaf trouwens het beste advies aan het begin van mijn promotie: „En, veel plezier!"

Dr. Zuidema, beste Sytse; ja, met jou is het allemaal begonnen: Waalbed-I toen het nog allemaal gewoon Waalbed heette. Ik heb het beloop van jouw oorspronkelijke studie uitgevoerd en ik ben blij dat jij mij hebt begeleid in het uitvoeren van onze gezamenlijke interesse in dementie-gerelateerde neuropsychiatrische symptomen. Jij hebt mij eigenlijk als geen ander begeleid (analyses, schrijven, enthousiasmeren) en de juiste weg getoond; meer dan je weet…
(hopelijk ben ik die waardige opvolger geworden zoals je mij noemde in jouw proefschrift! ☺.
Jij als Prof!: dit gaat je lukken in het hoge noorden en ik hoop dat wij blijven samenwerken).

Dr. de Jonghe, beste Jos, wat een energie en inzicht heb jij. Ik heb genoten van onze samenwerking en het schrijven van artikelen. Jij had maar kleine hints nodig om mij nieuwe wegen in te laten slaan en met wat voor een succes! Jij hebt volgens mij echt door wat het is en nodig blijkt om ook internationaal succesvol te zijn. Een eenmaal toegestoken vinger werd gretig gevolgd. Dank!
Jij hebt mij laten inzien dat wetenschappelijk schrijven een vorm van marketing is!
(wanneer word jij eens prof?)

Dr. Lavrijsen, beste Jan, jij hebt een paar goede opmerkingen gemaakt: niet op de laatste plaats: "eerst monniken, dan missionarissen." Welk een vooruit ziende blik!

Dr. Gerritsen, beste Debby, dank voor je inspanningen omtrent die verschrikkelijke ADL-schaal! Zonder jouw expertise en inzet was en bleef deze schaal onbedoeld onduidelijk voor mij. Overigens, jij gaf mij eigenlijk het beste advies voor het schrijven… ☺
(en wat leuk dat wij samenwerken in nieuwe projecten! Ondanks deze vooralsnog prille samenwerking, heb je een al plekje in mijn hart…. ;-))

Ik wil aanvullend nog drie mensen bedanken die hebben bijgedragen, niet direct, meer op de achtergrond en over mijn schouder instemmend hebben meegekeken, maar toch niet onbelangrijk:

Allereerst mijn vader: arts en voorbeeld, en Betty, enorme steun met je inzicht. Door jou Pa, ben ik uiteindelijk arts geworden; niet voor niets hebben wij de zelfde Alma Mater. Tuurlijk heb ik veel van je geleerd; al bij geboorte inclusief (50% zelfde genen!); al die boeken -wel duizend- in jouw studeerkamer wachtend om gelezen te worden, en ook die groene Amerikaanse psychiatrische tijdschriften die je elke maand ontving (American Journal of Psychiatry; meerdere jaargangen) waren een aanwijzing van je zucht naar kennis, en een voorbeeld van je ziel van nieuwsgierigheid en toonbeeld van je enthousiasme. De liefde om 'te willen weten' heb ik van jou geërfd, zou ik zo denken. Zomaar, ergens in een restaurant leerde je mij -als kleine jongen- de eerste medische termen: o.a. Musculus Sternocleidomastoïdeus en Protuberantia occipitalis externa. Ik straalde toen ik ze ging begrijpen, zelf kon uitspreken en opschrijven. En wat moest ik toch lachen toen ik deze anatomische structuren op de snijzaal tegen kwam: ik wist ze al!

Betty, jij hebt mij wegwijs gemaakt op het levenspad, niet geheel onbelangrijk omdat ik nog veel te leren had. Hiervoor dank Pap en Bet, maar ook dat jullie mij in het begin in Rotterdam zo ontzettend goed geholpen hebben….

En wat goed dat wij, jij, Bet en ik, elkaar weer zien en spreken! En ons contact is nog nooit zo intens en wederzijds geweest. Wat een genot!

..In the living years..

Secondly, I would like to thank Dr. D.J. Cohen. Although deceased, you never cease to inspire me! I had met you the first time in Utrecht in 1991 and had met you several times afterwards. Never have I ever met a colleague so intelligent and shrewd and enthusiastic like you! Not even in Boston. The energy and wisdom you so easy, effortlessly portrayed: amazing, stimulating! While we drove to Manhatten in your car, we talked about the brain and its workings, and you talked about the tectonics of personal development using additional metaphors and you allowed me a glimpse into your mental department of knowledge and wisdom. I enjoyed these moments and I do thank you for your time spent with me in New Haven and in the Netherlands….

….this endeavour is partly due to you; moreover, you should have been on the Corona, but time passed us both by.

..Wish you were here..

Andere collega´s op de afdeling: Esther, jij hebt mij zien ploeteren op het review dat maar niet wilde lukken; en uiteindelijk zowaar lag daar toch nog het product. Jij vertelde over jouw ervaringen in het schrijven en op internationaal toneel. Dank voor je interesse en luisterend oor en bemoedigende woorden. Gé, de korte momenten die wij gebruikten om onze wederzijdse interesses uit te wisselen, niet in de laatste plaats: auto´s: de Aston Martin DB9. en welk een verbazing dat wij zonder dat we het wisten in het zelfde schuitje zaten in onze privésituatie…

Het secretariaat van onze afdeling; het zenuwcentrum; brandpunt van activiteiten. Mw. van Dalen-van Teylingen, beste Mathilde ik vond het altijd prettig met je s'ochtends -voor iedereen op

de afdeling (want wij waren steevast de eersten!)- al koffie te drinken en de laatste stand van zaken door te nemen.

Iepke Jansen en Jos van Berkel, de paranimfen.
Iepke, met mooie uitspaken, zoals: "*Net zolang cijfers kneden totdat ze bekennen*!". Jij was het die het boek "A primer in longitudinal data analysis" onder mijn aandacht bracht. Welk een goede actie, niet de enige die je gedaan hebt als onderzoeksassistent! Jouw kritische blik en onderzoekende *'mind'* waren voor mij een stimulans en spiegel tegelijkertijd. Wat een domper dat je ziek werd, maar je hebt je hier vrouwmoedig door heen geslagen; net zoals je die cijfers *kneedde*. ;-)
Jos, de altijd onverdroten volle energie, collega en werkmaat. Ik ben blij dat je mij wilt bijstaan tijdens dat *ene* uurtje… ;-). Het begrip verlies heeft voor ons allebei een betekenisvolle betekenis gekregen.

Mijn broer Frank, en dan is je broertje toch nog gepromoveerd. We delen meer dan alleen een gemeenschappelijke oorsprong…

Mijn collega's van SZR-Vrijthof. Van de artsenclub: Bob, Eveline, Nel, Casper, Janien, Jobje, Margriet en Willemijn. Ons secretariaat: Francis, Leonie, Lizzy en Angela (meid, wat hebben wij veel aan elkaar gehad tijdens onze *struggles,* goed en fijn dat je er was! ;-)).
Maar ook van de verzorging, allemaal bedankt voor jullie belangstelling in de afgelopen jaren…

Frits van Es, directeur-bestuurder en arts, en Marie-Josée Andringa-Zalmann, hoofd behandeling en begeleiding en arts, dank voor de financiële middelen om naar het buitenland te gaan voor deze studie.
Ook bedankt voor jullie interesse in de voortgang van het boekje; maar, nog meer, ook dank voor jullie speciale belangstelling in mijn veranderde privéleven gaandeweg tijdens de fase van voltooiing. In het bijzonder dank voor jullie ideeën, suggesties en adresjes.

Mijn buurman Ben Deutschman, voor het proofreaden van het Qol-verhaal.

Iedere muzikant die prachtige muziek (o.a. *Curtis Mayfield, Marvin Gaye, Evanescence, Pink Floyd, Rachmaninoff, Anthony, New Order*; *Adele* to name only a few…) heeft gemaakt en mij heeft bijgestaan door de afgelopen jaren en mijn leven hebben geïntensiveerd.
Ik heb mijn Alpe d'Heuz bedwongen… ;-)

Verder wil ik nog een paar, geweldige vrouwen bedanken (naast mijn familie) die mij geholpen hebben te zijn wie ik nu ben…. : … vrij van *matrimonial mess*, vrij in mijn *geest*, comrad in sorrow en vriendinschap: Danielle, Laura, Roelien, Saskia.

xxR/B

“ I feel so extraordinary
something ‘s got a hold on me
I get this feeling I’m in motion
A sudden sense of liberty ”

Tjeee,
..heb mijn dankwoord toch een paar keer moeten herschrijven, maar het einde nu, is toch echt voor jou!

…Pap, dit boekje is voor jou! ;-)… alhoewel je niet hebt kunnen genieten van dit boekje, voltooid en tastbaar in je handen, heb ik de waardering in je ogen gezien en gehoord van jou en van Bet, ook na je overlijden.
En, ik weet dat je boven zit te genieten en te glimlachen hoe ik het eraf breng tijdens *my 60 minutes of fame*… trots dat je bent…

Eenmaal uitgesproken, vielen puzzelstukjes op hun plaats en je wist het, en je gaf jouw blijk van erkenning en je zei dat het goed was….

Pa, ik ben je veel verschuldigd en veel dank komt jou toe… …nou, bij deze, middels dit boekje! ☺

„ Losing, it comes in a cold wave
of guilt and shame all over me
Forgive me
Let live me
set my spirit free “

Roland B. Wetzels werd geboren in Nijmegen op zeven januari 1969. Na het behalen in 1988 van het atheneumdiploma aan het Kottenpark College te Enschede, werd de tienerperiode afgesloten met een lange rondreis door de Verenigde Staten van Amerika. Bij terugkomst wachtte de studie geneeskunde aan de Erasmus Universiteit te Rotterdam.

Na een aanvankelijk moeilijke start ging de studie voortvarend: het doctoraalexamen werd in 1992 afgelegd en drie jaar later het artsexamen. Na het behalen van het propedeuse werd hij lid van studentenvereniging RSC en heeft hij nog enige tijd filosofie als tweede studie gevolgd. Voornamelijk in weekeinden en tijdens vakanties, werkte hij van 1990 tot 1995 als verpleegassistent in het psychogeriatrisch verpleeghuis "De Hofstee". Hier leerde hij voor het eerst omgaan met mensen in verschillende stadia van dementie. Uiteindelijk moest hij stoppen omdat de studie afgerond was; met veel plezier had hij evenwel hier gewerkt. Gedurende de wachttijd voor het starten van de co-schappen, werd nog een postdoctoraal examen in de neuroanatomie, handelend over geheugenprocessen, afgelegd. Zijn doctoraalscriptie handelde over de relatie tussen corpus callosum en het Gilles de la Tourette-syndroom. Dit onderzoek vond plaats in 1992 in de VS aan het Child Study Center, Yale University School of Medicine te New Haven. Hier leerde hij Dr. DJ. Cohen, Dr. JF. Leckman en Dr. BS. Peterson goed kennen. De tijd van zijn leven: omringd door mensen met liefde voor kennis, nieuwsgierigheid en enthousiasme. Tijdens dit verblijf heeft hij op een vrijdag in een gehuurde Chevrolet door de straten van Manhatten gereden, tegen het advies in van collega's: "Ooh no, you will get stuck in traffic in NYC!" Hij had echter de tijd van zijn leven met de radio blasting songs: "*Right here, right now, there's no other place I wanna be*" intussen onder andere langs de Twin Towers rijdend. Een jaar later keerde hij terug naar Amerika voor het volgen van meerdere co-schappen: neurologie en kinderneurologie aan de afdelingen van het Massachusetts General Hospital van Harvard Medical School

in Boston. Hard werken en wat een geweldig academisch, enthousiasmerende sfeer! Na het afleggen van het artsexamen (cum laude) begin 1995 werd de dienstplicht vervuld als officierarts bij de Koninklijke Landmacht. Na dit jaar werkte hij in zijn eerste, echte artsenbaan op de afdeling neurologie van het Radboud ziekenhuis. Na een halfjaar interne geneeskunde in het Catharina ziekenhuis in Eindhoven heeft hij nog ruim driekwart jaar op de afdeling –wederom- neurologie in Maastricht gewerkt. Uit praktische overwegingen woonde hij kortdurend in België. Sindsdien weet hij dat de Belg helemaal niet kan autorijden! Na meer dan twee jaar in het ziekenhuis gewerkt te hebben, werd evenwel de keus gemaakt voor het werken met de oudere medemens en wel buiten het ziekenhuis. De praktijkopleiding tot specialist ouderengeneeskunde werd in verpleeghuis Kalorama te Beek/Ubbergen volbracht: een prachtige periode van twee jaar: vooral de lunches met Ruud Harbers, Ton Moors & Bert Houkes waren legendarisch! Man, wat een tijd; veel geleerd, maar belangrijker: veel gelachen. Ook leerde hij hier van Prof. Froeling de finesses van het vak en het enthousiasme. Het theoretische onderdeel aan de Radboud Universiteit afdeling verpleeghuisgeneeskunde.

Na het afronden van de opleiding in 2000 werkt hij als specialist ouderengeneeskunde in Tiel. Sinds 2006 werkte hij gedurende twee dagen in de week aan dit proefschrift. En sinds september 2010 werkt hij ook als docent kennis en wetenschap in de opleiding tot specialist ouderengeneeskunde aan Radboud Universiteit Nijmegen. Bovendien begeleidt hij nu promovendi sinds begin 2011.

Naast deze werkzaamheden in Tiel en Nijmegen was hij van 2004-2009 secretaris/penningmeester van Verenso regio-Arnhem/Nijmegen.

Per begin 2012 gaat hij met zijn poezen wonen in de stad waar hij ook werkt: Tiel. Hier heeft hij een mooi, vrijstaand huis gekocht alwaar hij o.a. s'avonds piano kan spelen of muziek wat harder kan zetten en kan gaan doen wat zijn motto is geworden voor het leven: *Live my life & Enjoy it!*

„ It is a little bit funny this feeling inside “

„ Never opened myself this way
Life is ours, we live it our way
All these words I don't just say
and nothing else matters “