Sytse Zuidema

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COLOFON

This research presented in this thesis was performed by a researcher of the care organisation 'Kalorama' in Beek-Ubbergen, in co-operation with the Department of Nursing Home Medicine of the Radboud University Nijmegen Medical Centre and the Nijmegen University Nursing Home Network (UVNN), The Netherlands.
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Neuropsychiatric symptoms in Dutch nursing home patients with dementia

Een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

Proefschrift

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aan de Radboud Universiteit Nijmegen,
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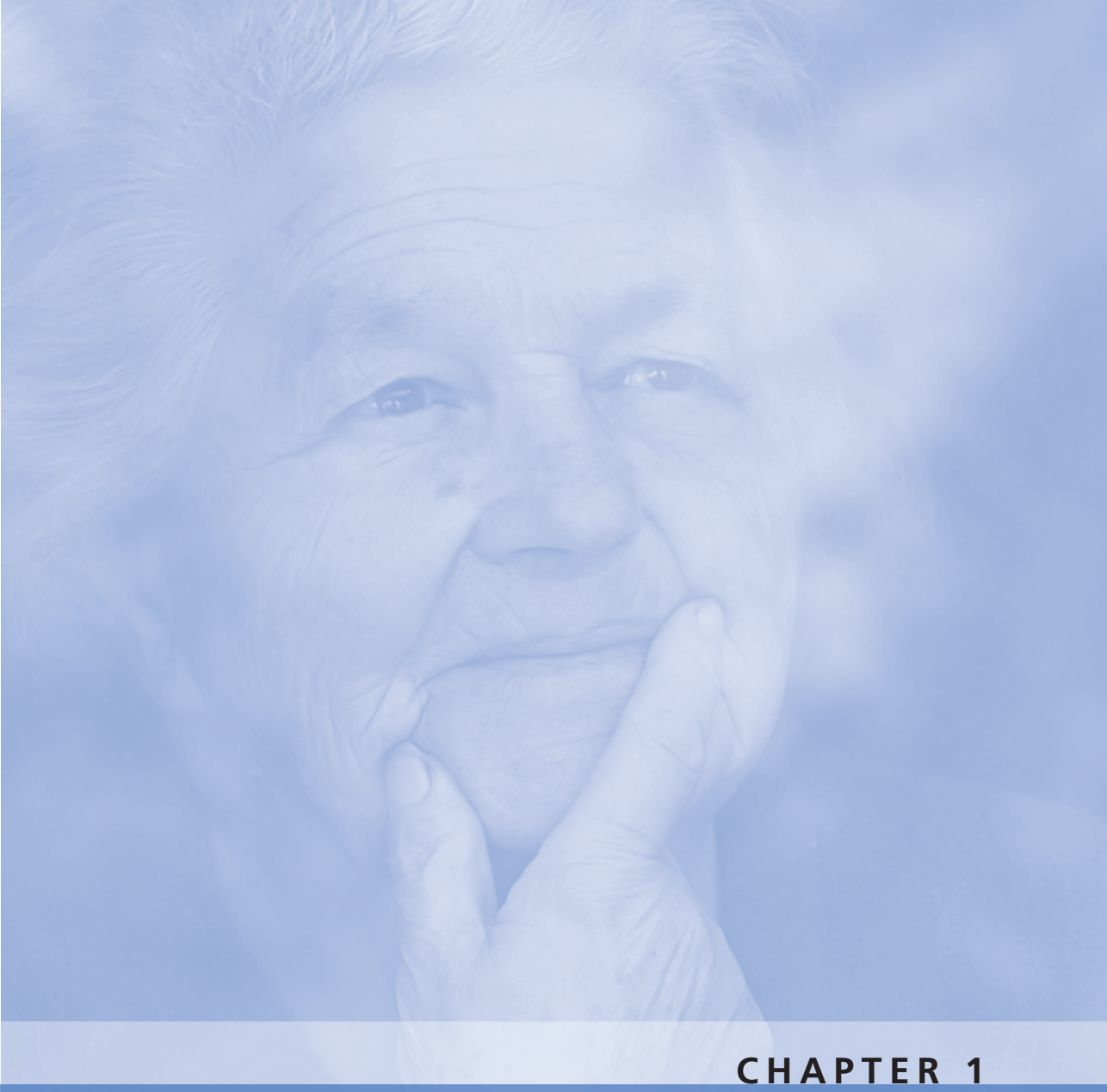

CHAPTER 1

General Introduction

Introduction

In our ageing society, dementia can cause considerable morbidity and mortality. Over the last decades this progressive disease shows ever increasing prevalence and incidence rates. The estimated worldwide prevalence is 27.7 million demented persons.[1] Of the 16 million inhabitants in the Netherlands, dementia is prevalent among 175,000 people. As the Dutch population itself is ageing, the prevalence will rise to 355,000 in the year 2030.[2] The effect of the disease on cognition, activities of daily living and behaviour causes considerable loss of quality of life in both patient and caregivers. Particularly the behavioural problems, such as agitation/ aggression are a burden for the caregiver [3-5] and are often the main reason for institutionalization.[6-8] Consequently, neuropsychiatric symptoms are highly prevalent in nursing home patients, are difficult to deal with and can be a serious burden to the staff.[9, 10] Psychotropic medications [11-17] and physical restraints [18, 19] are often used to manage behavioral changes in nursing home patients.

Neuropsychiatric symptoms, definition and taxonomy

Definitions of what constitutes behavioural changes and 'problem behaviours' in particular, vary widely. To some extent this variation in definitions reflects the emerging new area of research and the accompanying ideological differences in point of view of those defining symptoms in dementia. In 1996, the International Psychogeriatric Association launched the concept of Behavioural and Psychological Symptoms in Dementia (BPSD), which are 'signs and symptoms of disturbed perception, thought content, mood, or behaviour that frequently occur in patients with dementia'.[20] This umbrella term not only covered behavioural problems, such as agitation or aggression, but also includes psychological symptoms as delusions, hallucinations, misidentifications, anxiety, depressed mood, or apathy. The concept of BPSD was meant to focus attention on the non-cognitive symptoms in dementia, and initiated a lot of scientific research on this subject. However, it is disputable whether this umbrella term is useful for both research and clinical practice,[21] because neuropsychiatric symptoms are heterogeneous and may not reflect one single unifying concept. [22]

The Dutch association of nursing home physicians (NVVA) advocates using the term 'problem behaviour'. It is defined as 'any type of patient behaviour that is difficult to be dealt with by patients themselves and/or their carers'.[23] However, the NVVA guideline is not specifically developed for dementia patients only and covers a wide range of symptoms in different patient populations including such as dementia and stroke. Problem behaviour in this guideline focuses on overt behaviour such as agitated and aggressive behaviour and apathy. Psychosis and depression are not considered as behaviour, but as mental disorders underlying problem behaviour.

We feel that the term neuropsychiatric symptoms – most widely used in the U.S.A. and recently re-adopted by the International Psychogeriatric Association [24] – is a more neutral term better suited for the broad range of behaviours and mood-disturbances common in dementia. Neuropsychiatric symptoms can be clustered into aggression, (psychomotor) agitation, psychosis, depression / affective behaviour, and apathy. [22, 25] This terminology is clinically meaningful and can be used for practical purposes such as in clinical trials.
Throughout this thesis, the term neuropsychiatric symptoms will be used, unless it is meant to focus on specific symptoms such as agitation.

Dutch nursing home care

In the Netherlands, 30,000 of the institutionalized patients with dementia are residing in nursing homes and another 30,000 in residential homes.[2]
Nursing homes in the Netherlands differ from their counterparts in other countries in that the staff includes specially trained nursing home physicians (one full-time doctor per 100 patients), physical therapists, occupational therapists, speech therapists, pastoral workers, dietarians, psychologists, social workers and, occasionally, music therapists and psychomotor therapists, all of whom are employed by the nursing home.[26-28] Multidisciplinary care for people with dementia is provided in special care units (SCUs). SCUs are designed to provide care for 6–40 people with dementia (per unit). The SCU's environment is usually adapted to meet the needs of the patient with dementia, by the presence of camouflaged closed-door systems, (therapeutic) gardens and patios, presence of an walking circuit, tape lines on the floor or devices to improve orientation.
Due to capacity problems in the institutional health care sector and the expected increase of the number of (demented) patients making an appeal to nursing home care, nursing homes try to adapt to these developments by delivering nursing home care in the community and in residential homes (so-called 'outreaching nursing home care'). The aim of providing outreaching nursing home care is enabling people with dementia to stay in their (residential) homes as long as possible and thereby postpone or prevent nursing home admission.[29]
In recently built nursing homes, the ward-unit size tends to be smaller, in order to mimic the home situation. Currently the usefulness and efficacy of this 'small scale housing units' is a matter of debate. Clinicians and workers in the field who support this concept claim that the quality of care in these particular units is higher with more person-centered care, which increases quality of life, preserves ADL functioning, and reduces the amount of neuropsychiatric symptoms with less prescription of psychotropic medication as a consequence.[30] Yet, there is no evidence in favour of small scale housing or other interventions that may improve the quality of the physical environment of nursing homes in the Netherlands.

Aim of this thesis

Determinants of psychopathology are probably multifactorial in nature and include biological, psychological, social factors. The biopsychosocial model proved to be useful in explaining behavioral changes in community-dwelling dementia patients in the Maastricht Study of Behaviour in Dementia (MAASBED) study.[31, 32] It is against this background that hypotheses on the biopsychosocial correlates of neuropsychiatric symptoms in nursing home patients with dementia were generated.
To examine the magnitude of the neuropsychiatric symptoms in patients with dementia and the usefulness of the biopsychosocial model in Dutch nursing homes, we conducted a large cross-sectional study, the WAAL Behaviour in Dementia (WAALBED) study – a name obviously derived from the MAASBED study.
Insight in prevalence and predictors of neuropsychiatric symptoms has consequences for efficient use of staff, and could provide valuable information for psychosocial and pharmacological interventions to improve quality of life. Insight in the relation of neuropsychiatric symptoms and the physical environment could have consequences for development of appropriate services for nursing home residents.
The aim of the thesis is to gain further insight in (1) the prevalence of neuropsychiatric symptoms in dementia patients residing in Dutch nursing homes and in residential homes (receiving outreaching nursing home care) and (2) the patient- and environmental correlates of neuropsychiatric symptoms.

Research questions and general outline

The following research questions are addressed:

1. *What is the prevalence of neuropsychiatric symptoms in dementia patients receiving nursing home care?*

Chapter 2 gives an overview of the literature on the prevalence and predictors of neuropsychiatric symptoms in cognitively impaired nursing home patients. Few nursing home based studies evaluated neuropsychiatric symptoms in dementia patients using specific diagnostic criteria. Therefore, also studies on the prevalence of neuropsychiatric symptoms in ´cognitively impaired´ patients are reviewed. Only a limited number of studies showed some evidence that specific environmental characteristics of the dementia special care units are associated with neuropsychiatric symptoms, a finding that – among other factors related to dementia severity – distinguishes these SCU patients from those residing in the community.

Chapter 4 describes the actual prevalence rates of neuropsychiatric symptoms in the WAALBED study in patients with dementia in Dutch nursing homes and patients receiving outreaching nursing home care in residential homes.

Neuropsychiatric symptoms in general and agitation in particular were assessed with the Neuropsychiatric Inventory – Nursing Home version (NPI-NH) and the Cohen-Mansfield Agitation Inventory (CMAI), specifically. These assessment instruments are very often used in both prevalence studies and in intervention studies.

2. *What is the efficacy and adverse events of antipsychotic medication for neuropsychiatric symptoms in patients with dementia?*

Chapter 3 gives a systematic overview of the current evidence of the efficacy and adverse events of antipsychotic drugs as the main pharmacological therapy for neuropsychiatric symptoms. These drugs are frequently prescribed to patients with dementia, who are prone to develop adverse events, due to the age, co-morbidity and frailty.

3. *What is the factor structure of the NPI-NH and CMAI in Dutch nursing home patients with dementia?*

Chapters 5 and 6 are methodological chapters concerning the NPI-NH and CMAI. The chapters describe the factor structure of the NPI-NH (chapter 5) and CMAI (chapter 6) of the WAALBED study. Factor analysis is a statistical technique used to examine validity of a rating scale, to gain a better understanding of the behavioural dimensions that underlie many different neuropsychiatric symptoms in general (NPI-NH) or -in this case- agitation/aggression (CMAI) in particular. Factor structure invariance was examined in different stages of dementia to investigate whether findings were robust across different patient samples (chapter 5). Factor analysis of the CMAI was used to investigate whether specific symptom clusters can be used as subscales, for both research or practical purposes (chapter 6).

4. *What is the influence of patient-related factors on the prevalence of neuropsychiatric symptoms in nursing home patients with dementia?*

Chapter 2 gives an overview of the literature of factors associated with patient demographics (gender, age, race, marital status) and factors associated with the type and severity of the disease on neuropsychiatric symptoms.
Chapter 7 describes the patient related factors of neuropsychiatric symptoms in the Dutch nursing home population with dementia (WAALBED study), in specific the influence of dementia severity and gender. These factors were considered as important predictors in community-dwelling patients, but there is only limited evidence of the contribution of this factors on neuropsychiatric symptoms in nursing homes.

5. *What is the influence of factors associated with the physical and psychosocial environment of the special care units on the prevalence of neuropsychiatric symptoms in Dutch nursing home patients with dementia?*

Chapter 2 gives an overview of the current literature of the environmental factors on neuropsychiatric symptoms, such as the use of physical restraints and factors associated with the physical and social environment.
Chapter 8 describes the influence of environmental characteristics related to the special care unit on the prevalence of the neuropsychiatric symptoms in the nursing home population of the WAALBED study. In this chapter the differences of SCU symptom prevalences are described and related to the environmental characteristics of the SCU, such as the number of patients, the number of staff, presence of an walking circuit in order to gain further insight in the influence of the physical and psychosocial environment on neuropsychiatric symptoms.

Finally, in chapter 9 the main findings of this thesis were summarized by addressing the research questions. We discussed the strengths and limitations of the study followed by the clinical implications for researchers, physicians and psychologists, carers, architects, nursing home management and policy makers. This chapter ends with suggestions for future research and a general conclusion.

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CHAPTER 2

Prevalence and Predictors of Neuropsychiatric Symptoms in Cognitively Impaired Nursing Home Patients

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Abstract

The prevalence of neuropsychiatric symptoms and the influence of predictive factors in cognitively impaired nursing home patients were reviewed. Articles were identified by means of a MEDLINE and PsycInfo literature search. Neuropsychiatric symptoms were present in more than 80% of the cognitively impaired patients. Prevalences ranged considerably, from 3 to 54% for delusions, 1 to 39% for hallucinations, 8 to 74% for depressed mood, 7 to 69% for anxiety, 17 to 84% for apathy, 48 to 82% for aggression or agitation, and 11 to 44% for physical aggression. Neuropsychiatric symptoms seemed to be predicted not only by dementia type or stage but also by the psychosocial environment and the amount of psychoactive medication and physical restraints used. Neuropsychiatric symptoms are common and influenced by both the disease itself and the psychosocial environment of the institutional setting. The latter may have important consequences for staff planning and education and the future design of care facilities.

Introduction

Patients presenting with neuropsychiatric symptoms cause considerable suffering to themselves as well as to family members and other caregivers.[1-3] The behaviour itself [4-6] or accompanying caregiver distress[7] may result in the patient being institutionalized in a nursing home or another type of care facility. This institutional setting provides the ideal framework for reviewing this particular aspect of dementia, because the already high prevalence rates of these symptoms can be expected to be enhanced further by the social environment, in which patients with severe dementia are usually spending a considerable portion of their daytime hours with other patients. Patients with neuropsychiatric symptoms can be a serious burden to the staff of nursing homes and other long-term care facilities, possibly leading to an increase in staff distress,[8, 9] and the patients themselves are often subjected to high levels of psychotropic medication[10, 11] and physical restraints.[12] Moreover, the care for patients with neuropsychiatric symptoms results in high economic costs.[13]

Many studies have estimated the prevalence of neuropsychiatric symptoms in demented or cognitively impaired patients. The majority of these studies has included community-dwelling patients or patients temporarily admitted to hospitals or research clinics. However, a considerably large group of demented patients are admitted to institutions; for example, in the Netherlands, 35% of dementia patients reside in nursing homes or other long-term care facilities, such as residential homes.[14] An assessment of the prevalence of symptoms in cognitively impaired nursing home patients and an insight into possible factors influencing these symptoms are indispensable for accurately planning both the short-term and long-term efficient use of staff in healthcare facilities against reasonable costs. Moreover, such an assessment could provide valuable information on psychosocial and pharmacological interventions to improve the quality of life of these patients. The objective of this study was: (a) to determine the prevalence of neuropsychiatric symptoms in cognitively impaired nursing home patients and (b) to provide an overview of possible predictors of these symptoms based on a review of the literature.

Methods

A computerized search in MEDLINE and PsycInfo was carried out for English-language citations of 'prevalence or predictors or correlates' of 'neuropsychiatric symptoms' in 'dementia or Alzheimer or cognitively impaired' patients (included MESH-terms) between 1966 and August 2005. We also performed a search using related terms such as aggression, agitation, anxiety, apathy, depression, disinhibition, euphoria, hallucinations, irritability, misidentifications, negativism, psychosis, restlessness, and wandering. The reference lists of the articles identified were also used to identify other articles.

We screened all retrieved titles and abstracts by hand. The inclusion criteria were (a) studies of institutionalized patients in nursing homes, chronic or long-term care facilities, or dementia special care units; and (b) studies of patients with dementia based on a chart diagnosis or using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) or other criteria, or cognitively impaired patients, as operationalized by Mini-Mental State Examination (MMSE) scores <24. Excluded were articles that considered (a) patients on social care, assisted living care or residential care; and (b) cognitively impaired patients with other diagnoses, such as delirium, psychiatric or other neurological disorders.
Studies that considered the influence of predictors in a population specifically selected on high symptom rates were not considered in the present review on prevalence. Neuropsychiatric symptoms were defined using a variety of terms. Since there is no solid, widely accepted classification of these symptoms, we categorized them into (a) psychosis, including delusions, and hallucinations; (b) mood disorders, including depression as syndrome, depressed mood as a symptom, anxiety, crying, apathy; and (c) agitation and aggression, including verbal and physical aggression, irritability, disinhibition, wandering, restlessness, and repetitive or aberrant motor behaviour/ mannerisms, self-injurious behaviour.

Results

Based on a preliminary assessment of 548 retrieved abstracts, we chose 81 articles which met or seemingly met the inclusion criteria. After the full text of each abstract had been evaluated, only 25 were judged to have met these inclusion criteria. Prevalence rates were discussed in 19 of these papers,[15-33] and predictors in 18.[15, 16, 18-20, 22-25, 27, 29, 32, 34-39] The influence of predictors in a selected population of patients with high prevalence rates of the specific behaviour of interest was studied in 5 articles.[34-36, 38, 39]

Patient Population

In 2 articles, the study cohort consisted of patients residing in chronic or long-term care facilities;[27, 28] all of the remaining articles dealt with patients residing in nursing homes, with 4 of these involving patients admitted into dementia special care units.[16, 17, 19, 34] In 7 studies, there was evidence of a diagnosis of dementia based on DSM-III-R/DSM-IV,[25, 30, 32, 33] or other criteria[18, 26, 31] (table 1). In 5 other studies a further classification of dementia into Alzheimer's dementia, vascular dementia, mixed type dementia, and other dementias according to standard criteria[15, 17, 28, 29, 37] or neuropathological examination[27] was available. In 7 other studies the diagnosis of dementia was based on consensus between physicians,[16, 39] was based on a chart or clinical diagnosis,[35, 38] or was not specified at all.[19, 22, 23] The remaining 4 studies dealt with cognitively impaired patients as assessed by MMSE <24.[21, 24, 34, 36]

Table 1.
Patient characteristics and study design of 19 studies estimating the prevalence of neuropsychiatric symptoms in cognitively impaired nursing home patients

Author, Year	Country	Multi centre	Number of patients	Diagnosis	Criteria	Mean MMSE (SD) [range]	Study design/ aim
Drachman, 1992	USA	1	36	53%AD, 19%VaD/mix, 28% other	Clinical diagnosis	6.6 (13) [0-45] (stand. MMSE)	Reliability COBRA scale in community-dwelling and institutionalized patients
Wagner, 1995	USA	70	614	Dementia	Clinical diagnosis	7.8 (6.1) [0-23]	Prevalence and predictors of behaviour in patients newly admitted on special care units
McCann, 1997	USA	2	177	AD	NINCDS-ADRDA	8.9 (5.9)	Concordance between direct observation and staff rating of behaviour in AD
Cohen, 1998	USA	3	286	Dementia	GDS, MMSE	13.6 (4.6) black/ 15.7 (5.3) white	Differences in predictors of depression, agitation and psychosis in black and white patients
Sloan, 1998	USA	53	951	Cognitively impaired	MDS-Cog	4.9 (1.3) [2.7-6.8] (MDS-Cog)	Point prevalence agitation and environmental correlates
Kolanowski, 1999	USA	4	84	Dementia	MMSE	5.0 (6.3)	Relation between physical aggression and personality to refine the need-driven dementia-compromised behaviour model
Wood, 2000	USA	1	69	Cognitively impaired	MMSE	6.7 [0-17]	Validity NPI-NH, comparing responses of certified nurses' aides and licensed vocational nurses
Schreiner, 2000/2001 [1)]	Japan	6	392	Dementia	NR	NR	Prevalence of agitation and aggression in Japanese nursing homes
Brodaty, 2001	Australia	11	484	Cognitively impaired	AMTS	NR	Prevalence and predictors of behaviour in Australian nursing homes
Margallo, 2001 [2)]	UK	3	231	Dementia	AGECAT	7.0 (7.0)	Differences in prevalences between social and nursing home care, relationship with cognition and psychotropic drugs

Author, Year	Country	Multi centre	Number of patients	Diagnosis	Criteria	Mean MMSE (SD) [range]	Study design/ aim
Payne, 2002	USA	1	201	60% AD, 12% VaD, 8% mix, 20% other	NIN(C)DS-ADRDA/ AIREN	NR	Incidence, prevalence and persistence of depression in newly admitted patients
Suh, 2004	Korea	2	257	52% AD, 48% VaD	DSM-IV	NR	Validation of Korean version of the CMAI
Pitkala, 2004 [2)]	Finland	7	160	Dementia	DSM-IV	NR	Differences in prevalences of behaviour in nursing home and acute geriatric wards
McCarthy, 2004 [2)]	USA	Several	1883	Dementia	ICD-9	NR	Prevalences of mental illness, differences in behaviour in patients with and without dementia
de Jonghe-Rouleau, 2005	The Netherlands	1	110	Dementia	DSM-IV	80% severe cognitive impairment	Prevalence of SIB, construct validity, relation with other symptoms, cognition, psychotropic drugs and restraints

Note:

AD = Alzheimer's dementia, **Mix** = Mixed type of dementia, **VaD** = vascular dementia; **AGECAT** = computer based diagnostic system formulation 8 diagnostic clusters (organic, schizofrenic/paranoia, mania, depression, obsessionality, hypochondriasis, phobia, anxiety), **AMTS** = Abbreviated Mental Test Scale, **DSM** = diagnostic and statistical manual of mental disorders, **GDS** = global deterioration scale, **ICD-9** = International Classification of Diseases (9th version), **MDS-Cog** = Minimal Dataset-Cognition Scale, **MMSE** = Mini-Mental State Examination, **NINCDS-ADRDA** = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, **NINDS-AIREN** = National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences; **NR** = Not reported; **COBRA** = Caretaker Obstreperous-Behaviour Rating Assessment, **CMAI** = Cohen-Mansfield Agitation Inventory, **NPI-NH** = Neuropsychiatric Inventory – Nursing home version, **SIB** = self-injurious behaviour,

1) Articles of Schreiner were combined (addressed same patients population)

2) Only a subgroup of nursing home patients was presented

3) Only a subgroup of dementia patients was presented

Prevalence

The 19 studies addressing the prevalence of neuropsychiatric symptoms were very different with respect to patient population, design/aim of the study, and the rating scale used (table 1); the patients participating in these studies not only differed with regard to their diagnosis (Alzheimer's dementia, vascular dementia, or unspecified dementia), but had different levels of cognitive impairment as well, with mean MMSE scores ranging from 5.0[20] to 15.7.[18] Mean age ranged from 78 years[31] to 87 years.[21] The majority of these patients were female, with the proportion ranging from 66%[27] to 83%[32], except for a study of military veterans (94% male).[31] The prevalence rates of neuropsychiatric symptoms are presented in 19 studies, but only 10 of these were primarily designed to assess the prevalence (and predictors) of newly admitted[16, 28, 33] or long-stay[22, 23, 24, 32] patients in nursing homes or long-term care facilities or to assess cultural differences[18] or differences in prevalence between care settings[26, 30] in a cross-sectional design.

A variety of rating scales were used to assess different symptoms, with only 3 inventories used in more than 1 study: the Behavioural Pathology in Alzheimer's disease rating scale (BEHAVE-AD),[18, 24] Neuropsychiatric Inventory- Nursing Home version (NPI-NH),[21, 26] and Cohen-Mansfield Agitation Inventory (CMAI)[17, 22, 23, 29] (Table 2.). Five studies estimated the (overall) prevalence of any one neuropsychiatric symptom in nursing home patients, which was found to range from 82% to > 90%[16, 24, 26, 30]; a low prevalence (38%) of any one symptom was found in one study that used a Clinical Interview Schedule, in which symptoms were only observed or reported during a semi-structured interview.[33]

Table 2.

Prevalence Estimates of Neuropsychiatric Symptoms in Cognitively Impaired Nursing Home Patients in 19 studies

Author, Year	Assessment Instrument	Prevalence (All)	Psychosis	Depression, anxiety, apathy	Agitation
Drachman, 1992	COBRA		36 delusions, 13 hallucinations		64 aggression (33 verbal/25 physical), 67 motor behaviour (22 wandering)
Wagner, 1995	MBPC-NH	>90	49 delusions, 39 hallucinations	37 depressed mood, 48 anxiety, 41 apathy	71 wandering, 61 restlessness
McCann, 1997	CMAI				37 verbal, 25 physical aggression, 47 wandering, 32 aberrant motor behaviour
Cohen, 1998	CSDD, CMAI, BEHAVE-AD		23 psychosis	23 possible depression, 4 major depression	

Author, Year	Assessment Instrument	Prevalence (All)	Psychosis	Depression, anxiety, apathy	Agitation
Sloan, 1998	RSOC (direct observation)				10 agitation (4 aberrant motor behaviour, 6 wandering), 0 aggression
Kolanowski, 1999	RAS				44 physical aggression
Wood, 2000	NPI-NH		17 delusions, 19 hallucinations	74 depressed mood, 46 anxiety, 84 apathy	77 aggression/agitation, 67 irritability, 30 disinhibition, 51 aberrant motor behaviour
Schreiner, 2000/2001	CMAI				45 aggression (39 verbal / 25physical), 37 wandering, 38 restlessness
Brodaty 2001	BEHAVE-AD	92	54 delusions, 33 hallucinations (60 psychosis)	44 depressed mood, 69 anxiety	53 agitation, 77 aggression
Menon, 2001	PGDRS, CSDD		1 psychosis	21 depressed mood	10 verbal, 11 physical aggression
Evers, 2002	DSM-IIIR			29 major depression	
Payne, 2002	CSDD			20 depressed mood	
Wancata, 2003	CIS	38	3 delusions, 1 hallucinations	8 depressed mood, 7 anxiety	6 aggression
Suh, 2004	CMAI				82 aggression /agitation (39 physical), 82 motor behaviour (28 wandering)
Pitkala, 2004	Nurse questionnaire	88	36 delusions (56 psychosis)	4 major depression, 51 depressed mood, 51 anxiety, 17 apathy	28 agitation, 18 aggression, 17 wandering
McCarthy, 2004	ICD-9, PAI			4 major depression	22 verbal, 19 physical aggression, 61 inappropriate behaviour
de Jonghe-Rouleau, 2005	Nurse rating scale				22 self-injurious behaviour

Note:
All data are presented as percentages; **BEHAVE-AD** = Behavioural Pathology in Alzheimer's disease rating scale, **CMAI** = Cohen-Mansfield Agitation Inventory, **CIS** = Clinical Interview Schedule, **COBRA** = Caretaker Obstreperous-Behaviour Rating Assessment, **CSDD** = Cornell Scale for depression in dementia, **MBPC-NH** = Memory and Behaviour problems Checklist- Nursing home version, **NPI-NH** = Neuropsychiatric Inventory- Nursing Home version, **PAI** = Patient Assessment Instrument, **PGDRS** = Psychogeriatric Dependency Rating Scale, **RAS** = Ryden Aggression Scale, **restl** = restlessness, **RSOC** = Resident and Staff Observation Checklist.

Psychosis

Prevalences of psychosis reported in 3 studies varied from 23 to 60%.[18, 24, 30] Only Menon et al[25] reported a remarkably low prevalence of psychosis (1%), defined as the presence of hallucinations or delusions measured with the Psychogeriatric Dependency Rating Scale (PGDRS). Some studies described psychotic symptoms (i.e., delusions or hallucinations) separately. Delusions were present in 16 to 54%[15, 16, 21, 24, 26, 30] of the patients, whereas hallucinations were reported in 5 to 39% of the patients.[15, 16, 21, 24, 26] Visual and auditory hallucinations were reported in 21% and 16% of the patients, respectively.[30] Low prevalences of delusions and hallucinations – 3% and 1%, respectively – were recorded when symptoms were observed during a semi-structured interview.[33]

Mood disorders, anxiety, apathy

In the study of Evers et al,[27] 29% of the demented patients were judged to suffer from a major depression, whereas Cohen et al[18] found prevalences for possible depression of 19% and 34% for black and white patients, respectively. Using the more strict DSM-IV criteria for probable major depression, Cohen et al[18] found much lower frequencies for both groups (3% and 9%, respectively). The overall percentages of major depression in the total group was 4%, which is similar to that found in two other studies.[30, 31]

Several studies described the prevalence of depressive symptoms rather than the frequency of major or minor depression. Prevalences of dysphoria or depressed mood ranged from 8% to 74%[16, 21, 24-26, 28, 30, 33]. Crying occurred in 22% of the demented patients.[16] Prevalences of anxiety ranged from 7% to 69%.[16, 21, 24, 26, 30, 33] Euphoria, a mood symptom less well studied, occurred in 3 to 7% of the demented patients.[26, 33] The prevalence of apathy varied from 17% to 84%[16, 21, 26, 30] with major difference in prevalence between the 2 Neuropsychiatric Inventory (NPI) studies.

Agitation and Aggression

The overall prevalence of agitated or aggressive behaviours was found to range from 48% to 82%, depending on the rating scale used to assess a wide range of symptoms.[21, 26, 29] Agitation (aggression not included) was prevalent in 28% and 53% of the respective patients of 2 studies.[24, 30] With respect to the different manifestations of agitation, frequencies of 18% and 30% were reported for disinhibition,[21, 26] 31% and 67% for irritability,[21, 26] 38% and 61% for restlessness,[16, 22] 17 to 71% for wandering,[15-17, 22, 29, 30] and 32 to 51% for aberrant motor behaviour.[17, 21, 26] In some studies, symptoms such as wandering, pacing, hyperkinesias, and repetitive sorting were grouped as motor abnormalities, which occurred in 67% and 82% of the patients.[15, 29] Frequencies of aggression showed a considerable degree of variation, from 6 to 77%.[15, 23, 30, 33] When aggression was specified as either verbal or physical aggressive behaviour, the frequencies ranged from 10% to 39%[15, 17, 23, 25, 31] and from 11% to 44% [15, 17, 20, 23, 25, 29, 31]

respectively. Self-injurious behaviour, a symptom very rarely studied, was found to be prevalent in 22% of the patients in 1 study.[32] Low prevalences of agitation, aberrant motor behaviour, and wandering of 10% or less were found in 1 study.[19]

Predictors

Patient Demographics

Age. In 2 studies a significant effect of age on neuropsychiatric symptoms was found; younger patients were more aggressive,[24] restless,[16] and depressed,[16] whereas older patients were more suspicious.[16] Other studies failed to demonstrate a significant effect of age on the prevalence of such symptoms as aggression or agitation[15, 22, 23]

Gender. In most studies, agitated behaviour, such as physically nonagressive behaviour,[35] (physically) aggressive behaviour,[23, 24] verbal aggression,[25] or vocal agitation,[35] was more prevalent in male patients; the 3 exceptions were studies showing that agitation and aggression in general[15, 39] and verbal agitation[38] appeared to be more prevalent in female patients. One study found a relationship between male gender and depressed mood[24], whereas another study was unable to find this association.[27]

Race. Cohen et al[18] reported a lower prevalence of depression and lower levels of agitation in black patients with dementia than in white patients, with no interracial differences between African Americans and African Carribeans. Evers et al[27] did not find an effect of race on the prevalence of depression.

Marital status. In 2 studies, nursing home patients who had lived alone before admission showed a higher prevalence of psychosis[18] and physical aggression[25] than those who were married. However, in another study physical aggression appeared to be more common in married patients.[35]

Dementia-related factors

Dementia type. Because dementia type was established only in a minority of the nursing home studies reviewed here, little evidence is available on the influence of different types of dementia on neuropsychiatric symptoms. There was some evidence of more aggression and agitation or physically non-aggressive behaviour and hiding/hoarding behaviour in patients with Alzheimer's dementia than in those with vascular dementia or other dementing disorders.[15, 29]

(Global) disease severity. Some studies discussed the relationship between neuropsychiatric symptoms and dementia stage, the latter considered to be a mixture of cognition, language disability and activities of daily living (ADL). During the deterioration of cognitive function that occurs with progressive dementia, these

domains can not easily be disentangled and hence will be discussed together. Almost all neuropsychiatric symptoms were found to be related to a more pronounced cognitive or ADL dysfunction. Significant correlations were found between cognitive dysfunction and the presence of suspicious behaviour,[16] agitation in general,[37] physically agitated or vocally or verbally agitated/aggressive behaviour,[35, 38] physical or verbal aggression,[25] repetitive questioning,[16] and between ADL dysfunction and the presence of delusions,[24] depression,[25] anxiety,[24] agitation,[19] verbally agitated behaviour,[38] (physical) aggression,[23-25] or immobility and self-injurious behaviour.[32] In black patients, cognitive dysfunction seemed to be correlated with the presence of agitation and psychosis, but this was not true for white patients.[18] Other studies were unable to demonstrate a significant relationship between the presence of cognitive dysfunction and physical aggression[15, 34] and between ADL dysfunction and the presence of psychosis,[18] depression,[18] agitation,[18, 35] and physically non-aggressive behaviour.[38]
Although, in general, symptoms were more frequent as the disease progressed, only depression was associated with less severe stages of the dementia.[27]

Comorbidity. Two studies found that the number of physical disorders registered in the minimum data set was a predictor of agitation,[18, 19] but not of depression or psychosis.[18] An inverse relationship was found between the number of medical chart diagnoses and the prevalence of physically non-aggressive behaviour.[38] In another study, a relationship between the number of medical diagnoses obtained from the participant's charts and physically and vocally agitated (disruptive) behaviour could not be demonstrated.[35]

Premorbid personality
Only 1 study investigated the relationship between premorbid personality and neuropsychiatric symptoms, and it failed to show a significant correlation between physical aggression and premorbid personality.[20]

Psychoactive medication
Higher rates of aggression were found in antipsychotic and anxiolytic drug users,[36] and lower rates of aggression were found in antidepressant users.[36] Self-injurious behaviour was associated with prescribed benzodiazepines but not with anti-psychotics or anti-depressants.[32]

Environmental factors
To determine the influence of environmental factors, more direct observational methods were used, such as a structured time-sampling technique with a 5-min paper-and-pencil recording,[17] computer-assisted real-time observational systems,[34, 39] or agitated behaviours mapping instruments (ABMI),[38] all of which enabled a

more continuous recording of behaviours. These techniques enables to investigate not only diurnal variations, such as a late-day peak in pacing and verbal or physically aggressive behaviour,[37] but also antecedents directly preceding agitated behaviour. For example, it was shown that agitated behaviour was preceded by staff verbal and touch interactions.[39] Physically aggressive behaviour was shown to be preceded by verbal aggression or the non-compliance of residents toward staff or defiance toward any staff's request to the client. Physical aggression also occurred in response to intrusion into the resident's own personal space, especially in the context of bathing, toileting, grooming, dressing, or during redirection of the resident.[34]

Physical restraints. Two studies showed that the use of physical restraints was a predictor of physically aggressive behaviour[36] or self-injurious behaviour,[32] independent from the use of psychoactive medication. In another large study in 53 Alzheimer's disease special care units, it was found that the proportion of the residents restrained was a predictor of the mean agitation level at a care unit, independent from other variables such as ADL dependency and the number of diagnoses per resident.[19]

Social environment. Only 1 study could be retrieved from the literature in which neuropsychiatric symptoms were directly compared between community-dwelling and nursing home patients with dementia.[15] Whereas in the former setting patients showed more delusions, hallucinations, and mechanical/motor abnormalities, in the latter setting patients had more aggressive behaviour.
Within the setting of nursing homes or other long-term care facilities, 6 articles investigated neuropsychiatric symptoms in relationship to the social environment.[18, 19, 38] size of the living group[19] or institution,[24] or type of care delivered to the patient.[36, 37] Whereas large nursing homes in general[24] or large units in particular[19] were related to higher levels of agitation in the patient[19] or other neuropsychiatric symptoms,[24] the presence of social support – as measured with the number of visitors or telephone calls per week[18, 38] or frequency of communication with staff or other residents[38] – seemed to coincide with a lower prevalence psychoses (in black patients)[18], verbal agitation[38] or disruptiveness of agitation.[38] The relative importance of the therapeutic (psychosocial) environment was supported by a positive association between low (mean) agitation rates at a special care unit and favorable scores on measures of physical environment and staff treatment activities, such as general design, space, lighting, noise, maintenance, resident rooms, the quality of the staff interaction with residents, and the proportion of residents engaged in planned activities.[19] In this study no difference in prevalence of agitation could be shown between patients in dementia special care units and those in traditional care units. Finally, it was shown that residents on secured units were more physically aggressive (but also more cognitively impaired) than patients not on secured units.[36]

Discussion

This review of the literature clearly shows that neuropsychiatric symptoms in cognitively impaired nursing home patients are very common, with more than 5 out of 6 institutionalized patients suffering from 1 or more symptoms. The ranges in prevalences were considerable, from 3 to 54% for delusions, 1 to 39% for hallucinations, 8 to 74% for depressed mood, 7 to 69% for anxiety, 17 to 84% for apathy, 48 to 82% for aggression or agitation, and 11 to 44% for physical aggression. The prevalence of neuropsychiatric symptoms was associated with factors such as dementia type and global severity and can be modified with factors related to the interaction of the patient with others or with the (physical) environment. In addition, patients with neuropsychiatric symptoms were administered more psychoactive medication and were more often physically restrained than those without symptoms. There was considerable variation in the frequencies of neuropsychiatric symptoms reported in different studies. This large variability may be based on the degree of uncertainty with respect to defining dementia itself, its type and/or severity or on variations in the methodology used to evaluate neuropsychiatric symptoms. Consequently, only a few studies dealt with patients with accurately diagnosed dementia. Moreover, the adoption of different inventories, with different ratings or symptom definitions, probably influenced the prevalence outcome as well and makes pooling of symptom frequencies in different studies impossible.

Prevalence rates of neuropsychiatric symptoms, especially agitation, in residents of nursing homes are high and probably higher than in patients living in other types of care facilities, such as residential care/assisted living facilities,[40] social care,[24] or in community-dwelling patients,[15] probably attributable to a selection effect. Behavioural problems, such as agitation and global severity of the disease, are the main reasons for patients to be admitted to a nursing home. Moreover, it is also during the subsequent progression of the disease in long-stay patients that behavioural symptoms are expected to occur more frequently. An additional exacerbating factor is that nursing home patients usually spend a considerable portion of their daytime hours in overcrowded communal living rooms in which agitated and aggressive behaviour is likely to be enhanced further by the behaviour of other patients. In this review we have shown that more and more studies have concluded that the psychosocial environment in nursing homes is a significant factor in determining the prevalence of neuropsychiatric symptoms. For assessing the influence of this psychosocial environment on neuropsychiatric symptoms, commonly used (global) rating scales are not adequate as they have not been designed to study and describe in detail a resident's behaviour during the day and the preceding behaviours. For that purpose dementia care mapping or continuous observation techniques (by video taping caregiving activities) seem to be more accurate and reproducible.[17]

Insight into the prevalence of neuropsychiatric symptoms, especially into its

exacerbating or modifying factors, has important practical consequences. Both the numbers of patients showing resistance to (morning) care and of those with wandering in the afternoon should be important factors in determining the number of staff to be employed during the day. As to less-predictable behaviours, such as physical aggression, more detailed knowledge of the derailing factors and the exact circumstances in which this form of aggression occurs (or diminishes) in each individual patient is indispensable and should be conveyed to the staff in order that they can adequately deal with these stressful events in the daily practice of caregiving. With that objective, the continuing education of inadequately trained staff (by means of practical experience under supervision or other techniques such as role playing or video-interaction techniques) should also be encouraged.

Because dementia is not curable, most biological and disease-related predictors cannot be removed or treated, and because psychoactive medication has only limited effect on neuropsychiatric symptoms,[41] both psychosocial interventions[42] and those made in the patient's social and physical environment should be used more often as a means to adapt the current personal living space and to design (small-scale) facilities for use in the near future. Consequently, more research is needed on the effects of manipulating the physical and social environments in nursing homes. A better understanding of these effects would facilitate the development of appropriate services for nursing home residents as a means of minimizing behavioural problems and increasing the quality of life.

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CHAPTER 3

Efficacy and adverse reactions of anti-psychotics for neuropsychiatric symptoms in dementia: a systematic review

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Abstract

Aim of this study
To assess the efficacy and adverse events of antipsychotics in the treatment of neuropsychiatric symptoms associated with dementia and to verify the evidence warning against the cerebrovascular adverse events of atypical antipsychotics.

Design
Systematic review.

Methods
A selection of double-blind randomised studies with intention-to-treat analysis in Medline, Cinahl, PsycInfo, EMBASE and Cochrane (1980-2005) that researched the efficacy and adverse events of antipsychotics against neuropsychiatric disorders in dementia. These studies were assessed for quality in a standardised manner.

Results
Of the 950 articles found, 14 publications were selected on the effect of haloperidol, risperidone, olanzapine, quetiapine, tiapride, loxapine and perphenazine. Haloperidol, risperidone and olanzapine proved to be more efficacious against aggression and psychosis than placebo in seven out of ten cases. However, a direct comparison between typical and atypical antipsychotics revealed no statistically significant difference. The most frequent adverse events were extrapyramidal symptoms and drowsiness. These adverse events were less severe with low-dose risperidone than with haloperidol and olanzapine, but risperidone and olanzapine were shown in two studies to be associated with a higher risk for cerebrovascular adverse events.

Conclusion
Typical and atypical antipsychotics show a comparable efficacy, and only risperidone – predominantly at lower doses – seems to have fewer (extrapyramidal) adverse events. The profile of the adverse events has been inadequately described in the published research and, consequently, the warnings for an increased mortality cannot be confirmed.

Introduction

Dementia is often complicated by manifestations of agitation, psychosis, apathy and depression. In the international literature these symptoms have been grouped together under the combined heading of neuropsychiatric symptoms. Such neuropsychiatric symptoms occur frequently, are highly taxing for the patient and her/his partner and oftentimes lead to an earlier admission in a nursing home. The treatment of such neuropsychiatric symptoms, especially those of agitation/aggression and psychosis, consists of pharmacological and psychosocial intervention strategies. Antipsychotics form one of the most important pharmacological therapies, but their use can result in major adverse events, such as extrapyramidal symptoms, drowsiness, orthostatic hypotensia and an increased proneness to falling. Atypical antipsychotics have been reported to cause fewer extrapyramidal adverse events [1,2] – while still being considered to be as efficacious as typical antipsychotics. However, the American Food and Drug Administration (FDA), the UK government and the European Registration Authority (EMEA) released a warning stating that there is a relationship between atypical antipsychotics and an increased risk of stroke and mortality.[3-5] A great deal of attention has been paid to these topics, including an article published by van Marum and Jansen.[6]

In the present systematic review, we will conduct an in-depth assessment of (a) the evidence of warnings for these and other adverse events, and (b) the proposed equal efficacy of typical (such as haloperidol) and atypical antipsychotics (such as olanzapine and risperidone).

Methods

Search strategy

A search of the relevant literature was carried out in the databases of Medline, PsycInfo, Cinahl, EMBASE, and the Cochrane Trial Register from 1980 to 2005 using general search terms and the following medical subject headings: (1) dementia; (2) antipsychotics; (3) randomised, controlled trial; (4) neuropsychiatric symptoms and related terms. Publications prior to 1980 were not taken into account because the criteria used for diagnosing dementia prior to 1980 were substantially different from those currently in use.

Selection

One author (M.B.v.I.) made a selection from all of the titles and abstracts mined from the databases using the following criteria for inclusion: (1) randomised, double-blind studies in which an antipsychotic was compared to another antipsychotic or to a placebo; (2) effects on neuropsychiatric symptoms or adverse events as the primary result of medication; (3) the cohort consisted of patients with dementia; (4) administration was oral. The publications which met these criteria were subsequently

studied in detail by two of the authors (M.B.v.I., S.U.Z.), who applied the following criteria for exclusion: (1) there was no 'intention-to-treat'; (2) dementia was not diagnosed according to internationally accepted criteria currently in use (Diagnostic Statistical Manual-IV), National Institute for Neurological Disorders and Stroke and the Association International pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), National Institute for Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).

Methodological Assessment

The same researchers made a mutually independent assessment of the methodological quality of these articles included in the review using an assessment form for the therapeutical studies.[4] This assessment form has been applied in numerous meta-analyses and consists of 12 methodological criteria; for each of these criteria, a maximum number of points can be scored (the combined maximum amounts to 100 points), so that the higher the score, the better the quality of the study in question.

Efficacy Assessment

The assessment of efficacy was expanded with a responder-analysis when deemed possible. Numbers Needed to Treat (NNT) and Numbers Needed to Harm (NNH) were calculated as measures of the number of patients that have to be treated with the medication researched as compared to placebo in order to obtain one added successful treatment (responder) or one extra adverse event. By using this approach, we were able to transform the results of these studies so that they became relatively comparable.

Results

About 950 publications were found, of which 70 articles were selected on the grounds of the criteria for inclusion. After applying the criteria for exclusion, we were left with 14 articles considered to be appropriate.[8-21] Of the 56 excluded articles, 22 were excluded because they had been published before 1980, three were excluded because the antipsychotics had been administered only intramuscularly and 31 were not taken into account because of various combinations of the other exclusion criteria.

Quality assessment

Table 1 shows the quality assessment of the 14 studies available, presented in rank order of quality. The number of quality points assigned to the different studies varied from 49 to 85. No one study satisfied all criteria, and each study showed various methodological limitations.

Table 1.
Assessment of methodological quality of 14 randomized controlled trials on the efficacy of antipsychotics for neuropsychiatric symptoms in dementia, published between 1980 and 2005

First author, publication year	A	B	C	D	E	F	G	H	I	J	K	L	Total
Maximum score	**8**	**5**	**10**	**12**	**10**	**8**	**7**	**12**	**8**	**5**	**5**	**10**	**100**
De Deyn [11], 1999	7	5	10	8	4	6	0	12	7	5	5	10	85
Katz [14], 1999	5	5	10	8	4	6	0	12	7	5	5	10	77
Brodaty [10], 2003	6	5	10	10	8	6	0	4	7	5	5	10	76
Teri [8], 2000	6	5	6	6	4	6	7	10	2	5	5	10	72
Street [15], 2000	6	5	6	6	4	6	7	6	7	3	5	10	71
Devanand [13], 1998	4	5	4	6	8	4	7	12	8	3	0	10	71
Verhey [20], 2005	6	5	6	6	4	6	0	6	8	5	0	10	64
Ballard [19], 2005	4	5	6	5	10	6	0	6	8	5	0	10	64
De Deyn [12], 2004	3	5	10	6	4	8	0	6	7	3	0	10	62
Deberdt [21], 2005	3	5	10	4	4	4	0	4	7	5	5	10	61
Allain [9], 2000	5	5	10	2	6	6	0	4	7	3	5	8	61
Pollock [16], 2002	5	5	4	4	8	8	7	0	7	3	0	8	59
Auchus [18], 1997	2	5	2	8	8	6	7	0	7	3	0	10	58
Carlyle [17], 1993	3	5	4	2	8	6	0	4	3	3	5	6	49

Notes:

A. Homogeneity of the study population, **B.** Treatment allocation randomized and blinded, **C.** Group size, **D.** Prognostic comparability at baseline, **E.** Loss-to-follow up (% drop-out and loss-to-follow-up not leading to bias), **F.** Adequate description of intervention (both active drug and placebo), **G.** Co-intervention (comedication and rescue medication) described and comparable between study groups, **H.** Patient, therapist and observer blinded, **I.** Adequate outcome measures (and measurements were carried out blinded), **J.** Duration of follow-up and timing comparable for each group, **K.** Adequate description of side effects, **L.** Data presentation and statistical analysis

Interventions

Of the 12 placebo-controlled studies, five evaluated the effect of haloperidol, four that of risperidone, three that of olanzapine, one that of tiapride, one that of perphenazine and one that of quetiapine. In two non-placebo controlled studies haloperidol was compared to loxapine and olanzapine. The time frame of the studies in question varied from 2.5 to 26 weeks.

Patients

We found a large heterogeneity in terms of the composition of the patient groups between the included studies (see Table 2). The average age of the patients in the study cohorts of the studies ranged from 72 to 84 years. The patients had a moderate to severe cognitive impairment, characterised by a mean Mini Mental State Examination score varying from 5.5 to 15.2 (the maximum is 30, representing no cognitive impairment) and a diagnosis of Alzheimer's dementia (36-100%), vascular dementia (0-31%) or a mixture of both (0-16%).

Table 2.
*Characteristics of patient groups of 14 randomized controlled doubleblind trial on the efficacy of antipsychotics for neuropsychiatric symptoms in dementia, 1980-2005 *(see table 3 for the study outcomes)*

Author, publication year	Intervention and and daily study dosage (mg)	N	Duration of intervention (weeks)	Wash out period of previous medication (days)	Mean age (SD) [range]	Gender (%female)	Dementie type	Mean MMSE (SD) [range]	Setting
De Deyn, [11] 1999	risperidone 1.1† haloperidol 1.2† placebo	115 115 114	12	<14	81.3 [56-97]	56%	67%AD, 26%VaD, 7%mix	8.4 (7.7)	Nursing home
Katz, [14] 1999	risperidone 0.5 risperidone 1 risperidone 2 placebo	146 148 162 161	12	3-7	82.7 (7.2)	68%	73%AD, 15%VaD, 12%mix 6.6 (6.3)	6.6 (6.3)	Nursing home
Brodaty, [10] 2003	risperidone 0.95† placebo	167 170	12	<7	83.0 (7.2)	72%	58%AD, 29%VaD, 13%mixed	5.5 (5.7)	Nursing home
Teri, [8] 2000	haloperidol 1.8† trazodone 200† BMT placebo	34 37 41 36	16	14	82.8 (6.6)	55%	100%AD	13.0 (7)	Community
Street, [15] 2000	olanzapine 5 olanzapine 10 olanzapine 15 placebo	55 49 51 47	6	3-14	82.8 (6.6)	61%	100%AD	6.7 (6.6)	Nursing home
Devanand [13] 1998	haloperidol 2.65† haloperidol 0.71† placebo	20 20 20	4	7	72.1 (9.6)	65%	100%AD	15.2 (4.6)	Community

Author, publication year	Intervention and and daily study dosage (mg)	N	Duration of inter-vention (weeks)	Wash out period of previous medication (days)	Mean age (SD) [range]	Gender (%female)	Dementie type	Mean MMSE (SD) [range]	Setting
Ballard, [19] 2005	quetiapine 50-100 rivastigmine 9-12 placebo	31 31 31	26	NR	83.8 (7.7)	80%	100%AD	-	Residential care
De Deyn, [12] 2004	olanzapine 1.0 olanzapine 2.5 olanzapine 5.0 olanzapine 7.5 placebo	129 134 125 132 129	10	<14	76.6 (10.4)	75%	100%AD	13.7 (5.1)	Nursing home
Deberdt, [21] 2005	olanzapine 5.2† risperidone 1.0† placebo	204 196 94	19	3-14	78.3 (7)	66%	81% AD, 6% VaD, 13% mix	14.4 (5.6)	Community/ resident care/ nursing home
Allain, [9] 2000	haloperidol 3.5† tiapride 175† placebo	101 102 103	3	NR	79.6 (7.6)	64%	AD, VaD, mix, %NOS	NR	Nursing home/ hospital
Pollock, [16] 2002	perphenazine 6.5 citalopram 20 placebo	33 31 21	2.5	3-5	80.1 (8.2)	65%	72%AD, 7%VaD, 2%mix, 19%NOS	7.7 (6.7)	Hospital
Auchus, [18] 1997	haloperidol 3 fluoxetine 20 placebo	5 5 5	6	14	76 (8)	67%	100%AD	15.2 (4.6)	Community
Carlyle, [17] 1993	haloperidol 7† loxapine 36†	20 20	4	2-7	79 [65-91]	45%	AD, mix, %NOS	NR	Hospital

Notes:

AD = Alzheimer dementia, **mix** = features of Alzheimer dementia and vascular dementia, **MMSE** = Mini Mental State Examination, **NOS** = not otherwise specified, **SD** = standard deviation, **VaD** = vascular dementia. * Studies are listed in rank order of quality (see table 1), **†** = mean daily dose

Efficacy

In four studies, specific symptoms were used as the primary measure of outcome, such as irritability,[9] agitation,[9] aggression [9, 10, 17] and psychosis;[12] in the other studies a global clinical assessment [8] or the total score on a specific assessment scale was used. Very diverse instruments were used as the secondary measure of outcome to measure behaviour, cognition, functional condition and global impression.

Haloperidol, risperidone and olanzapine were found to have significantly favourable effects on the Behavioural Pathology in the Alzheimer's Disease Rating Scale (BEHAVE-AD) and Neuropsychiatric Inventory- Nursing Home version (NPI-NH) scores (Table 3). In addition a dose of 1.2–3 mg haloperidol proved to be significantly more efficacious than placebo in treating psychosis and agitation [13], irritability [9] and aggression.[9, 11] Risperidone, in a daily dose of 1.1 mg, proved to be more efficacious than placebo in treating aggression,[10, 11, 14] and it was reported to be efficacious in treating psychosis in two studies,[10, 14] but not in a third one.[11] In one study, risperidone was reported to be inefficacious against motor agitation;[10] the other two studies did not provide any specific information on this subject.[11, 14] Olanzapine was efficacious for treating agitation and aggression in two studies,[12, 15] but in only one of these studies was it also efficacious for treating delusions and hallucinations.[15] The remaining six studies did not reveal any difference in terms of efficacy between 1.8 [8] or 3 [18] mg haloperidol and placebo, between 1.0 mg risperidone or 5.2 mg olanzapine and placebo,[21] between 7 mg haloperidol and loxapine,[17] between 1.8 mg haloperidol and 4.7 mg olanzapine,[20] between 50-100 mg quetiapine and placebo [19] and between 6.5 mg perphenazine and placebo.[16]

Responders

The number of responders varied from 30 to 70% of the patients in the intervention group and from 30 to 66% of those in the placebo group (see Table 3). Six studies did not define responders at all.[10, 12, 16, 18-20] In two studies, the number of responders to haloperidol,[8] risperidone [21] or olanzapine [21] was not higher than that to placebo; in the remaining studies, the number of responders to usual doses of antipsychotics proved to be larger than that to placebo, with the NNTs for haloperidol being 3–6, [9, 11, 13] for risperidone 6–8 [14] and for olanzapine 3–5.[15] In the only direct comparison between typical and atypical antipsychotics, risperidone did not give a significantly higher number of responders than haloperidol.[11]

Adverse events

Haloperidol as well as olanzapine and risperidone caused extrapyramidal adverse events, with a large overlap between the NNHs of the three medications (haloperidol: 4–9; olanzapine: 6–15; risperidone: 7–13) (see Table 3). Only a dose of about 1 mg risperidone daily did not cause more extrapyramidal adverse events than placebo,[10, 11, 14] although more extrapyramidal adverse events were reported with haloperidol in doses of 1.2 mg [12] and 1.8 mg [8] and with olanzapine.[15, 21] In one study, 1 mg risperidone was found to cause more gait disorders than placebo,[21] but this dose of risperidone did cause less somnolence than olanzapine (NNH risperidone: 10–13 [11, 14, 21]; NNT olanzapine: 3–7 [15, 21]). In a direct comparison between risperidone and haloperidol, we were unable to determine any difference in terms of extrapyramidal adverse events (NNH not significant) and somnolence (NNH not significant).[11]

Haloperidol [11] as well as quetiapine [19] were associated with an accelerated cognitive decline, not only compared to placebo but also relative to both risperidone and rivastigmine.

Data on the number of cerebrovascular adverse events were incomplete in these studies. Two studies reported a significantly larger number of strokes with either risperidone use (NNH, with 95% Confidence Interval (CI) of 14 [8–41] [10] and 50 [25–2500][21]) or olanzapine use (NNH, with 95% CI of 40 [22–280] [21]) than with placebo.[10] In so far as has been reported in the available studies, the number of deaths as a result of a cerebrovascular events did not differ between patients administered placebo and those receiving haloperidol,[9] risperidone[10, 21] or olanzapine.[21] In addition, there were no differences in the number of deaths (also due to other causes) between patients receiving placebo and those receiving haloperidol,[9] risperidone[10, 14, 21] or olanzapine.[12, 21]

Discussion

There are very few published double-blind and placebo-controlled studies into the effects of antipsychotics for neuropsychiatric symptoms in dementia that also have an acceptably large number of patients. In addition, the methodological quality of the studies we assessed is highly variable. Haloperidol, risperidone and olanzapine have been tested numerous times in extensive trials (> 50 patients per group) of a reasonably acceptable quality.[9-12, 14, 15, 21] There has not been enough research on quetiapine, loxapine and perphenazine and, with particular reference to the latter two antipsychotics, those studies carried out were of moderate quality.

The results of most of the more extensive and large-scale investigations have revealed that haloperidol, risperidone and olanzapine are effective in treating aggression and psychosis. These typical and atypical antipsychotics do not seem to differ greatly from each other in terms of efficacy, with comparable NNTs of 3–6 and 3–8, respectively. Extrapyramidal symptoms and somnolence are seen with all these types of medication and, based on the results of the studies reviewed herein, the NNHs for risperidone were higher than those for haloperidol and olanzapine. This apparent advantage of risperidone seems to be limited to a daily dose of approximately 1 mg. A direct comparison of risperidone and haloperidol did not reveal any difference between them in terms of efficacy and the profile of adverse events.

While an increased risk for stroke has been reported in two studies on risperidone[10, 21] and one on olanzapine,[21] two retrospective studies on olanzapine, risperidone and

Table 3.

Primary and secundary endpoints and responder analysis of the efficacy and adverse events in 14 randomized controlled trials of antipsychotics for neuropsychiatric symptoms in dementia, published between 1980 and 2005 (see table 2 for characteristics of patient groups) [*,†]

	Primary endpoint (responders definition)	Effect	Secondary endpoint	Effect
De Deyn, [11] 1999	BEHAVE-AD total score (>30% decrease)	ris = pla hal > pla	BEHAVE-AD aggression, CGI, CMAI aggression	ris > pla hal > pla (except for BEHAVE-AD psychosis)
Katz, [14] 1999	BEHAVE-AD total score (>50% decrease)	ris‡ > pla	BEHAVE-AD psychosis and aggression, CGI, CMAI aggression	ris ‡ > pla
Brodaty, [10] 2003	CMAI aggression score (NR)	ris > pla	CMAI subscales, BEHAVE-AD total and psychosis, CGI	ris > pla (except CMAI physically non-aggressive behavior)
Teri, [8] 2000	CGI-C (% improvement)	hal = pla	BRSD, RMBPC, CMAI, SCB, ABID	hal = pla
Street, [15] 2000	NPI-NH FxS delusions+ hallucinations+agitation/aggression (>50% decrease)	ola§ > pla	NPI-NH, BPRS, MMSE	ola‖ > pla (except for MMSE, NPI depression)
Devanand [13] 1998	BPRS psychosis score, BSSD agitation, SADS psychose (>25% afname) **	hal ¶ > pla	MMSE, Blessed functional activities	hal = pla
Verhey, [20] 2005	CMAI total score (NR)	hal = ola	NPI, CGI, MMSE	hal = ola
Ballard, [19] 2005	CMAI total score (NR)	que = pla	SIB	que < pla
De Deyn, [12] 2004	NPI-NH FxS score psychosis (NR)	ola††= pla	NPI-NH, BPRS	ola > pla (NPI agression/anxiety, positive symptom BPRS)
Deberdt, [21] 2005	NPI FxS psychosis (30% decrease)	ola = ris = pla	NPI, CMAI, PDS, CSDD, MMSE	ola = ris = pla
Allain, [9] 2000	MOSES irritability/ aggressiveness subscale (>25% decrease)	hal > pla	MOSES (other subscales)	hal = tia = pla
Pollock, [16] 2002	NBRS total score, agitation, psychosis score (NR)	per = pla	None	-
Auchus, [18] 1997	CMAI total score (NR)	hal = pla	BEHAVE-AD, CSI	hal = pla
Carlyle, [17] 1993	aggression frequency total score (decrease)	hal = lox	None	-

	Responder analysis % responders	NNT [95% BI] vs placebo	EPS/abnormal gait NNH [95% BI] vs placebo	Somnolence NNH [95 % BI] vs placebo
De Deyn, [11] 1999	ris: 54% hal: 63% pla: 47% (hal vs ris: NS)	NS 6.3 [3.4-30]	ris 1.1mg: NS hal 1.2mg: 9.0 [4.9-67] (hal vs ris NS)	ris 1.1mg: 13 [6.7-137] hal 1.2mg: 8.2 [5.0-23] (hal vs ris: NS)
Katz, [14] 1999	ris: 0.5mg ris 1mg : 45% ris 2mg : 50% pla : 33%	NR 8.3 [4.4-85] 5.9 [3.6-16]	ris 0.5mg : NS ris 1mg : NS ris 2mg: 7.2 [4.7-16]	ris 0.5mg : NS ris 1mg : 11 [6.1-63] ris 2mg : 5.0 [3.6-8.4]
Brodaty, [10] 2003	NR		ris 0.95mg: NS	ris 0.95mg: 8.9 [4.8-70]
Teri, [8] 2000	hal: 32% tra: 41% BMT: 32% pla: 31%	NS NS NS	hal 1.8mg: 4.2 [2.4-18] tra 200mg: NS BMT: NS	hal 1.8mg: NS tra 200mg: NS BMT: NS
Street, [15] 2000	ola 5mg: 66% ola 10mg: 57% ola 15mg: 43% pla : 37%	3.3 [2.1-9.0] 4.6 [2.4-52] NS	ola 5mg : 5.7 [3.5-16] ola 10mg : 8.4 [4.5-71] ola 15mg : 6.4 [3.7-23]	ola 5mg : 5.4 [3.1-19] ola 10mg : 5.1 [3.0-18] ola 15mg : 3.4 [2.3-6.8]
Devanand [13] 1998	hal 2.7mg: 60% hal 0.7mg: 30% pla: 30%	3.3 [1.7-167] NS	hal 2.7mg: 5.0 [2.6-41] hal 0.7mg: NS	-
Verhey, [20] 2005	NR		hal 1.75 vs ola 4.71mg: NS	hal 1.75mg vs ola 4.71mg:NS
Ballard, [19] 2005	NR		-	-
De Deyn, [12] 2004	NR		-	-
Deberdt, [21] 2005	ola : 62% ris : 64% pla : 66%	NS NS	ola : 15 [8.3-15] ris : 13 [7.6-40]	ola : 6.8 [4.4-15] ris : 9.7 [5.5-40]
Allain, [9] 2000	hal: 69% tia: 63% pla: 49%	4.9 [3.0-14] 7.0 [3.6-143]	hal 3.5mg: 5.9 [3.5-20] tia 175mg: NS	hal 3.5mg: NS tia 175mg: NS
Pollock, [16] 2002	NR		-	-
Auchus, [18] 1997	NR		-	-
Carlyle, [17] 1993	hal: 55% lox: 70% (hal vs lox: NS)		-	-

Notes:

CI = confidence interval, **EPS** = extrapyrimidal symptoms, **NR** = not reported, **NS** = not significant (when the 95% confidence interval includes infinity (∞), the active drug is not significantly more efficacious than placebo or any other drug), **NNH** = number needed to harm, **NNT** = number needed to treat,

* Interventions: **BMT** = behavioural management techniques, **hal** = haloperidol, **lox** = loxapine, **ola** = olanzapine, **per** = perphenazine, **pla** = placebo, **que** = quetiapine, **ris** = risperidone, **tra** = trazodone, **tia** = tiapride

† Assessment instruments: **ABID** = Agitated Behaviour Inventory for Dementia, **BEHAVE-AD** = Behavioural Pathology in Alzheimer's Disease Rating Scale, **BPRS** = Brief Psychiatric Ratring Scale, **BRSD** = Behaviour Rating Scale for Dementia, **BSSD** = Behavioural Syndrom Scale for Dementia, **CGI(C)** = Clinical Global Impression of Change, **CMAI** = Cohen Mansfield Agitation Inventory, **CSDD** = Cornell Scale for Depression in Dementia, **CSI** = Caregiver Stress Inventory, **MOSES** = Multidimensional Observation Scale for Elderly Subjects, **NBRS** = NeuroBehaviour Rating Scale, **NPI(-NH) (FxS)** = Neuropsychiatric Inventory (-Nursing Home version)(Frequency X Severity score), **PDS** = Progressive Deterioration Scale, **RMBPC** = Revised Memory and Behaviour Problem Checklist, **SADS** = Schedule for Affective Disorders and Schizophrenia, **SCB** = Screen for Caregiver Burden, **SIB** = Severe Impairment Battery

‡ For risperidone 1mg and 2mg, § For olanzapine 5mg and 10mg (not for 15mg), ‖ olanzapine 5mg and not for 10mg and 15mg, ¶ Haloperidol standard dose only; ** other primary endpoints: BSSD agitation score showed a significant NNT for haloperidol 2.7mg only and SADS psychose score did not show significant NNT for 0.7mg or 2.7mg, †† only efficacious for olanzapine 7.5mg (Last Observation Carried Forward analyses) and not for olanzapine 1.0mg, 2.5mg en 5.0mg

quetiapine in patients with dementia did not find any such increased risk.[22, 23] These warnings of cerebrovascular adverse events with olanzapine as well as risperidone are based on an amalgamation of data sets from various registration studies that have only been published in part. Due to the absence of well-designed, large-scale investigations, a class-effect on cerebrovascular morbidity and mortality cannot be definitively excluded.[6] The presence of such a class-effect does seem likely on the basis of data from a recent meta-analysis.[24]

It is very important to be careful in interpreting the outcome of the various studies, notably because of the heterogeneity of the patient populations and the high and selective quantity of drop-outs, predominantly from adverse events. Another important limitation to obtaining valid data is the fact that various studies on this topic remain unpublished,[24] with the possibility that there is a publication bias.

Although a description of the efficacy and the adverse events in terms of NNTs and NNHs is the most commonly used approach for formulating a clinically relevant measure of outcome, the responder criteria vary between the different studies. For this reason we decided not to attempt a statistical pooling (meta-analysis) of the results.

To date, no unequivocal responder criteria are available for antipsychotics used in treating neuropsychiatric symptoms; consequently, the heterogeneity in the research results will remain for the time being, and extreme alertness is advised with respect to differences in definitions when interpreting NNTs and NNHs.

In summary, it can be stated that a large number of investigations have presented a credible case for the efficacy of haloperidol, risperidone and olanzapine in treating neuropsychiatric symptoms in dementia and that atypical and classic types of medication are equally efficacious. In the case of equal efficacy, a choice will have to be made based on the profile of adverse events, which has, in the studies assessed here, generally been described both too concisely and incompletely. The importance of the formal warnings could not properly be assessed on the grounds of the investigations published. In principle, however, the atypical medications olanzapine and risperidone are contra-indicated in the case of cardiovascular comorbidity. Given the obscurity that surrounds potentially severe adverse events – even after our assessment of all of the relevant published studies – we strongly advocate imposing an obligation on pharmaceutical companies to be forthcoming about all of the data on adverse events. We suggest that they should be obliged to publish these data after receiving warnings from the regulatory authorities on severe adverse events of one (or more) of their medications.

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CHAPTER 4

Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia

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Abstract

Objective

To estimate the prevalence of neuropsychiatric symptoms of dementia patients in Dutch nursing homes.

Methods

Cross-sectional study in a large sample of 1322 demented patients living in 59 dementia special care units (SCUs) in the Netherlands. Symptoms were observed by licensed vocational nurses during regular care-giving in a two-week observational period prior to assessment. Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory- Nursing home version (NPI-NH; frequency × severity score ≥ 4) and the Cohen-Mansfield Agitation Inventory (CMAI; symptoms occurring at least once a week).

Results

More than 80% of these patients suffered from at least one clinically significant symptom, as defined with the NPI-NH frequency × severity score ≥ 4. Measured with the NPH-NH agitation/aggression, apathy and irritability were the most frequently observed behaviours, with prevalences of 30-35%. Using the CMAI, 85% of the patients showed at least one symptom of agitation, of which general restlessness was observed most frequently (44%). Other frequently observed symptoms with prevalence rates of 30% were cursing or verbal aggression, constant request for attention, negativism, repetitious sentences, mannerisms, pacing, and complaining. Physically aggressive symptoms such as hitting, kicking, biting occurred less often (less than 13%).

Conclusions

Prevalence rates of neuropsychiatric symptoms in Dutch nursing home patients with dementia residing in SCUs are high, especially agitation and apathy. Insight into the prevalence rates of individual symptoms in patients with dementia has important practical consequences for the accurate planning of staff allotment and stresses the need for patient oriented care.

Introduction

Dementia is an incurable disease with substantial effects on cognition, activities of daily living and behaviour, resulting in a considerable loss in the quality-of-life of both patients and caregivers. Neuropsychiatric symptoms are a particularly heavy burden for the caregiver, [1, 2] and these are the main reason for institutionalization. [3-5] In the Netherlands, 30,000 dementia patients currently reside in nursing homes,[6] which is approximately 20% of all persons with dementia. Figures on the prevalence of neuropsychiatric symptoms are badly needed because of its consequences for the psychosocial and pharmacological interventions that are necessary to improve the quality of life of these patients. Furthermore these figures can assist in the development of caregiving plans that can provide appropriate care against reasonable costs.

Many authors have estimated the prevalence of neuropsychiatric symptoms – usually referred to as agitation/psychosis, depression/apathy – in demented patients.[7] The majority of these studies involved community-dwelling patients or patients temporarily admitted to hospitals or research clinics. Only recently have several studies addressed the neuropsychiatric symptoms of nursing home patients, being prevalent in more than 80% of the patients.[8-11] Agitation/aggression occurred in 48–83% of the patients, with 11–44% of these showing physical aggression.[8-12, 13 , 14-19] Apathy was prevalent in 17–41%,[8-11] delusions and hallucinations in 12–49% and 5–39%, respectively,[8-12] and depressive symptoms were seen in 10–51%.[8-11, 16, 20-22] The reported prevalence rates of specific symptoms varied because studies not only differed with respect to the assessment scales used and the population studied, but prevalence rates also seemed to differ between countries. To date, data on the prevalence of neuropsychiatric symptoms in demented patients are available from many countries. However, no figures are available on the prevalence of neuropsychiatric symptoms in large groups of Dutch nursing home patients with dementia. Nursing homes in the Netherlands differ from their counterparts in other countries in that the staff includes specially trained nursing home physicians (one full-time doctor per 100 patients), physical therapists, occupational therapists, speech therapists, pastoral workers, dietarians, psychologists, social workers and, occasionally, music therapists and psychomotor therapists, all of whom are employed by the nursing home.[23, 24] Care for people with dementia is generally provided in special care units (SCUs), where patients usually live in small groups of about 6–12 persons.

The objective of this study was to determine the prevalence of neuropsychiatric symptoms in general – and aggression and agitation in particular – in a large sample of patients residing in dementia SCUs in Dutch nursing homes.

Methods

Study design, selection of patients and ethical considerations

This was a cross-sectional cohort study. All of the 72 nursing homes providing the specialist training program for nursing home physicians in cooperation with the Department of Nursing Home Medicine of the Radboud University Nijmegen Medical Centre (the Netherlands) were asked to participate in the study. The 25 nursing homes that ultimately agreed to participate are situated in the eastern, northern and southern part of the Netherlands. Of the total amount of 117 dementia SCUs in the 25 nursing homes, 59 SCUs (50%) participated in this study. The managing director of these institutions selected the dementia SCUs to be assessed. The participating SCUs did not differ with respect to admission policy towards patients with neuropsychiatric symptoms or dementia stage/care level of non-participating SCUs. Although 5 SCUs are especially built for demented patients with high levels of neuropsychiatric symptoms, neuropsychiatric symptoms are not a prerequisite to be admitted on the other 54 SCUs.

Patients were considered for inclusion provided they (1) met the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria [25] for dementia and (2) resided in the nursing home more than four weeks . Terminally ill patients were excluded.

The study was undertaken in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. Approval of the regional research ethics committee was obtained. Informed consent was acquired from a primary family member or legal guardian of the patients.

Data collection and assessments

The assessments took place within a 4-week period in 2003. All licensed vocational nurses, who had been specifically assigned to individual patients, were trained and instructed to observe symptoms during a two-week period. At the end of the two-week observation period the vocational nurses were interviewed by trained nurse-assistants. The interviews were structured, following guidelines provided by a written manual, with the aim of eliciting specific observations of all neuropsychiatric symptoms. The interviewers were trained by two researchers (SZ, ED) during a two-hour session prior to the study.

Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory-Nursing Home version (NPI-NH), a scale originally developed by Cummings [26, 27] as a means to assess neuropsychiatric symptoms in demented outpatients. 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.[28, 29] The NPI-NH is the only nursing home instrument for assessing neuropsychiatric symptoms that has been translated into Dutch.[30] The NPI-NH includes 12 neuropsychiatric

symptoms: delusions, hallucinations, agitation, depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability, aberrant motor behaviour, night-time 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.

Agitation and aggression were assessed using the Cohen Mansfield Agitation Inventory (CMAI). This instrument, originally developed by Cohen-Mansfield,[31] is designed to assess 29 agitated or aggressive behaviours and has been extensively used for assessment purposes in nursing homes. The original CMAI has been validated by Miller [32] and is the only instrument specifically addressing agitation or aggression that has been translated into Dutch. The Dutch CMAI (CMAI-D) has been validated.[33] The frequency of each symptom is rated on a seven-point scale (1–7) ranging from 'never' to 'several times an hour'.

To describe the severity of the dementia the psychologist (or nursing home physician) assessed the disease stage using the Global Deterioration Scale,[34] which consists of a seven-point scale (1–7) ranging from no global impairment (1) to very severe global impairment (7). Baseline characteristics, such as age, sex, marital status and time of institutionalization, were retrieved from the patients' charts. Finally, data on the actual use of psychoactive medication on the day of assessment were registered. Psychoactive medications were classified using the Anatomical Therapeutical Chemical-classification 35 and grouped into antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants, anti-epileptics and miscellaneous (e.g. cholinesterase inhibitors).

Analysis

In this study, clinically relevant neuropsychiatric symptoms measured with the NPI-NH were defined by a F×S score for each individual symptom, with a score of ≥ 4 taken as being likely to represent patients with clinically significant behaviour.[9, 28] Agitation measured with the CMAI was defined as behaviour occurring at least once a week or more (frequency score ≥ 3).

Results

One proxy gave no informed consent, and this patient was subsequently excluded; all other eligible (n=1322) patients were included. The mean age of these patients was 83.0 years, and the female to male ratio was 4:1(table 1). At the time of the study, all of the participants had lived in the nursing home an average of 20 months. This mean age (95% Confidence Interval, 95%CI) of 83.0 years (82.6–83.4) was slightly higher and the percentage of males (20%) was lower than national figures derived from the

(total) number of patients in SCUs of nursing homes in the Netherlands (81.8 years and 25% male).[36] The majority of the patients were in Global Deterioration Scale (GDS) stage 6. Some kind of psychoactive medication was prescribed in more than 60% of the patients, mostly antipsychotics (37%) or antidepressants (27%).

Table 1.
Characteristics of the 1,322 Nursing Home Patients with Dementia Participating in the Study

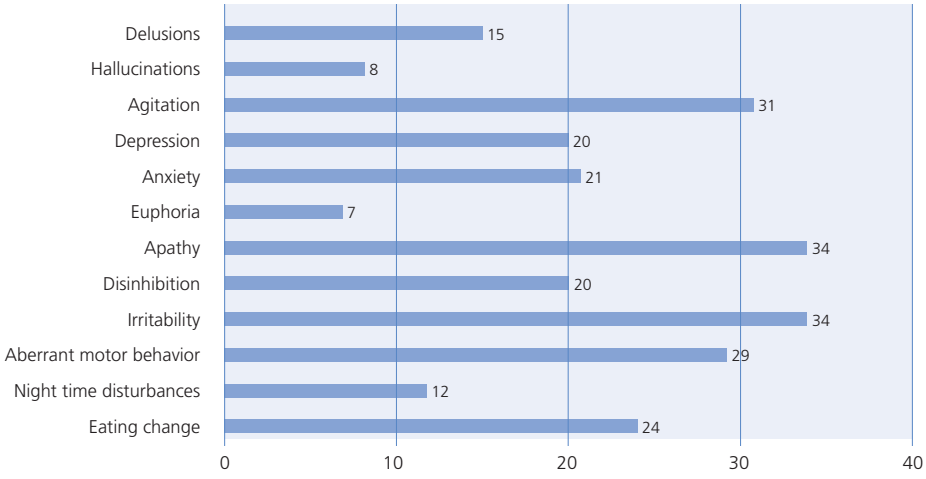
Age (years)		
	mean ± SD	83.0 ± 8.1
	Range	36–102
Sex		
	(% male)	20
Marital status		
	Married (%)	20
	Widow/Widower (%)	67
	Divorced (%)	5
	Unmarried (%)	9
Duration of institutionalization (months)		
	Mean	20
	Range	1–119
Global Deterioration Scale (GDS)		
	GDS 3 (%)	0.2
	GDS 4 (%)	3
	GDS 5 (%)	18
	GDS 6 (%)	51
	GDS 7 (%)	28
Psychoactive medication use (total, %)		**65**
	Antipsychotic drugs (%)	37
	Antidepressant drugs (%)	27
	Anxiolytic drugs (%)	16
	Hypnotics/sedatives (%)	15
	Antiepileptic drugs (%)	6
	Cholinesterase inhibitors or nootropil (%)	1

Note:

All percentage values are presented as percentages of the total group

Of the patients assessed, 81% had clinically relevant neuropsychiatric symptoms, with a NPI-NH FxS score ≥ 4 for at least one symptom. A majority of the patients (61%) had multiple symptoms, with 18% scoring ≥ 4 on two items, 14% scoring ≥ 4 on three items, 11% on four items and 19% on more than four items. Apathy, irritability, aberrant motor behaviour and agitation/aggression were the most prevalent neuropsychiatric symptoms, with rates of about 30% (figure 1). Psychotic symptoms, such as delusions and hallucinations, appeared to occur in 15 and 8%, of the patients, respectively, while depression and anxiety occurred in 20% of the patients.

Figure 1.



Neuropsychiatric Inventory- Nursing home version (NPI-NH) prevalence rates of neuropsychiatric symptoms in 1,322 nursing home patients (Frequency × Severity symptom score ≥ 4). The numbers in the figure refer to percentages.

Some type of agitated behaviour, as measured by the CMAI, was shown by 85% of the patients (table 2); of these, 74% had two symptoms or more, and 63% had three symptoms or more. The median (range) number of symptoms was 4 (0–23). The most prevalent item was general restlessness, which occurred in 44% of the patients. Other frequently occurring symptoms were cursing or verbal aggression, constant request for attention, repeating sentences, mannerisms, negativism and pacing, all with prevalence rates of about 30%. Physical aggression, such as hitting, kicking and biting, was prevalent in 13%, 7% and 8% of the patients, respectively.

Table 2.
CMAI prevalence rates (%) in 1,322 nursing home patients, occurring at least once a week.

General restlessness	44
Cursing or verbal aggression	33
Constant request for attention	32
Negativism	31
Repetitious sentences/ questions	30
Pacing	29
Performing repetitious mannerisms	28
Complaining	26
Grabbing	24
Making strange noises	20
Inappropriate robbing/ disrobing	18
Handling things inappropriately	18
Get to different place	16
Hitting	13
Screaming	13
Hoarding things	12
Hiding things	10
Pushing	9
Scratching	8
Spitting	8
Kicking	7
Hurting oneself or others	5
Tearing things	5
Throwing things	4
Biting	3
Eating inappropriate substances	3
Verbal sexual advances	2
Physical sexual advances	2
Intentional falling	1

Discussion

The results of this study reveal that behavioural problems were very common among this large sample of Dutch nursing home patients with dementia. More than 80% of the study population had at least one clinically relevant symptom, while the majority of the patients had multiple symptoms. To date, five studies have used the NPI-NH [9, 11] and CMAI to estimate the prevalence of neuropsychiatric symptoms in nursing home patients with cognitive impairment.[11, 15, 17, 19] In the present study, the overall prevalence rates on any one symptom, as measured with the NPI-NH and CMAI (81 and 85%, respectively), were very similar to those reported in earlier studies – 84% [9] and 85% [11] using the NPI; and 82% [15], 83% [11, 19] using the CMAI. Also, the prevalence rates of individual symptoms assessed with the NPI-NH and CMAI were generally in line with those found in the earlier studies.[9, 11, 15, 17, 19]

To the best of our knowledge, the present study is the largest one of its kind to be carried out on the prevalence of neuropsychiatric symptoms in demented nursing home patients. The cohort population comprised 4.4% of all demented nursing home patients in the Netherlands. This study, however, may have some limitations with respect to the validity of generalizing the data to the nursing home population at a national level. Although there does not seem to have been a selection by the nursing home itself for any one specific SCU, the age and sex distribution of our patient sample differ slightly of those of the national nursing home population. A sampling error may occur, since only 25 of the 72 nursing homes asked to participate in the study complied with our request and no data on the reason for non-participation of the other 47 nursing homes were available. Moreover, no national data are available on the distribution of dementia stage and the use of psychoactive medication, which are both known to affect the neuropsychiatric symptom rates. [37-39] Consequently, there may be unknown differences between the distribution of the dementia stage and psychoactive medication use in our study cohort and demented patients in SCUs in other parts of the Netherlands, thereby making extrapolation to the Dutch national nursing home situation difficult.

In contrast to our expectations, the prevalence rates of neuropsychiatric symptoms in the Dutch special care setting, which differs from other comparable care settings throughout the world, was not lower than those elsewhere. This could be due to the tendency that patients with dementia prefer to live at home as long as possible and consequently nursing home admission is postponed. Neuropsychiatric symptoms are often the main reason for admission and may even be exacerbated by the typical nursing home environment, in which patients usually spend a considerable portion of their daytime hours in overcrowded communal living rooms. In the Dutch special care setting, patients' neuropsychiatric symptoms may also more likely to be accepted, which may result in a reduced number of patients with high prevalence of neuropsychiatric symptoms being transferred to geriatric or psychiatric hospitals.

The homogeneity of prevalence estimates of neuropsychiatric symptoms – 85% – that has been reported by both the present and numerous other studies suggests that symptoms are both ubiquitous in dementia and relatively independent of the care setting. One should therefore be cautious to consider the prevalence of neuropsychiatric symptoms as an indicator of quality of care, since certain amount of symptoms present could be more or less accepted and may not be influenced by any intervention.

In the present study, psychotropic medication use was high, and comparable with in other nursing home settings.[9, 10, 40, 41] Since psychotropic medication has limited efficacy,[42, 43] and considerable side effects [43, 44] with a possible negative influence on the patient's well-being,[41] it would be worthwhile to reduce the amount of prescription of psychotropics and put more effort in psychosocial interventions.

Insight into the prevalence rates of individual symptoms in patients with dementia has important practical consequences for the accurate planning of staff allotment. Both the numbers of patients showing resistance to (morning) care and of those with wandering in the afternoon should be important factors to be taken into consideration when determining the number of staff to be employed during the day. This stresses the need for tailored person-centred care. To accomplish this, a detailed knowledge of the derailing factors and exact circumstances in which the symptoms occur is indispensable. The staff should be made aware that neuropsychiatric symptoms can be considered to be a consequence of a patient's failing mechanism to cope with or adapt to their disease.[45] Also, a better understanding of the influence of physical (large or small SCUs) and psychosocial conditions on the development of neuropsychiatric symptoms could contribute to the reduction of symptoms and an improvement in the quality of life.

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CHAPTER 5

Neuropsychiatric symptoms in nursing home patients: Factor structure invariance of the Dutch Nursing Home version of the Neuropsychiatric Inventory in different stages of dementia

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Abstract

Background/Aims
To examine the influence of dementia stage and psychoactive medication use on the factor structure of the Neuropsychiatric Inventory-Nursing Home version (NPI-NH) in Dutch nursing home patients.

Methods
The NPI-NH was administered to a large sample of 1,437 patients with mild to severe dementia receiving nursing home care. Exploratory factor analysis was used to examine behavioural dimensions underlying neuropsychiatric symptoms indicated by the NPI-NH across dementia stages (as assessed with the Global Deterioration Scale -GDS) and in patients with or without psychoactive medication prescribed.

Results
In GDS stage 4/5, 6 and 7, a 4- or 5-factor solution was found, with factors referred to as agitation/aggression, depression, psychosis, psychomotor agitation and apathy. These symptom clusters were replicated in the group of drug-naive patients, but only partially in the group of patients on psychoactive medication.

Conclusion
The factor structure of the NPI-NH in nursing home patients is consistent with the clinical taxonomy of symptoms, is relatively stable across dementia stages, and is only moderately influenced by psychoactive medication use. The division of depression and apathy into separate behavioural dimensions – also in patients with severe dementia – may have important therapeutic consequences.

Introduction

Neuropsychiatric symptoms are highly prevalent in dementia.[1-3] Individual neuropsychiatric symptoms have been observed in variable frequencies across stages and subtypes of dementia,[4] thereby reflecting different biological correlates and psychosocial determinants.[5] Systematic assessment of neuropsychiatric symptoms is important not only for reasons of timely diagnosis and choice of treatment options, but also from a taxonomy perspective, i.e. whether these psychiatric symptoms are associated with dementia. In an attempt to redirect research and clinical attention to the so-called non-cognitive symptoms of dementia, the International Psychogeriatric Association introduced the concept of Behavioural and Psychological Symptoms in Dementia (BPSD).[6] However, others in the field have stated that neuropsychiatric symptoms are too heterogeneous to be considered within the context of one unifying concept.[5]

For practical purposes, e.g. in clinical trials, symptoms are often grouped together in clusters or 'syndromes'.[7-9] The European Alzheimer's Disease Consortium (EADC) has proposed grouping neuropsychiatric symptoms into hyperactive (agitated) behaviours, affective behaviours, psychosis and apathy.[10, 11] Others have proposed splitting hyperactive behaviour into (physical) aggression/agitation and psychomotor agitation.[12] However, the underlying relationships or behavioural dimensions of these symptoms may differ between various types and stages of dementia and between residential settings. Consequently, both for clinical and research purposes it is important to determine whether these underlying behavioural dimensions are robust and invariant in different patient samples.

The Neuropsychiatric Inventory (NPI)[13] is a well-known informant-based rating scale for assessing neuropsychiatric symptoms in dementia. It measures a wide range of neuropsychiatric symptoms and it has been validated for use in epidemiological [14] and intervention studies.[7-9] Few studies using the NPI were done in nursing home patients at different stages of dementia.

Several authors used factor analysis to explore the behavioural dimensions that underlie different neuropsychiatric symptoms15-24 and others examined different clusters of patients using latent class analysis.[25] In most studies 3-5 syndromes were identified with various terminologies assigned to each syndrome. Intrinsic differences in the populations studied and in the severity and type of dementia assessed in these patients may have influenced these analyses, resulting in a great diversity of results with respect to the taxonomy of neuropsychiatric symptoms. To date, studies have been conducted in outpatient departments,[18-20] memory clinics[16] and/or Alzheimer units[15] within a general hospital and in psychiatric hospitals,[16, 22] other hospital settings[21] or a mixed setting of outpatients and nursing home patients[23] or on a special care unit for temporarily admitted patients.[24] However, no data are exclusively available on chronic nursing home patients with different stages of cognitive

deterioration. The prevalence rates of neuropsychiatric symptoms are particularly high in this type of setting, since these symptoms may have been the primary reason for the patient to have been placed in an institution initially.[26] Moreover, some behaviours (especially agitation and aggression) are likely to be influenced by social interaction, in the large groups with which patients residing in a nursing home must interact during the day [27] and/or during care deliver situations.[28]

In all NPI factor-analytic studies, psychoactive medication use was allowed, but not separately analysed.[15-24] Psychoactive medication is meant to reduce neuropsychiatric symptoms, but some symptoms could more likely respond to these drugs than others.[12] This selective response could affect the prevalence rate of some neuropsychiatric symptoms (more than others) and therefore influence the factor structure.

The objective of this study was to explore the stability of the different behavioural dimensions that may underlie neuropsychiatric symptoms in dementia patients across different stages of cognitive deterioration, and in patients with or without psychoactive medication. To our knowledge, this is one of the few studies that has evaluated symptom associations in a large sample of nursing home patients with dementia.

Methods

Study design and subjects

This study is part of a cross-sectional cohort study evaluating the prevalence and correlates of neuropsychiatric symptoms in Dutch nursing home patients with dementia.[29] Patients were recruited from 27 nursing homes in the Eastern, Northern and Southern parts of The Netherlands. Patients of 59 dementia special care units and 13 units for outreaching nursing home care situated in residential homes were included in the study. Nursing home care in The Netherlands is not restricted to the nursing home setting but is also provided in residential homes. This complementary outreaching nursing home type of care is provided by members of multidisciplinary nursing home teams (i.e. nurses, nursing home physician, physical therapists, occupational therapists and a psychologist) to demented patients still residing in a residential home, with the aim of postponing the admission of a patient to a nursing home.[30]

Patients were considered for inclusion provided: (1) they met the criteria for dementia established by the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV)[31], and (2) they had resided in the nursing home for more than 4 weeks. Terminally ill patients were excluded. The presence of neuropsychiatric symptoms was not a prerequisite to be included in the study. The study was undertaken in accordance with the Declaration of Helsinki and the guidelines for Good Clinical

Practice. The local Research Ethics Committee approved of the study. Family members or legal guardians of the patient gave informed consent. All eligible patients with an informed consent were included.

The study cohort comprised 1,437 patients (male:female, 1:4), most of whom were over 80 years of age (Table 1). The median length of residence in the nursing home at the time of the study was 18 months. Psychoactive medication was prescribed to 65% of the patients, antipsychotics to 37%, antidepressants to 27% and both anxiolytic drugs and hypnotics/sedatives to 15%. The majority of patients (77%) had severe or very severe cognitive deterioration (Global Deterioration Scale (GDS) stage 6 or 7). GDS scores reflect different stages of dementia on a seven-point scale in which stage 1 indicates no cognitive decline and stage 7, very severe cognitive decline (severe dementia). [32]

Table 1.
Patient characteristics of 1,437 nursing home patients with dementia

Age, years		
	Median	83
	Range	37–102
Gender, male		276 (19)
Duration of residence in institution, months		
	Median	18
	Range	1–191
Global Deterioration Scale (GDS)		
	GDS stage 4, mild dementia	59 (4)
	GDS stage 5, moderate dementia	282 (20)
	GDS stage 6, moderately severe dementia	728 (51)
	GDS stage 7, severe dementia	368 (26)
Psychoactive medication use [a]		925 (65)
	Antipsychotic drugs	532 (37)
	Antidepressant drugs	390 (27)
	Anxiolytic drugs	222 (16)
	Hypnotics/sedatives	214 (15)
	Antiepileptic drugs	84 (6)
	Cholinesterase inhibitors, nootropics	15 (1) [b]

Notes:

Figures in parentheses indicate percentages. All percentage values are percentages of the total group, [a] Total number of patients on psychoactive therapy, [b] Cholinesterase inhibitors are not prescribed in Dutch nursing homes

Procedures

Licensed vocational nurses, each of whom had been specifically assigned to individual patients for care management purposes, were instructed to observe 'their' patients' neuropsychiatric symptoms during a 2-week period. At the end of the 2-week observation period vocational nurses were interviewed by trained nurse assistants who had been trained by two researchers during a 2-hour session prior to the study. Supervision of the interviewers was provided by a psychologist or nursing home physician. The interviews were structured in that they followed guidelines laid down in a written manual that were aimed at eliciting specific observations of neuropsychiatric symptoms.

Neuropsychiatric symptoms were assessed with the Dutch translation of the Neuropsychiatric Inventory-Nursing Home version (NPI-NH).[33] This scale was originally developed by Cummings et al.[13] and Cummings [34] as a means to assess neuropsychiatric symptoms in demented outpatients. The nursing home version was developed for the use of professional caregivers within institutions and has been translated into Dutch;[33] it has proven to be a valid and reliable assessment tool for trained nursing staff.[14, 22] The NPI-NH consists of an assessment rating on 12 neuropsychiatric symptoms: delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, night-time disturbances and appetite/eating change. Both the frequency (F) and severity (S) of each symptom are rated on a 4- and 3-point Likert scale, respectively. A specific and distinct score can be calculated for each symptom by multiplying the frequency and severity scores, resulting in a score range of 0-12. A total score can be calculated by summing the 12 F x S scores, yielding a range from 0 to 144. Clinically relevant neuropsychiatric symptoms were defined by an F x S score ≥ 4 as being likely to represent patients with clinically significant behaviour. [14,35]

Data analysis

The factor structure of the NPI-NH was evaluated using exploratory factor analysis (SPSS 9.0.1; SPSS Inc., Chicago, Ill.). Separate analyses were performed for patients in GDS stages 4/5, 6 and 7; and for groups of patients with or without prescribed psychoactive medication. In the first analysis, factors with eigenvalues >1 (a measure of the percentage of variance) were extracted and orthogonally rotated to achieve simple structure (Varimax). In the second analysis, oblique rotation of the factors was applied (Direct Oblimin), as we expected significant correlations between NPI-NH factors. Items with factor loadings (a measure of the degree of correlation) higher than or equal to 0.4 were considered to be relevant.

Results

Prevalence rates (for NPI items with an F x S score ≥ 4) and mean F x S scores of neuropsychiatric symptoms are given in table 2. High prevalence rates were shown for apathy, agitation, irritability and aberrant motor behavior (about 30%). Euphoria and hallucinations are the lowest occurring symptoms (about 7%).

Table 2.
F x S scores and prevalence of individual neuropsychiatric symptoms in 1,437 Dutch nursing home patients with dementia, measured with the Dutch version of the NPI-NH

NPI-NH symptoms	F x S score mean ± SD	Prevalence (F x S score ≥ 4)
A. Delusions	1.17 ± 2.70	14.4
B. Hallucinations	0.64 ± 1.94	7.7
C. Agitation/aggression	2.59 ± 3.64	31.0
D. Depressed mood	1.76 ± 3.19	20.1
E. Anxiety	1.80 ± 3.26	20.9
F. Euphoria	0.61 ± 2.05	7.2
G. Apathy	3.20 ± 4.42	34.2
H. Disinhibition	1.69 ± 3.27	19.7
I. Irritability	2.70 ± 3.60	33.3
J. Aberrant motor behaviour	2.51 ± 4.09	28.4
K. Night-time behaviour	1.02 ± 2.50	12.1
L. Eating change	1.97 ± 3.67	23.4

Factor analysis

The factor analyses of patients in GDS stage 4/5, 6 and 7 and of patients with or without prescribed psychoactive medication are presented in tables 3 and 4, respectively. Medication use was not independent of dementia stage and was highest in GDS stage 6. In GDS stage 6, 71% used one or more psychoactive drugs, compared to 60% in GDS stage 4/5 and 56% in GDS stage 7 (χ^2, $p < 0.0005$).
Factor analysis of GDS stage 4/5 data showed a 4-factor solution that explained 57% of common variance (Table 3). Factor 1 consists of agitation, disinhibition, irritability and delusions and was named 'agitation/aggression'; factor 2 ('mood/psychosis/psychomotor agitation') consists of depression, anxiety, delusions, hallucinations, aberrant motor behaviour, and night-time behaviour; factor 3 ('apathy') includes apathy and eating disorders; and factor 4 euphoria.

Table 3.
Results of the factor solution analysis of the NPI-NH (F×S score) in 1,437 Dutch nursing home patients with dementia in GDS stages 4/5, 6 and 7.

NPI-NH symptoms	Delusions	Halluci-nations	Agitation	Depres-sion	Anxiety	Euphoria	Apathy	Disinhi-bition	Irritability	Aberrant motor behaviour	Night-time behaviour	Eating disorders	Cumulative explained variance (%)
GDS stage 4/5 (n=341)													
Factor 1: Agitation/ aggression	0.580		0.821					0.793	0.796				20
Factor 2: Mood/psychosis/Psychomotor agitation	(0.472)	0.588		0.617	0.648					0.566	0.476		37
Factor 3: Apathy and eat disorder							0.780					0.670	48
Factor 4: Euphoria						0.906							57
GDS stage 6 (n=728)													
Factor 1: Agitation/ aggression			0.756			0.499		0.722	0.771				17
Factor 2: Depression				0.747	0.759								30
Factor 3: Psychosis	0.688	0.871											41
Factor 4: Psychomotor agitation										0.730	0.725		52
Factor 5: Apathy and eating disorder							0.746					0.780	61
GDS stage 7 (n=368) 2)													
Factor 1: Agitation/ aggression			0.846					(0.426)	0.842				15
Factor 2: Psychosis	0.808	0.680						0.506					28
Factor 3: Depression				0.749	0.722								40
Factor 4: Apathy + aberrant motor behaviour							0.514			0.778			51
Factor 5: night-time behaviour + eating disorders											0.591	0.851	61

Only factor loadings > 0.40 are presented. Factor loadings in parentheses imply that a specific item loads to more than one factor and the factor loading to the other factor is higher.

Table 4.

Results of the factor solution analysis of the NPI-NH (F×S score) in 1,437 Dutch nursing home patients with dementia with or without psychoactive medication.

NPI-NH symptoms	Delusions	Hallucinations	Agitation	Depression	Anxiety	Euphoria	Apathy	Disinhibition	Irritability	Aberrant motor behaviour	Nighttime behaviour	Eating disorders	Cumulative explained variance (%)
Drug naive patients (n=512)													
Factor 1: Agitation/ aggression	(0.415)		0.755					0.706	0.847				17
Factor 2: Depression				0.769	0.748								30
Factor 3: Psychomotor agitation						0.633				0.439	0.744		41
Factor 4: Psychosis	0.528	0.871											51
Factor 5: Apathy and eat disorder							0.833					0.519	61
Patients using psychotropic medication (n=925)													
Factor 1: Agitation/ aggression			0.736			0.464		0.728	0.762				17
Factor 2: Depression				0.670	0.761					(0.406)			31
Factor 3: Psychosis	0.651	0.799									0.451		42
Factor 4: Apathy + psychomotor agitation							0.700			0.491	(0.431)	0.583	53

Only factor loadings > 0.40 are presented. Factor loadings in parentheses imply that a specific item loads to more than one factor and the factor loading to the other factor is higher.

For GDS stage 6 a 5-factor solution was found that explained 61% of the variance, with a factor 'agitation/aggression' for agitation, disinhibition, irritability (and euphoria); a factor 'depression' for depression and anxiety; a factor 'psychosis' for delusions and hallucinations; a factor 'psychomotor agitation' for aberrant motor behaviour and night-time behaviour; and a factor 'apathy' for apathy and eating disorders. For GDS stage 7, a 5-factor solution was found (explaining 61% of the variance) also with a factor 'agitation/aggresion' including agitation and irritability, a factor 'psychosis' including delusions, hallucinations and disinhibition, a factor 'depression' including depression and anxiety, a factor 'apathy' including apathy and aberrant motor behaviour and a factor for night-time behaviour and eating disorders. The factor structure of patients in drug-naive patients was somewhat different from that of those patients using psychoactive medication (table 4). In the drug-naive patients the same 5-factor solution was found with factors for agitation/aggression, psychosis, depression, apathy and psychomotor agitation as in GDS stage 6. Only euphoria loaded on the psychomotor agitation cluster instead of the agitation/aggression cluster. In patients using one or more psychoactive drugs, a 4-factor solution was revealed, in which symptoms in the factors apathy and psychomotor agitation clustered together. Night-time behaviour also loaded on the psychosis cluster.

Results after oblique rotation of factors were very similar to those described after orthogonal rotation; in different GDS stages and with or without psychoactive medication the same number of factors were found and the same combination of symptoms loaded to each factor, except for GDS stage 7 where disinhibition loaded on the 'psychosis' factor.

Discussion

This study shows that neuropsychiatric symptoms in nursing home patients with dementia were related. While some associations between individual symptoms – as measured with the NPI-NH – were influenced by dementia severity, the behavioural dimensions or 'syndromes' underlying neuropsychiatric symptoms, i.e. agitation/aggression, psychosis, depression, psychomotor agitation and apathy were not.

The stability of the factor structure has been replicated by others.[19, 23] With respect to the 5 factors, the cluster agitation in this study generally corroborates the findings of 3 other studies [21-23], the cluster psychosis is consistent with that found in 6 other studies [16, 19, 21-24] and the cluster depression is consistent with the results of 3 other studies.[15, 23, 24] Psychomotor agitation (a combination of aberrant motor behaviour and night-time disturbances) is only replicated by 2 studies.[14, 22] Apathy as a single symptom or together with eating disorders or disinhibition has never been replicated by any other study.

Our finding that apathy and depression belong to different underlying dimensions is supported by 2 studies using the NPI.[16, 21] In two other studies, however, apathy and depression belong to the same underlying behavioural dimension.[19, 23] A possible explanation for the conflicting results may be that the clustering of apathy and depression depends on the severity of cognitive deterioration. Apathy and not depression appeared to be associated with cognitive dysfunction.[36] Depression tends to occur more frequently during the earlier stages of dementia,[2] while the prevalence of depressive symptoms or major depression is relatively low in more severely demented patient samples,[2, 37, 38] perhaps due to the patient's loss of awareness of deterioration or his inability to communicate these symptoms; in contrast, apathy is more prevalent in the latter group.[37] The shift from depression towards apathy in the severe stages of the disease may (partially) explain why apathy and depression are based on two distinct behavioural dimensions in this study (with patients with moderate to severe dementia) as well as in the study by Hollingworth et al. (in the subgroup of patients with GDS 5-7)[23], while in patients with relatively mild stages of dementia,[19, 23] apathy and depression are part of the same cluster. In addition, the relationship between depression and apathy may change over the course of dementia: while it may be part of an affective disorder in the early stages, apathy may develop into a phenomenon in its own right with a separate, probably more neurobiological pathogenesis in advanced stages due to frontal lobe (or widespread cortical) dysfunction.[39]

Aberrant motor behaviour was associated with night-time disturbances in severe cognitive deterioration (GDS stage 6). Aberrant motor behaviour comprises symptoms like pacing, constant opening/closing wardrobes, repeatedly dressing or undressing and picking/fiddling or other repetitive behaviour. This finding is consistent with the cluster concept psychomotor agitation, described by Lawlor and Bhriain.[12]

The 5 clusters (underlying behavioural dimensions), i.e. agitation/aggression, psychosis, depression, psychomotor agitation and apathy, were also found in a subgroup of drug-naive patients. However, in the group of patients on psychotropic medication, symptoms of the cluster 'apathy' and 'psychomotor agitation' were grouped together. Possibly, adverse events of psychoactive medication such as somnolence or extrapyramidal symptoms have been misinterpreted as apathy and psychomotor agitation, respectively. Moreover, the correlation between symptoms could change – and the factor structure accordingly – because of a selective reduction of prevalence and severity of some behavioural symptoms by the effect of the psychoactive medication.

To the best of our knowledge the present study is the largest factor-analytic study of patients with severe dementia. The sample covers 4.4% of all demented patients that receive nursing home care in the Netherlands. The study cohort was a relatively homogeneous and representative sample of patients without a priori behavioural

problems receiving nursing home care, not only in dementia special care units within nursing homes but also in residential homes through outreach care programmes. Special care was taken to ensure the reliability of the data through special training and supervision of the interviewers and the requirement that registered nurses make the assessments, thereby ensuring that the best qualified person was available for each patient.

There are a number of limitations to this study. (1) We did not have reliable data on dementia subtype. Some authors found similarities across diagnoses of dementia subtypes,[1] others did not.[40-43] However, the latter findings would not necessarily imply that the correlation between symptoms would be affected by dementia subtype. In fact, in a separate analysis of patients with Alzheimer's disease the same factor structure was found.[19] (2) We have tried to distinguish neuropsychiatric symptoms in different stages of dementia from adverse reactions of psychoactive medication, and have tried to test whether the effect of medication could (selectively) have influenced the correlation between symptoms, by performing a separate analysis in drug-naive patients and in patients with prescribed psychotropic medication. However, psychoactive medication use is not independent of dementia stage (medication was most frequently described in GDS stage 6). (3) We used the NPI as a measure of neuropsychiatric symptoms. The NPI is a rating scale with established validity which has been used on many diverse patient cohorts. Therefore, although it is possible that some symptoms were difficult to assess in the moderate to severe dementia patients, the procedure used in this study can be considered to be a valid measure of neuropsychiatric symptoms.

Our findings may have two important implications for clinicians as well as researchers interested in the taxonomy of neuropsychiatric symptoms in dementia. First, the results of this study imply that the severity of dementia only partially influences the correlation between individual symptoms, but that the clusters of the neuropsychiatric symptoms, i.e. agitation/aggression, psychosis, depression, psychomotor agitation and apathy (as proposed by Lawlor and Bhriain[12]), are valid and stable across dementia stage. Even in severe dementia, when some behaviours dealing with patients' inner experience (depression, anxiety, delusions, hallucinations) are more difficult to observe, different factors can clearly be distinguished. Our findings are in accordance with the results of pharmacological studies, which have shown that treatments have a consistent effect on behavioural problems in dementia when studying behavioural sub-syndromes,[7, 12] but not when studying individual symptoms. Symptom clusters can therefore be used to study populations with further deterioration of the disease, e.g. in longitudinal research involving clinical trials. However, one would be cautious about interpreting clusters at the level of individual symptoms. Second, the finding that apathy and depression are distinct 'syndromes' may have important therapeutic consequences. Clearly apathy without depressive symptoms should not be treated

with antidepressants because of the risk of adverse reactions. Also depression should not be mistaken for apathy because of the treatment options for depression. We emphasize that the timely diagnosis of depression and the correct diagnosis of depression as opposed to apathy are of major importance also in patients with severe cognitive dysfunction.

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CHAPTER 6

Agitation in Dutch institutionalized patients with dementia: factor analysis of the Dutch version of the Cohen-Mansfield Agitation Inventory

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Abstract

Background/aims
To establish the construct validity of the Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI-D) in institutionalized patients with dementia.

Methods
The CMAI-D was administered in a large sample of 1437 patients with moderate to severe dementia, receiving nursing home or outreaching nursing home care. Exploratory factor analysis was used to examine the behavioural dimensions underlying CMAI-D observations.

Results
A restricted three factor solution showed three factors, i.e. physical aggression, physically non-aggressive behaviour and verbally agitated behaviour, with prevalences of 62%, 67%, and 62% respectively. An unrestricted factor solution revealed three additional behavioural dimensions: hiding/hoarding, vocal agitation and a factor of miscellaneous items (i.e. repetitious mannerisms, spitting), which occurred respectively in 30%, 28% , and 35% of the patients.

Conclusion
The three factor solution of physical aggression, physically non-aggressive behaviour and verbally agitated behaviour corroborates earlier findings in other patient samples and therefore establishes the constructed validity in institutionalized patients with severe dementia. The robustness of these findings across different care settings suggests that agitated behaviours have a common basis. In addition, unrestricted factor analysis showed three other important independent behavioural symptoms in dementia, but are in fact too small to be used as a subscale. These findings might add to the taxonomy of agitation and aggression in dementia.

Introduction

Agitation is a common neuropsychiatric phenomenon of dementia. The estimated prevalence of agitation in nursing home patients with dementia ranges from 45 to 83 %.[1-8] Disruptive or agitated behaviours can be very distressing to patients, carers and nursing home staff alike.[9, 10] It may lead to institutionalization,[11] the (excessive) use of psychotropic medication [12] and physical restraints.[13] Some debate exists on whether agitation or aggression in dementia is a unitary concept or not and on which aspects of agitation research we should focus on when designing intervention trials so as to maximize outcome effects.

The debate somewhat centers around the 'lumping or splitting' of different symptoms. Agitation in dementia can be defined as inappropriate verbal, vocal or motor activity [14] and includes a variety of different (physically and verbally) behaviours, such as hitting, kicking, wandering, general restlessness, complaining or hoarding. Furthermore, agitation may vary according to dementia type (e.g., it is highly prevalent in frontal-temporal dementia)[15-17], severity of dementia [18, 19] and the physical environment and social interaction within institutions. [20-23]

The Cohen-Mansfield Agitation Inventory (CMAI), is a 29-items nurse based rating scale and it has been used in different studies evaluating the prevalence of agitation in nursing home patients and therapeutic effects of psychoactive medication.[24-28]

Factor analysis studies in different countries have shown that CMAI symptoms reflect three or four behavioural dimensions.[5, 29-34] However, some studies included a heterogeneous sample of patients with or without dementia.[5, 29, 32-34] In both the original and other studies three factors were found: i.e. physical aggression, physically non-aggressive behaviour and verbally agitated behaviour.[30, 31, 33] Recent studies have proposed a four factor model, adding hoarding/ hiding as another independent behavioural dimension.[5, 29] Some behavioural changes such as repetitive behaviours or vocalizations and screaming may be more typical of severe dementia in nursing home patients [35] and they may reflect an behavioural dimension of agitation that is different from those found in other patient samples.[24-26]

Three studies have evaluated the construct validity of the CMAI in institutionalized patients residing in nursing homes.[30, 31] In the Netherlands, nursing home care can also be given in residential homes by means of complementary outreaching nursing home care. This type of shared care is delivered by family physicians, nurses and nursing home physicians to patients in residential homes, in order to prevent or postpone nursing home admission.[36] To our knowledge, this is the first study to explore different behavioural dimensions that may underlie agitation in institutionalized patients with dementia receiving nursing home care or complementary outreaching nursing home care in a representative sample without a prior behavioural problems.

Methods

Study design and subjects

This cross-sectional cohort study is part of a study evaluating the prevalence and correlates of neuropsychiatric symptoms in Dutch nursing home patients with dementia. Patients were recruited from 27 nursing homes in the Eastern, Northern and Southern parts of the Netherlands. The nursing homes supplied 59 dementia special care units and 13 units providing programs for outreaching nursing home care situated in homes for the elderly. Patients were considered for inclusion provided (1) they met Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria [37] for dementia, (2) their cognitive decline was judged to be moderate to very severe, as defined by the Global Deterioration Scale stages 4-7,[38] (3) and they had resided in the institution for more than four weeks. Terminally ill patients were excluded. Presence of agitated behaviour or other behavioural changes was not a prerequisite to be included in the study.

The study was undertaken in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. The local Research Ethics Committee approved of the study. Eligible patients were only included after informed consent of the patients or legal guardian was obtained.

Procedures

Licensed vocational nurses were instructed to observe patients' behaviour during a two week period. These nurses were all specifically assigned to individual patients for managing the care process. At the end of the two week observation period vocational nurses were interviewed by trained nurse-assistants. The structured interviews were based on a written manual and aimed to elicit specific observations of agitated behaviours. Prior to the study interviewers were trained by two researchers during a two-hour session. Nursing home psychologists or resident physicians supervised the interviewers on a regular basis. Agitation was measured with the 29-items CMAI Dutch version (CMAI-D). CMAI-D items are rated on a 7-point scale (1-7) ranging from 'never' to 'several times an hour'. The CMAI has well-established (test-retest and interrater) reliability,[31,39] and (concurrent) validity [31] in both community samples [39] and in nursing homes patients.[31] Preliminary data supports construct validity of the CMAI-D in a mixed sample of demented and elderly psychiatric patients.[34]

The nursing home psychologist or resident physician assessed dementia severity on the Global Deterioration Scale, which is a well-known severity measure of dementia and scores ranges from no dementia (stage 1) to very severe dementia (stage 7).[38] Baseline characteristics, such as age, sex, marital status, time of institutionalization and psychoactive medications used were retrieved from patients' charts.

Data analysis

Construct validity of the CMAI-D was evaluated using exploratory factor analysis (SPSS 9.0.1). Items with a prevalence < 10% were excluded from analysis. Initially, factors with eigenvalues > 1 were extracted and orthogonally rotated to achieve simple structure (Varimax). Secondly, the number of extracted factors was limited based on inspection of the factor scree-plot. Limiting the number of factors extracted was considered useful, because a large number of factors with very few items would not reflect to be clinically meaningful entities/ behavioural syndromes. It has been recommended that the number of items loading on any given factor should be at least three or more.[40] In a second analysis, oblique rotation of factors was used (Direct Oblimin), as we expected agitation symptoms to be associated in dementia.
Items with factor loadings higher or equal than 0.4 were considered relevant. The highest factor loading of a particular item determined to which factor the item was assigned. Of each factor, both the variance explained and the overall factor prevalence – defined as at least one item present within a factor – was given. Prevalence of individual items of the CMAI were described elsewhere.[8]

Results

Patient characteristics

The study population consisted of 1,437 patients. The (median) age of the patients was 83 years, the female - male ratio was 4:1 and the median length of stay in the nursing home was 18 months (Table 1.). The majority of patients had severe to very severe cognitive decline (GDS stage 6 or 7). Psychoactive medication was prescribed to 65% of the patients, with prescriptions of antipsychotics in 37%, antidepressants in 27% and both anxiolytic drugs and hypnotics/sedatives in 15% of the patients. Very few patients were prescribed acetylcholinesterase inhibitors.

Table 1.
Patients characteristics of 1,437 nursing home patients with dementia

Age, years		
	Median	83
	Range	37-102
Gender, male		276 (19)
Duration of institutionalization, months		
	Median	18
	Range	1-191
Global Deterioration Scale (GDS)		
	GDS stage 4, mild dementia	59 (4)
	GDS stage 5, moderate dementia	282 (20)
	GDS stage 6, moderately severe dementia	728 (51)
	GDS stage 7, severe dementia	368 (26)
Psychoactive medication use		925 (65)
	Antipsychotic drugs	532 (37)
	Antidepressant drugs	390 (27)
	Anxiolytic drugs	222 (16)
	Hypnotics/sedatives	214 (15)
	Antiepileptic drugs	84 (6)
	Cholinesterase inhibitors, nootropics	15 (1)

Note:

Figures in parentheses indicate percentages. All percentage values are percentages of the total group

Factor analysis

The prevalence of nine behavourial symptoms was less than 10% (i.e. kicking, throwing things, biting, intentional falling, eating or drinking inappropriate substances, hurt self or others, tearing things or destroying property, verbal sexual advances and physical sexual advances). These symptoms were therefore excluded from subsequent analyses.

Factor analysis of the remaining 20 items revealed an initial six factor solution (table 2), explaining 60% of variance. The initial six factor solution included the three factors also found in other studies, i.e. physical aggression (hitting, pushing, cursing, scratching), verbally agitated behaviour (complaining, constant unwarranted request for attention, negativism, repetitive sentences or questions), physically non-aggressive behaviour (pace/aimless wandering, trying to get to a different place, general restlessness), and additionally three other factors which were labeled 'hiding/hoarding' (hoarding things, hiding things, handling things inappropriately), 'vocal

agitation' (strange noises, screaming), and a miscellaneous factor (performing repetitious mannerisms, spitting). Handling things inappropriately, grabbing onto people and general restlessness, loaded on the miscellaneous factor (>0.40) also.

Table 2:
Results of initial factor structure of CMAI in 1,437 Dutch nursing home patients with dementia

	Factor 1 Physically aggressive behaviour	Factor 2 Verbally agitated behaviour	Factor 3 Physically nonaggressive behaviour	Factor 4 Hiding/ hoarding	Factor 5 Perseverative behaviour	Factor 6 Vocal agitation
7. Hitting (including self)	0.80					
10. Pushing	0.74					
4. Cursing/ verbal aggression	0.60					
15. Scratching	0.55					
9. Grabbing	0.50				(0.40)	
18. Complaining		0.79				
5. Constant unwarr.req.attention help		0.76				
6. Repetitive sentences or questions		0.67				
19. Negativism		0.66				
1. Pace, aimless wandering			0.79			
16. Trying to get to a different place			0.77			
29. General restlessness			0.60		(0.44)	
24. Hoarding things				0.83		
23. Hiding things				0.82		
22. Handling things inappropriately				0.50	(0.44)	
26. Repetitious mannerisms					0.71	
3. Spitting (including at meals)					0.44	
12. Strange noises						0.81
13. Screaming						0.78
Explained variance	12%	12%	11%	10%	8%	7%
Prevalence (any item)	54.2%	61.6%	57.2%	30.4%	34.7%	28.1%

Notes:

Factor loadings > 0.40 presented ('inappropriate dressing or disrobing' failed to load on any factor).

Inspection of the factor scree-plot suggested limitation of the number of factors to be examined to three. Results of this three factor model are presented in table 3, explaining 42% of the variance.

Table 3:
Results of limited 3- factor solution analysis of CMAI in 1,437 Dutch nursing home patients with dementia

	Factor 1 Physically nonaggressive behaviour	Factor 2 Physically aggressive behaviour	Factor 3 Verbally agitated behaviour
1. Pace, aimless wandering	0.69		
23. Hiding things	0.65		
24. Hoarding things	0.64		
16. Trying to get to a different place	0.61		
22. Handling things inappropriately	0.60		
29. General restlessness	0.59		
2. Inappropriate dressing or disrobing	0.57		
7. Hitting (including self)		0.75	
10. Pushing		0.63	
15. Scratching		0.60	
4. Cursing or verbal aggression		0.58	
9. Grabbing		0.55	
13. Screaming		0.48	
3. Spitting (including at meals)		0.47	
12. Strange noises		0.41	
5. Constant unwarr.req.attention help			0.78
18. Complaining			0.75
6. Repetitive sentences or questions			0.68
19. Negativism			0.63
Explained variance	15%	14%	13%
Prevalence (any item)	66.6%	62.4%	61.6%

Factor loadings > 0.40 presented ('performing repetitious mannerisms' failed to load on any factor).

Items loading on the first factor (15% explained variance) were pacing, hiding, hoarding, trying to get to a different place, handling things inappropriately, general restlessness, inappropriate robbing/disrobing. The factor was labeled physically non-aggressive behaviour. Items loading on the second factor (14% explained variance) were hitting, pushing, scratching, cursing, grabbing, screaming, spitting, and strange noises. This factor was labeled physical aggression.

Items loading on the third factor (13% explained variance) were constant unwarranted request for attention or help, complaining, repetitive sentences or questions, negativism. The third factor was labeled verbally agitated behaviour. Repetitious mannerisms did not load on any of the factors.
Factor analysis with oblique rotated factors produced very similar results to the previous analyses.
The overall prevalence of any item of the three factors physical aggression, physically non-aggressive behaviour and verbally agitated behaviour in the initial six factor and final three factor solution ranged from 54-62% and 62%-67% respectively. The prevalence of hoarding/ hiding, vocal agitation and the miscellaneous cluster was lower, i.e. 30%, 35% and 28% respectively.

Discussion

This study explored construct validity of CMAI-D ratings in a large sample of nursing home patients with moderate to severe dementia. Three underlying behavioural dimensions were found.
The present findings corroborate those of others. Previous studies have shown that agitation as measured with the CMAI consists of physically aggressive behaviour, physically non-aggressive behaviour and verbally agitated behaviour.[30, 31, 33, 34] In this study 20 out of 29 items were factor analyzed. Of the 20 items, 18, 20, 15 and 17 items loaded on similar factors found in previous studies. [30, 31, 33, 34] These studies have been done in different settings, i.e. nursing homes,[30, 31] hospitals [33] or psychiatric observation clinic for older persons [34] with [33, 34] or without [30, 31] a confirmed diagnosis of dementia. In three studies agitated patients were included only.[31, 32] Also in the other CMAI-D study, agitation was probably highly prevalent in patients admitted to a psychiatric hospital;[34] in the other two studies agitation was not an inclusion criterion.[30, 33]
The present study is, to our knowledge, the largest factor analytic study in patients with dementia. The sample covered 4.4% of all demented patients that received nursing home care in the Netherlands. It has been carried out in a relatively homogeneous and representative sample of patients without a priori behavioural problems receiving nursing home care, not only in dementia special care units within nursing homes, but also in residential homes by means of outreaching care. Special care was taken to ensure reliability of the data, with respect to training and supervision of the interviewers and the requirements of the licensed nurses, so that the best informant was available for each patient. In this sample of patients with severe dementia, the factor structure was similar compared to what was found by others. These robust findings support construct validity of the CMAI-D across different settings and severity of dementia.

In our initial unrestricted factor model, we were able to find three additional dimensions of agitated behaviour. Our large database enabled us to detect additional clusters containing less frequent items which might not have been found in other studies. The additional three factors are important, not so much as to add to the construct validity of the CMAI-D, but as they add to the taxonomy of agitation.
(1) The first additional factor hiding/hoarding has also been found by two other studies in demented nursing home patients[5, 29] Although hoarding is associated with other manifestations of agitation,[41] it can occur without other physically non-aggressive behaviours. Since hiding and hoarding behaviour is associated with mild cognitive deterioration and less ADL impairment,[41] because it requires relatively intact ambulatory function, it can be separated from other physically non-aggressive behaviours, such as general restlessness, occurring in more advanced dementia. Hoarding may also have a distinct underlying mechanism as opposed to other physically non-aggressive behaviours in dementia and may be related to complex compulsive behaviours as have been described as a temporal variant of frontotemporal dementia [42] or to imitation and/or utilization behaviour.[43]
(2) Vocal agitation or vocally disruptive behaviour is typical verbally agitated behaviour in severe dementia with declining communicative abilities and might be considered as an indirect request for help, in patients with discomfort or other unmet needs.[44] The exact mechanisms inducing vocal agitation are yet unknown,[45] but might be explained by interruption of the frontal subcortical circuits.[35] Vocal agitation has also been associated with severe cognitive impairment [46] or severe dementia with total dissolution of speech,[35] depression,[47, 48] psychosis,[48] under-treated pain [46, 48] or environmental factors such as noise levels, or over/understimulation.[48, 49] There may be different types of disruptive vocalizations.[44] However, the two CMAI items (i.e. strange noises and screaming) are incomplete to assess different types of disruptive vocalizations.
(3) The cluster of miscellaneous symptoms contained 'performing repetitious mannerisms', 'spitting', and (possibly) 'handling things inappropriately', 'grabbing onto people' and 'general restlessness'. These symptoms may be regarded as stereotyped and perseverative, or hyperoral behaviour typical of frontal lobe degeneration, as opposed to complex ritualistic behaviour in the early stages of this disease.[50-52]
A closer look of the factor structure of the CMAI revealed different symptom clusters of agitation and aggression. This might add to understanding specific end-stage phenomena, such as vocal agitation and executive dysfunction in dementia, such as hoarding and stereotypical repetitive behaviour. The three additional dimensions found included too small a number of symptoms to construct separate CMAI subscales,[40] but this study gives rise to the discussion to extent the CMAI-D with specific items on these dimensions. Until this issue has been settled, these symptoms can be measured more reliably with other assessment scales such as the stereotypic

and ritualistic behaviours subscale as an addendum to the NPI [52, 53] or the typology of vocalizations.[44]

The robust findings of three behavioural dimensions underlying agitation in this large study of Dutch nursing home patients with moderate to severe dementia support construct validity of the CMAI-D. Implications are, that given the similar results found in different studies in several countries and across different care settings, agitated behaviour in dementia may have a strong common (biological) basis. Our initial 6 factor model that comprises the original three factors, not only support the construct validity of the CMAI-D, but it also suggests that aggressive or agitated behaviour and its underlying mechanisms should be further explored.

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CHAPTER 7

Predictors of neuropsychiatric symptoms in nursing home patients with dementia: influence of gender and disease severity

Submitted

Abstract

Background/aims

To assess the influence of disease-related predictors on neuropsychiatric symptoms in nursing home patients with dementia.

Methods

Agitation and other neuropsychiatric symptoms were assessed in a large sample of 1319 Dutch nursing home patients using the Cohen-Mansfield Agitation Inventory (CMAI) and the Neuropsychiatric Inventory–Nursing Home version (NPI-NH). The influence of gender and severity of cognitive decline, assessed with the Global Deterioration Scale (GDS), was investigated using logistic regression analysis and subsequently corrected for possible confounders, such as age of the patient, duration of institutionalization and psychoactive medication use.

Results

While physically aggressive behaviour was more common in patients with very severe cognitive deterioration (GDS stage 7), disinhibition, irritability, physically non-aggressive and verbally agitated behaviour were more common in patients in GDS stage 5 or 6. Physically aggressive behaviour was more common in men, whereas female patients demonstrated more verbally agitated behaviour. With respect to other neuropsychiatric symptoms, delusions and depression were also more common in patients in GDS stage 5 and 6, while prevalences of anxiety and apathy further increased in severely demented patients (GDS stage 7). Apathy was more prevalent in male patients, while depression and anxiety were more common in female patients

Conclusion

In this large sample of nursing home patients, agitation and other neuropsychiatric symptoms were associated with the severity of dementia, with most symptoms occurring in patients showing (moderately) severe cognitive decline. Only physical aggression, anxiety and apathy were more common in patients with very severe cognitive decline (GDS stage 7). Disease-related factors and gender were important predictors of neuropsychiatric symptoms in this patient cohort. More research is needed to explore the environmental correlates of neuropsychiatric symptoms in nursing homes.

Introduction

Neuropsychiatric symptoms are ubiquitous in dementia and are important predictors of institutionalization.[1,2] The prevalence of neuropsychiatric symptoms in nursing homes has been estimated to be between 72 and 92%.[3-7] Agitation in particular is regarded as one of the most troublesome behavioural changes in dementia. To date, only a few studies have examined correlates of agitation, [8,9] and our understanding of the factors that contribute significantly to this and other neuropsychiatric symptoms in nursing home patients with dementia is still quite limited. In general terms, these factors may be disease related, such as dementia type or severity, psychological in nature or related to the nursing home environment.

With respect to disease-related factors, some studies in nursing home patients with dementia have established the relationship between (increased) cognitive and global deterioration associated with dementia and agitation or aggression,[7,10,11,12,13] psychosis,[7] or apathy.[7] There is also some evidence that gender is an important predictor of agitation in nursing home patients, with men tending to show more physically non-aggressive behaviour,[11] physically aggressive behaviour [14] or vocal agitation [11] than women, whereas the results on verbally aggressive/agitated behaviour are conflicting.[10,12]

The prevalence of neuropsychiatric symptoms may also be influenced by the use of psychoactive medication, such as antipsychotics, which are frequently prescribed to patients with agitation, psychosis and anxiety.[7] Such medication may confound the effect of other predictors on these symptoms.

To date, no data on predictors of agitation are available on Dutch nursing home patients with dementia. Nursing homes in The Netherlands differ from their counterparts in other countries in that the staff comprise not only nursing personnel but also specially trained nursing home physicians, physical therapists, psychologists and social workers,[15,16] all of whom are employed by the nursing home. Moreover, care is provided in dementia special care units (SCUs), where patients usually live in small groups of about 6-12 persons.

It is relevant to investigate the importance of disease-related predictors on neuropsychiatric symptoms in an institutional setting in which such behaviour may not only be influenced by disease-related factors but also by nursing home environment characteristics. The objective of this study was, therefore, to assess the influence of the severity of dementia and gender on neuropsychiatric symptoms in nursing home patients with dementia corrected for possible confounders.

Methods

Study design and subjects

This cross-sectional cohort study is part of the WAAL Behaviour in Dementia (WAALBED)-study evaluating the prevalence and correlates of neuropsychiatric symptoms in Dutch nursing home patients with dementia. Patients were recruited from 26 nursing homes in different parts of the Netherlands, and these nursing homes provided a total of 59 dementia SCUs. Patients were considered for inclusion in the study when (1) they met Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria [17] for dementia, (2) their cognitive decline was staged as moderate to very severe, as defined by Global Deterioration Scale (GDS) stages 4–7 [18] (3) and they had resided in the institution for more than 4 weeks. Terminally ill patients were excluded. The presence of neuropsychiatric symptoms was not a prerequisite to be included in the study. Detailed information of the study method has been published elsewhere. [3]

The study was undertaken in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. The local Research Ethics Committee approved the study. Eligible patients were only included after the informed consent of the patients or legal guardian was obtained.

Data collection and assessments

Data were collected between February 2003 and October 2003. To rule out any longitudinal effects, the assessments took place within a 4-week period. All licensed vocational nurses assigned to individual patients were instructed to observe symptoms during a 2-week observation period. At the end of this 2-week period, the vocational nurses were interviewed by trained nurse-assistants who had received special training from two researchers in a 2-h session prior to the study. The interviews were structured, following guidelines provided by a written manual, and had the aim of eliciting specific observations of all neuropsychiatric symptoms. Supervision of the interviewers was provided by a psychologist or a nursing home physician.

Agitation and aggression were measured using the Cohen Mansfield Agitation Inventory (CMAI). This instrument, originally developed by Cohen-Mansfield et al.,[19] is designed to assess 29 agitated or aggressive behaviours and has been extensively used for assessment purposes in nursing homes. The CMAI has been validated by Miller et al.[20] and subsequently translated into Dutch and validated by de Jonghe.[21] The frequency of each symptom is rated on a seven-point scale (1–7) ranging from 'never' to 'several times an hour'. The CMAI has a well-established (test–retest and interrater) reliability [20,22] and (concurrent) validity [20] in both community samples [22] and nursing home patients.[20] Preliminary data support the construct validity of the CMAI-D in a mixed sample of demented and elderly psychiatric patients.[21] For the study reported here, symptoms were clustered in three behavioural dimensions

– physically aggressive, physically non-aggressive and verbally agitated behaviour. The clusters were obtained using factor analysis of the CMAI-D in a larger but partly overlapping population of dementia patients receiving nursing home care in nursing homes and outreaching nursing home care projects.[23] The items within each cluster are comparable with those reported by others.[20, 21, 24, 25] Aggressive or agitated behaviour within each cluster was considered to be relevant when one or more items occurred at least once a week (any individual items score ≥ 3).

Other neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory–Nursing Home version (NPI-NH). Cummings originally developed the NPI as a means to assess neuropsychiatric symptoms in demented outpatients.[26, 27] The nursing home version was developed for the use of professional caregivers within institutions and has been translated into Dutch by Kat and de Jonghe;[28] it has proven to be a valid and reliable assessment instrument for trained nursing staff.[29, 30]

The NPI-NH includes 12 neuropsychiatric symptoms: delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, night-time 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, resulting in values ranging from zero to 12 for each symptom. We considered neuropsychiatric symptoms with an F × S score ≥ 4 to be clinically relevant, which is in accordance with previous studies.[31, 32]

To describe the severity of the dementia, the psychologist (or nursing home physician) used the Global Deterioration Scale (GDS),[18] which consists of a seven-point scale (1–7) ranging from no cognitive decline (1) to very severe cognitive decline (7). GDS scores of 4, 5 and 6 denote moderate, moderately severe and severe cognitive decline, respectively. Baseline characteristics, such as age, sex, marital status and time of institutionalization, were retrieved from patients' charts. Data on the actual regular use of psychoactive medication on the day of assessment were registered. Psychoactive medications were classified using the Anatomical Therapeutical Chemical-classification [33] and grouped into antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants, anti-epileptics and miscellaneous (e.g. cholinesterase inhibitors).

Analysis

Data on prevalences are presented on subgroups of male and female patients and/or with different severities of cognitive decline (GDS stages 4–7). Differences in prevalences of agitation and other neuropsychiatric symptoms by gender and GDS were tested using chi-square statistics. A p-value of < 0.05 was considered to be statistically significant. The influence of predictors on neuropsychiatric symptoms were also simultaneously assessed in a logistic regression analysis. Dependent variables

were presence or absence of agitated behaviour on the CMAI clusters and the presence or absence of individual symptoms on the NPI-NH (F × S cut-off score < or ≥ 4). Independent variables entered in the model were gender and dementia severity. The influence of both gender and dementia severity on neuropsychiatric symptoms was corrected for possible confounders, such as age of patient, duration of institutionalization and psychoactive medication use. Age was categorized in 5-year intervals, and duration of institutionalization in intervals of 6 months – 1 year. Antipsychotics, anxiolytics, hypnotics, antidepressants and antiepileptics were simultaneously entered as dichotomous variables. Interaction terms were also entered in the model to make allowance for possible effect modification, but were left out of the final analysis when they did not appear to reach statistical significance ($p < 0.05$).

Results

Patient characteristics

The (median) age of the study population (1319 patients) at enrollment was 83 years, the female/male ratio was 4:1 and the median length of stay in the nursing home was 18 months (Table 1). The majority of patients had been assessed to have severe to very severe cognitive decline (GDS stage 6 or 7). Psychoactive medication had been prescribed to 65% of the patients in the form of antipsychotics (in 37% of patients), antidepressants (27%) and both anxiolytic drugs and hypnotics/sedatives (15%). Very few patients (<1%) used cholinesterase inhibitors.

Prevalences of agitation and other neuropsychiatric symptoms

Prevalences of physically aggressive, non-aggressive and verbally agitated behaviour were 56%, 62% and 56%, respectively (Table 2). Prevalences of agitation as measured with the NPI-NH were 31% for agitation, 20% for disinhibition, 29% for aberrant motor behaviour and 34% for irritability. Prevalences of other neuropsychiatric symptoms ranged from 8% to 34% (delusions, 15%; hallucinations, 8%; depression, 20%; anxiety, 21%; apathy, 34%) (see also Chapter 4 for detailed description of the prevalence rates)[3].

Table 1.
Patient characteristics of 1,319 nursing home patients with dementia

Age, years		
	Median	83.0
	Standard Deviation	8.1
	Range	36–102
Gender, male		266 (20)
Duration of institutionalization, months		
	Median	20
	Range	1–191
Global Deterioration Scale (GDS)		
	GDS stage 4, moderate cognitive decline	38 (3)
	GDS stage 5, moderately severe cognitive decline	234 (18)
	GDS stage 6, severe cognitive decline	681 (51)
	GDS stage 7, very severe cognitive decline	366 (28)
Total psychoactive medication use		857 (65)
	Antipsychotic drugs	488 (37)
	Antidepressant drugs	356 (27)
	Anxiolytic drugs	211 (16)
	Hypnotics/sedatives	198 (15)
	Antiepileptic drugs	79 (6)
	Cholinesterase inhibitors, nootropics	13 (1)

Figures in parentheses indicate percentages. All percentage values are percentages of the total group

Influence of dementia severity

Prevalences of physically aggressive behaviour significantly increased from GDS stage 4 to GDS stage 7. (Table 2). Physically non-aggressive behaviour and verbally agitated behaviour were highly prevalent in GDS stages 5 and 6. Disinhibition, irritability and aberrant motor behaviour also showed different prevalences at various stages of cognitive decline, with the highest prevalences of disinhibition and irritability in patients with GDS stages 5 and 6 and the highest prevelances of aberrant motor behaviour in patients with GDS stage 6. The prevalences of agitation, as measured with the NPI-NH, and anxiety were not significantly different between GDS stages. Delusions and depression were highly frequent in patients with GDS stage 5 and 6. Hallucinations and apathy showed increasing prevalences with further cognitive decline, with the highest prevalences occurring in patients with GDS stage 7.

Table 2:
Prevalence (%) of agitation and other neuropsychiatric symptoms by gender and cognitive decline (GDS) in nursing home patients with dementia

	Males (n=266)	Females (n=1053)	p-value [3]	GDS 4 (n=38)	GDS 5 (n=234)	GDS 6 (n=681)	GDS 7 (n=366)	p-value [3]	Overall (n=1319)
CMAI [1]									
Physically aggressive	61.3	54.5	0.047 (*)	26.3	42.3	58.6	62.6	0.000 (*)	55.9
Physically non-aggressive	62.8	61.3	0.647	44.7	62.0	69.5	48.4	0.000 (*)	61.6
Verbally agitated behaviour	51.1	56.7	0.103	50.0	66.7	65.3	30.9	0.000 (*)	55.6
NPI-NH agitation [2]									
Agitation	33.1	30.9	0.492	15.8	27.8	33.6	31.0	0.062	31.3
Disinhibition	22.6	19.1	0.207	13.2	21.4	24.5	10.7	0.000 (*)	19.8
Irritabilility	33.6	33.5	0.977	23.7	40.2	38.6	20.8	0.000 (*)	33.5
Aberrant motor behaviour	27.8	29.4	0.618	10.5	15.8	34.9	28.7	0.000 (*)	29.1
NPI-NH other items [2]									
Delusions	15.4	14.3	0.657	7.9	17.1	19.2	4.9	0.000 (*)	14.6
Hallucinations	9.4	7.2	0.232	0.0	3.8	8.5	9.3	0.018 (*)	7.7
Depression	13.5	21.5	0.004 (*)	18.4	23.1	23.5	11.2	0.000 (*)	19.9
Anxiety	15.4	21.8	0.020 (*)	10.5	16.3	22.0	21.6	0.104	20.5
Apathy	39.8	32.2	0.018 (*)	18.4	20.1	31.3	48.6	0.000 (*)	33.7

Notes:
GDS, Global Deterioration Scale; **CMAI**, Cohen-Mansfield Agitation Inventory; **NPI-NH**, Neuropsychiatric Inventory-Nursing home version,[1] Any-item occurring once a week or more,[2] NPI-NH frequency (F) × Severity (S) score ≥ 4,[3] (*) indicates $p < 0.05$ (Chi-square statistics)

Influence of gender

Physically aggressive behaviour was more common in male patients (Table 2). No gender differences were found for physically non-aggressive behaviour or for the NPI-NH items on agitation. Depression and anxiety were more frequent in female patients and apathy in male patients.

Logistic regression analyses

The logistic regression analyses (Table 3) confirmed the existence of significant differences between GDS stages for all symptoms described in the univariate analyses, with the exception for hallucinations. Anxiety also appeared to be significantly influenced by dementia severity in the logistic regression analysis, with the highest prevalences appearing in patients with GDS stage 7. The gender differences in the

univariate analyses were confirmed by the results of the logistic regression analyses. Verbally agitated behaviour, which was not significantly different between both sexes in the univariate model, appeared to be more common in female patients in the logistic regression analysis. The influence of dementia severity and gender on the neuropsychiatric symptoms were corrected for age of patient, duration of institutionalization and psychoactive medication use.

Table 3:
Results of logistic regression analysis of the influence of GDS and gender on agitation and other neuropsychiatric symptoms in nursing home patients with dementia [1)]

	GDS	(GDS 7=reference)		Gender
	GDS stage 4	GDS stage 5	GDS stage 6	male vs. female
CMAI [2)]				
Physically aggressive	0.2 [0.1–0.6]*	0.5 [0.3–0.7]*	0.8 [0.6–1.1]	1.4 [1.0–1.8]*
Physically non-aggressive	0.7 [0.3–1.4]	1.5 [1.0–2.2]*	2.0 [1.5–2.7]*	0.9 [0.7–1.3]
Verbally agitated behaviour	2.0 [0.98–4.1]	3.8 [2.6–5.6]*	3.4 [2.5–4.6]*	0.7 [0.5–0.97]*
NPI-NH agitation [3)]				
Agitation	0.4 [0.2–1.1]	1.0 [0.7–1.5]	1.1 [0.8–1.5]	1.0 [0.8–14]
Disinhibition	1.2 [0.4–3.2]	2.2 [1.4–3.6]*	2.5 [1.7–3.7]*	1.1 [0.8–1.6]
Irritabilility	1.3 [0.6–2.9]	3.1 [2.0–4.6]*	2.4 [1.7–3.3]*	0.9 [0.7–1.2]
Aberrant motor behaviour	0.3 [0.1–0.8]*	0.5 [0.3–0.7]*	1.3 [0.95–1.8]	0.8 [0.6–1.1]
NPI-NH other items [3)]				
Delusions	1.5 [0.4–5.6]	3.8 [2.0–7.0]*	3.8 [2.2–6.5]*	1.1 [0.7–1.6]
Hallucinations	- [4)]	0.5 [0.2–1.1]	0.9 [0.6–1.5]	1.3 [0.8–2.1]
Depression	1.1 [0.4–2.9]	1.8 [1.1–2.9]*	1.9 [1.3–2.8]*	0.5 [0.3–0.8]*
Anxiety	0.3 [0.1–0.9]*	0.6 [0.4–0.9]*	0.9 [0.6–1.3]	0.5 [0.4–0.8]*
Apathy	0.2 [0.1–0.6]*	0.3 [0.2–0.5]*	0.5 [0.4–0.7]*	1.5 [1.1–2.0]*

Notes:

GDS = Global Deterioration Scale, **CMAI** = Cohen-Mansfield Agitation Inventory, **NPI-NH** = Neuropsychiatric Inventory- Nursing home version, ***OR** = 1 not included ($p < 0.05$), [1)] After correction for psychoactive medication use, duration of institutionalization and age. Interaction terms were allowed but did not appear to be significant ($p > 0.05$) and therefore were left out of the final analysis, [2)] Any-item occurring at least once a week ,[3)] NPI-NH Frequency (F) x Severity (S) score ≥ 4, [4)] Prevalence = 0

Discussion

The results of this study show that prevalences of neuropsychiatric symptoms were high and that they were influenced by the severity of the dementia and the gender of the patient. Apathy, hallucinations, anxiety and physical aggressive behaviour showed the highest prevalences in patients with very severe cognitive decline. Other symptoms, such as physically non-aggressive behaviour, verbally agitated behaviour, disinhibition, irritability, delusion and depression were most prevalent in patients with GDS stage 5 or 6.

The finding of a prevalence peak in patients with a (moderately) severe cognitive deterioration is in contrast with results from other nursing home studies in which agitation in general,[7, 13] physically non-aggressive or vocally/verbally agitated behaviour,[11, 12] physically non-aggressive or vocally/verbally agitated behaviour,[11, 12] physical or verbal aggression,[10] aberrant motor behaviour,[7] delusions [7] and disinhibition [7] were found to increase with further cognitive (MMSE) [10-13] or global deterioration (Clinal Dementia Rating Scale).[7] Only the positive correlation between decreasing prevalences of depression and increasing severity of the dementia in the present study is consistent with the results of two studies in patients residing in nursing homes and social care facilities [6] and in a Dutch population of community dwelling patients with dementia.[34] This discrepancy between the results of previous studies and those of our study may be related to the differences in dementia severity. Although we cannot directly compare our GDS data with the cognitive and global disease measurements used in the other studies, our population included a reasonable percentage (23%) of patients with severe dementia (very severe cognitive deterioration). As the disease progresses, any exploration of the patient's inner experiences becomes more problematic due to the increasing loss of cognitive and communicative abilities. At severe to very severe stages of the disease, the symptoms can only be indirectly observed as overt behaviour, such as physically aggressive behaviour and apathy. Consequently, delusions, depression and verbally agitated behaviour (such as complaining, constant request for attention) become less frequent. The concomitant functional impairment at the more severe stages of the disease may also explain the less appearance of physical non-aggressive behaviour (wandering, hiding/hoarding things, trying to get to a different place).

The gender differences in prevalence rates found in this study are consistent with those reported in other nursing home studies on patients with dementia in terms of physically aggressive behaviour [5, 14] and verbally agitated behaviour,[12] but they differ for verbally agitated behaviour [10] and depressed mood.[5] In contrast to the present study, in which we found no gender differences for physically non-aggressive behaviour, two other studies have reported that this behaviour occurs more often in males.[5, 14] Only in a recent Norwegian nursing home study was gender not a predictor of any neuropsychiatric symptoms.[7]

The results have important clinical implications. Firstly, the concomitant decrease of the prevalence of depression and increase of the prevalence of apathy during cognitive deterioration support existing evidence that depression and apathy are two distinct syndromes [35] with different neurobiological underpinnings,[36, 37] which should be treated differently. We propose that apathy as a syndrome related to the global deterioration of dementia should receive more attention from both researchers and physicians. In contrast to depression, there is no broadly accepted pharmacological therapy for apathy. Evidence of the efficacy of cholinesterase inhibitors [38] or methylphenidate [39] for treating apathy is limited. Therefore, the use of efficacious psychosocial interventions, such as snoezelen [40, 41] or music therapy,[42] should be encouraged. Patients with apathy also benefit from personal attention from the activity therapist.[43]
Secondly, the finding that physically aggressive, physically non-aggressive and verbally agitated behaviour were in different ways predicted by gender and dementia severity supports the view that agitation is not a unitary concept, but should be distinguished into three separate entities,[25] possibly with different efficacies for antipsychotics.[44] Further research on this particular issue is required.

One of the major strengths of our study is the large and representative sample, which enabled us to perform logistic regression analyses with reasonably large (sub)groups. This type of analysis is more appropriate than univariate statistical testing [6, 7, 10] or linear regression models/correlations used in other studies,[11-13] since logistic regression analysis has the power to correct for possible confounders and is not based on linear assumptions of the relation between symptoms and dementia stage. Moreover, we did not only use the NPI-NH, but also the three symptom-clusters of the CMAI for the assessment of agitation, which appeared to be helpful in finding differences between stages of the disease.
The limitations include methodological concerns about the use of the GDS to reflect dementia severity. The GDS is a global measure used to assess severity of dementia for primary degenerative dementia. One could argue that assessing the severity of dementia using, for example, MMSE in combination with a functional assessment would be a superior approach. Furthermore, GDS also includes neuropsychiatric symptoms (delusions, anxiety and aggression), especially in GDS stage 6. This could be a possible source of bias. Another limitation concerns psychotropic medication use, which (while effective) may have decreased prevalence rates and weakened the relationship between the symptoms and other predictors, such as dementia severity. However, we found a strong and significant relationship between severity and symptoms, even after a correction for the use of different groups of psychoactive medication. We did not perform a sub-analysis on drug-naive patients since that would require removing more than 65% of the patients from the study, so that the remaining sample does not represent the reality of nursing home practice.

In conclusion, in this large representative sample of nursing home patients neuropsychiatric symptoms are ubiquitous in dementia and predicted by dementia severity and gender.

Most symptoms are associated with patients with mild-to-moderate dementia; only (physical) aggression, anxiety, apathy and hallucinations are more common in patients with severe dementia. This relationship is statistically independent of psychoactive medication use, age of the patient and duration of institutionalization. In this specific institutional setting, where neuropsychiatric symptoms of agitation are also supposed to be influenced by environmental factors, the relationship between neuropsychiatric symptoms and dementia severity and gender is evident. There is an urgent need for more research on the environmental correlates of neuropsychiatric symptoms in nursing homes.

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CHAPTER 8

Environmental correlates of neuropsychiatric symptoms in Dutch nursing home patients with dementia

Submitted

Abstract

Purpose

To estimate the influence of environmental correlates of neuropsychiatric symptoms in Dutch nursing home patients with dementia.

Methods

Patients with dementia residing in 56 Dementia Special Care Units (SCUs) (n = 1,289) were assessed using the Neuropsychiatric Inventory–Nursing Home version (NPI–NH) and the Cohen-Mansfield Agitation Inventory (CMAI). Potential correlates of the neuropsychiatric symptoms studied were gender and age of patient, dementia severity as measured with the Global Deterioration Scale (GDS), psychoactive medication use, the number of patients per unit or per living room, staff size/ patient ratio, time spent on care activities and presence of an walking circuit. Multilevel logistic regression analysis was used to estimate the relative contribution of the different factors in explaining neuropsychiatric symptoms variability.

Results

The prevalence of neuropsychiatric symptoms differed between nursing home units, even after correcting for patient-related factors such as cognition and psychoactive medication. Differences in symptoms between SCUs accounted for 3.9% (psychosis) to 14.3% (apathy) of the total variance in neuropsychiatric symptoms. Patient-related factors explained 7–21% of the total variance of neuropsychiatric symptoms. Environmental correlates, such as staff size, number of patients per unit or per living room or presence of an walking circuit in the SCU did not predict neuropsychiatric symptoms (<1% of the total variance). Only in SCUs of which the staff spent more time on care activities did the patients show lower levels of apathy.

Conclusion

We conclude that there is a substantial variation in the level of neuropsychiatric symptoms between SCUs. Although we failed to predict neuropsychiatric symptoms using the environmental correlates reported in this study, the large difference between SCUs – even after correcting for well-known patient factors (such as dementia stage) – suggests that other factors associated with the physical or psychosocial environment may explain the observed variation in the neuropsychiatric symptoms between SCUs in Dutch nursing homes.

Introduction

Neuropsychiatric symptoms, such as agitation, psychosis, depression and apathy, are ubiquitous in nursing home patients with dementia, with prevalence rates of more than 80%.[1] These symptoms can be a serious burden for nursing home staff, possibly leading to an increase in staff distress,[2,3] and they are associated with the use of physical restraints[4] and psychotropic medications[5,6] that in turn have the potential to cause negative side effects.[7]

Neuropsychiatric symptoms in demented nursing home residents are associated with the severity of dementia.[8] High prevalence rates of neuropsychiatric symptoms in nursing home patients may be due to a biased selection, as these symptoms are the main reason for institutionalization.[9,10] However, neuropsychiatric symptoms may also be associated with the characteristics of psychosocial/physical environment of the nursing home environment, such as crowded housing conditions leading to sensory overstimulation, for which patients with dementia are more susceptible,[11,12] the attitudes of the staff toward challenging behaviours and/or the size of the units in which patients reside throughout the day.

More insight into these factors and their effects on the emergence of neuropsychiatric symptoms may contribute to the identification of best nursing home practices. Studies evaluating the psychosocial and physical environment factors affecting patient behaviour are needed because of the important implications the results of such studies may have in terms of psychosocial interventions, adequate staff training and the development of appropriate services for nursing home residents, such as small-scale housing facilities.

To date, however, only limited data are available on the influence of the environment on the prevalence of neuropsychiatric symptoms.[1,13,14] Larger nursing homes in general and larger resident units in particular are associated with higher levels of agitation [15,16] and less social withdrawal.[17] The physical characteristics of a nursing home ward may have an impact on behavioural changes. Neuropsychiatric symptoms occurred less often in nursing homes with visual barriers on exit doors to prevent residents from leaving the SCU, when there was more privacy and more sensory comprehension.[17] Also, a sensory-enriched psychosocial environment in dementia special care units (SCUs) is associated with a lower level of agitation.[15]

Until now, no data are available on the environmental correlates of neuropsychiatric symptoms in Dutch nursing home patients with dementia. Care for people with dementia in Dutch nursing homes is provided in dementia SCUs, which differ considerably in terms of number of patients, staff/patient ratio and quality of care. We hypothesized that the prevalence and degree of the neuropsychiatric symptoms may differ among SCUs and that these differences may be associated with differences in the characteristic features and properties of the SCU, such as the physical and psychosocial environment. To test this hypothesis, we have used the ecological model [12]

and Progressively Lowered Stress Threshold Model [18] as underlying theoretical models. The aim of the study was to estimate the influence of the physical and psychosocial environment on the prevalence of neuropsychiatric symptoms in nursing home patients with dementia.

Methods

Study design and subjects

This cross-sectional cohort study is part of a larger study evaluating the prevalence and determinants of neuropsychiatric symptoms in Dutch nursing home patients with dementia. Patients were recruited from 26 nursing homes in the eastern, northern and southern parts of The Netherlands, including 59 SCUs for dementia. Patients satisfied the inclusion criteria when (1) they met Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria [19] for dementia, (2) their cognitive decline was judged to be moderate to very severe, as defined by the Global Deterioration Scale (GDS) scores stages 4–7,[20] (3) and they had resided in the institution for more than 4 weeks. Terminally ill patients were excluded. The presence of agitated behaviour or other behavioural changes was not a prerequisite to be included in the study. Detailed information on the study method and prevalence rates of individual symptoms has been published elsewhere.[21]

The study was undertaken in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. The local Research Ethics Committee approved of the study. Eligible patients were only included after informed consent of the patients or legal guardian was obtained.

Data collection and assessments

All assessments took place within a 4-week period. All licensed vocational nurses assigned to individual patients were instructed to observe symptoms during a 2-week observation period. At the end of this 2-week period, the vocational nurses were interviewed by trained nurse-assistants who had receiving special training from two researchers in a 2-h session prior to the study. The interviews were structured, following guidelines provided by a written manual, and had the aim of eliciting specific observations of all neuropsychiatric symptoms. Supervision of the interviewers was provided by a psychologist or a nursing home physician.

Neuropsychiatric symptoms were assessed using the Cohen Mansfield Agitation Inventory (CMAI) and the Neuropsychiatric Inventory Nursing home version (NPI–NH). The CMAI is designed to assess 29 agitated or aggressive behaviours,[22] and the frequency of each symptom is rated on a seven-point scale (1–7) ranging from 'never' to 'several times an hour'. The CMAI has a well-established reliability,[23, 24] and validity [24] in different patient samples.[23,24] The Dutch version was validated by

de Jonghe.[25] Symptoms are clustered in three behavioural dimensions – physically aggressive, physically non-aggressive and verbally agitated behaviour – based on a factor analysis of the CMAI–D in a larger and partly overlapping sample of dementia patients residing in nursing homes or included in outreaching nursing home care projects [26] and other studies.[24, 25, 27, 28] Aggressive or agitated behaviour within each cluster was considered to be relevant when one or more items occurred at least once a week (any individual items score ≥ 3).

The NPI–NH was originally developed by Cummings [29, 30]. The nursing home version has been adapted for use by professional caregivers in nursing home facilities and has proven to be valid and reliable for use by trained nursing staff.[31, 32] A Dutch translation of the NPI has also been shown to be reliable and valid.[33] The NPI–NH includes 12 neuropsychiatric symptoms: delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, night-time disturbances and appetite/eating change. The frequency (F) and severity (S) of each symptom is rated on a five- (0–4) and four-point (0–3) Likert scale, respectively. A separate score can be calculated for each symptom by multiplying the frequency and severity scores, resulting in values ranging from zero to 12 for each symptom. Neuropsychiatric symptoms with a F × S score ≥ 4 are considered clinically relevant. NPI–NH symptoms are grouped as psychosis (hallucinations and/ or delusions), agitation (agitation, disinhibition and/or irritability), depression/anxiety and apathy.

The severity of the dementia was assessed by a psychologist or a nursing home physician using the Global Deterioration Scale (GDS).[20] The GDS is a well-known dementia staging measure based on a seven-point scale (1–7) ranging from no cognitive decline (1) to very severe cognitive decline (7).

The environmental correlates measured were: the presence of an walking circuit, number of patients per unit or per living room, staff/patient ratio and hours spent on direct patient care. The number of patients per living room was defined as the number of patients per unit divided by the number of living rooms at the unit. Staff/patient ratio is defined as the number of staff at each unit engaged in direct patient care (i.e. licensed vocational nurses, nurses' aids, recreational therapists; volunteers or non-professional caregivers were not included) divided by the number of patients in the SCU. The hours spent on direct patient care is the time spent by staff on patient care during the working days (in hours per patient per day) divided by the number of patients in the SCU. Data on SCU environmental correlates were provided by the head of the SCU.

Data on the actual use of prescribed psychoactive medication on the day of assessment were recorded. Psychoactive medications were classified using the Anatomical Therapeutical Chemical-classification [34] and grouped into antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants.

Analysis

Proportions or means were used to describe the demographic and clinical characteristics of the study population. The odds of any one neuropsychiatric symptom being associated with patient characteristics, psychoactive medication use and environmental correlates were estimated using a multilevel logistic regression analysis approach (MLwiN, ver. 1.02.0002).[35] Multilevel analysis is an extended logistic regression analysis which can be used in two-level structured data (e.g. patients are clustered within SCUs). Because we hypothesized that the behaviour between patients of the same SCU is not independent, the estimates at the patient level must be corrected for the dependency at the SCU level (within SCUs) by adding an extra categorical variable (i.e. SCU) that provides an additional estimation of the variance at the SCU level (difference between SCUs).

Dependent variables were the presence or absence of CMAI or NPI clusters of symptoms. Independent (fixed) variables were baseline characteristics (gender, age and marital status of patient, duration of institutionalization), disease-related factors (GDS), psychoactive medication use (antipsychotics, anxiolytics, antidepressant and hypnotics) and environmental correlates. As some SCUs were specially equipped for patients with troublesome behaviours and others were not, an extra (dummy) variable was entered into the model to label these SCUs. Age of patient and duration of institutionalization were entered as continuous variables. Antipsychotics, anxiolytics, hypnotics and antidepressants were entered as dichotomous variables.

The Wald statistic was used to test the significance of the variance at the SCU level (variance compared to standard error of the variance) as well as the significance of independent variables at the patient level (estimates compared to standard error of the estimates). Patient factors and psychoactive medication use were entered stepwise (forward) into the model and left out in the final analysis when they did not reach statistical significance (p not < 0.05). In the final model, non-significant environmental correlates were also entered because of the specific aim of the study – i.e. the relationship between neuropsychiatric symptoms and environmental correlates.

To estimate the relative influence of fixed factors at the patient level in relation to the variance at the SCU level, we assumed that the total variance consists of variance(fixed) + variance(SCU level) + $\pi^2/3$, where the variance(fixed) denotes the variance of (fixed) patient factors, psychoactive medication use and environmental correlates, variance(SCU level) denotes the variance at the SCU level (i.e. due to differences between SCUs) and $\pi^2/3$ (=3.29) denotes the unexplained variance.[36]

We also evaluated whether observed symptom prevalence in any given SCU differed from what was to be expected based on individual patient factors. Predicted symptom prevalence rates were estimated for each SCU after correcting for relevant patient characteristics and psychoactive drug use. This was done by first calculating the odds for symptoms based on the presence or absence of all significant risk factors in each individual patient and then averaging results for that particular SCU. Actual

(observed) SCU prevalence rates were subsequently compared with the predicted SCU prevalence rates (estimate and 95% confidence interval of the standard error of the mean).

Results

Patient and SCU characteristics

A total of 1,322 patients residing in 59 SCUs met the inclusion criteria, but three SCUs were excluded from the analysis because of (an unacceptable amount of) missing data at the patient level (up to 50%). The study therefore comprised 56 participating SCUs with 1289 patients. The patient cohort had a mean age of 83 (SD: 8) years and a female/male ratio of 4:1. The GDS distribution was: stage 4, 3%; stage 5, 17%; stage 6, 52%; stage 7, 28%. Psychoactive medication was prescribed in 66% of all patients and consisted of antipsychotics (38% of total group), antidepressants (28%), anxiolytics (16%) and hypnotics/sedatives (15%). The median length of stay was 20 months (range: 1–191).

A total of 27 of the 59 SCUs (46%) had an walking circuit. The number of patients within an SCU ranged from 10 to 42 patients, with 5–31 patients in each living room (each SCU had one to four living rooms.) The time spent on direct patient care ranged from 2.3 to 4.1 h per patient per day. Staff/ patient ratio ranged from 0.4 to 0.9. Five SCUs with 76 patients (6% of the total sample) were specially equipped for patients with severe neuropsychiatric symptoms.

Predictors

Associations between patient factors, psychoactive medication use, environmental variables and neuropsychiatric symptoms are presented in Table 1.

Patient factors

Dementia severity was a significant predictor of physical aggressive behaviour and apathy, with higher symptom prevalence in more severe stages of dementia. The highest prevalence of physically non-aggressive, verbally agitated behaviour, agitation, disinhibition and irritability was found for patients with GDS stages 5 and 6. Male gender predicted physical aggressive behaviour and apathy, and female gender predicted verbally agitated behaviour and depression/anxiety. Younger patients expressed more physically non-aggressive behaviour and depression/anxiety than older patients. Patients who had been resident for a relatively shorter period of time had higher prevalence rates of depression/anxiety than those who had been there longer. Marital status did not predict any of the symptoms assessed.

Table 1.
Multilevel logistic regression analysis of patient related factors, psychoactive medication use, environmental correlates on neuropsychiatric symptoms in 1,289 nursing home patients with dementia

	CMAI Physically aggressive Behaviour	CMAI Physically nonaggressive behaviour	CMAI Verbally agitated behaviour	NPI-NH Agitation disinhibition irritability	NPI-NH Delusions hallucinations	NPI-NH Depression anxiety	NPI-NH Apathy
Patient related factors							
GDS 4 [1)]	0.19 [0.08–0.42]*	0.82 [0.39–1.74]	2.39 [1.11–5.14]*	0.71 [0.32–1.57]	0.61 [0.17-2.21]	-	0.16 [0.06–0.42]*
GDS 5 [1)]	0.38 [0.26–0.55]*	1.81 [1.23–2.66]*	4.50 [2.94–6.89]*	1.59 [1.08–2.33]*	1.67 [1.01-2.76]*	-	0.18 [0.11—0.29]*
GDS 6 [1)]	0.72 [0.54–0.96]*	2.41 [1.80–3.23]*	3.99 [2.90–5.49]*	1.54 [1.15–2.05]*	2.10 [1.42-3.11]*	-	0.45 [0.33–0.61]*
Gender (female vs. male)	0.72 [0.53–0.97]*	-	1.61 [1.18–2.20]*	-	-	2.62 [1.82–3.79]*	0.69 [0.50–0.94]*
Age (years)	- [6)]	0.98 [0.96–0.999]*	-	-	-	0.968 [0.951–0.985]*	-
Duration of institutionalization[2)]	-	-	0.992 [0.986–0.998]*	-	-	0.989 [0.983–0.995]*	-
Marital status	-	-	-	-	-	-	-
Psychoactive medication							
Antipsychotics	2.04 [1.58–2.62]*	2.31 [1.77–3.02]*	1.87 [1.43–2.44]*	2.37 [1.84–3.05]*	2.16 [1.60-2.92]*	1.38 [1.05–1.80]*	0.73 [0.56–0.96]*
Anxiolytics	2.24 [1.58–3.19]*	1.68 [1.17–2.42]*	2.58 [1.77–3.76]*	1.52 [1.09–2.12]*	1.73 [1.20-2.49]*	1.54 [1.09–2.16]*	-
Antidepressants	-	-	-	-	-	1.84 [1.40–2.43]*	-
Hypnotics	-	-	-	-	-	-	-
Environmental correlates							
Patients per unit[3)]	0.99 [0.96–1.01]	0.98 [0.95–1.00]	0.99 [0.97–1.02]	1.00 [0.97–1.02]	0.99 [0.97-1.02]	0.99 [0.97–1.02]	0.98 [0.95–1.02]
Walking circuit present	0.94 [0.68–1.30]	1.31 [0.90–1.92]	0.98 [0.65–1.48]	1.01 [0.68–1.51]	1.02 [0.71-1.48]	0.96 [0.62–1.50]	1.27 [0.77–2.11]
SCU for high symptomlevel[4)]	0.91 [0.48–1.75]	1.08 [0.49–2.36]	1.65 [0.73–3.72]	2.32 [1.07–5.04]*	1.54 [0.76-3.13]	1.72 [0.73–4.05]	1.15 [0.45–2.93]
Time spent on patient care [5)]	0.86 [0.57–1.31]	0.74 [0.46–1.17]	0.70 [0.48–1.04]	0.78 [0.49–1.23]	0.76 [0.46-1.27]	0.73 [0.42–1.26]	0.53 [0.28–0.98]*

Notes:

Data are presented as odds-ratios [95% confidence interval], *Significance (p-value Wald statistics < 0.05), [1] Compared to Global Deterioration Scale stage 7, [2] Measure in months, [3] Patients per living room yielded the same results (non-significant factors on each symptom), [4] SCU designed for patients with high levels of neuropsychiatric symptoms compared to regular SCUs [5] Time spent on direct patient care per patient (in hours each day), n = 1019 (due to 21% missing values), staff/ patient ratio yielded the same results (non-significant factor on each symptom, except for apathy), [6] Variable not entered in the (final) analysis (p-value Wald statistics > 0.05)

Psychoactive medication

Antipsychotic and anxiolytic drug use was positively associated with the presence of all symptom clusters. However, antipsychotics were less frequently prescribed to patients with apathy. Antidepressants were prescribed to patients with depression/ anxiety. A prescription for hypnotics was not associated with any of the symptoms.

Environmental correlates

The number of patients per unit or per living room, the presence of an walking circuit, staff/patient ratio or the time spent on direct patient care were associated with neuropsychiatric symptoms. Only apathy occurred less frequently in patients residing in SCUs where nurses spent more time on patient care and in SCUs where there was more staff per patient. Patients in SCUs equipped for patients with severe neuropsychiatric symptoms expressed more agitation/disinhibition/irritability than patients in regular SCUs.

Predictability of the multilevel model

Patient factors (including psychoactive medication) explained 7.3–20.2% of the total variance (see Table 2). Due to the large differences between SCU symptom prevalences (see below), the variance of all symptom clusters at the SCU level accounted for 3.5–14.8% of the total variance, for which only delusions/hallucinations did not reach statistical significance (Wald statistics: p not < 0.05). The addition of the environmental correlates to the model improved the explained variance by less than 1.1%. Verbally agitated behaviour was best predicted by factors at the patient level (20%), and apathy had the largest variance explained at the SCU level (15%).

Table 2.
Explained and unexplained variance of the multilevel model for neuropsychiatric symptoms predicted by patient factors, psychoactive medication use and environmental correlates in nursing home patients with dementia

	Explained variance at the patient level			Unexplained variance at the patient level	
	Model with patient factors and medication only	**Final model, environmental correlates included [1)]**	**Difference**	**Variance at the SCU level [2)]**	**Unexplained variance**
CMAI					
Physically aggressive behaviour	10.6	10.9	0.3	3.7	85.4
Physically non-aggressive behaviour	11.6	12.6	1.0	6.1	81.3
Verbally agitated behaviour	20.2	20.8	0.6	7.4	71.9
NPI-NH					
Agitation, disinhibition, irritabilility	7.3	8.4	1.1	7.9	83.8
Delusions, hallucinations	9.6	10.0	0.4	3.5	86.4
Depression, anxiety	13.6	14.2	0.6	9.4	76.4
Apathy	9.0	9.3	0.3	14.8	76.0

Notes:
[1)] n = 1,289. Time spent on direct patient care not included; time spent on patient care in a smaller population (n = 1019) enhanced the explained variance on the patient level by 3.7%, [2)] Variance for all symptoms are significant (Wald test : $p < 0.05$), with the exception of delusions/hallucinations

Comparison of mean SCU symptom prevalence

Large differences between SCUs were found, as shown in Table 3. The average prevalence of physically aggressive behaviour per SCU ranged from 15% to 89%. Even after correction for significant patient-related factors (including psychoactive medication use), the observed SCU prevalence rates of neuropsychiatric symptoms deviated in 55–79% of the cases from what was expected on the basis of patient factors only.

Discussion

The results of this study reveal that there are large differences in the prevalence of neuropsychiatric symptoms between nursing homes units (SCUs) for dementia patients, even when the model is corrected for patient-related factors such as cognition and psychoactive medication. In our model, the level SCU was significant for all symptoms (except for hallucinations/delusions), indicating that neuropsychiatric symptoms in patients residing on the same SCU were not independent. However, environmental correlates used in this study cannot explain the differences in the SCU symptom prevalence.

Table 3.
Observed SCU symptom prevalence and number of SCUs between and outside limits of expected SCU symptom prevalence

	Observed SCU symptom prevalence (%)			SCUs within and outside expected limits (number, % of total number of SCUs) [1)]		
	Mean	**SD**	**range**	**Within expected**	**Higher than expected**	**Lower than expected**
CMAI						
Physically aggressive behaviour	57	15	15–89	17 (30%)	20 (36%)	19 (34%)
Physically non-aggressive behaviour	63	15	33-100	16 (29%)	18 (32%)	22 (39%)
Verbally agitated behaviour	57	17	25-100	25 (45%)	13 (23%)	18 (32%)
NPI-NH						
Agitation, disinhibition, irritabilility	50	17	10–89	18 (32%)	19 (34%)	19 (34%)
Delusions, hallucinations	19	12	0–55	17 (30%)	20 (36%)	19 (34%)
Depression, anxiety	33	17	10–82	12 (21%)	23 (41%)	21 (38%)
Apathy	33	18	0–75	14 (25%)	21 (38%)	21 (38%)

Notes:

[1)] Expected on the basis of the presence or absence of significant factors (patient related predictors or psychoactive medication use) of each individual patient of that specific SCU

We failed to establish an association between neuropsychiatric symptoms and the physical environment, which is in contrast with two cross-sectional studies that did show a relationship between agitation or other neuropsychiatric symptoms and unit size or nursing home size [15, 16] and an experimental study.[37] One would expect that patients on less crowded SCUs would exhibit less agitation and that patients on SCUs with an walking circuit would be more likely to regulate/reduce their motor agitation. However, it is possible that this absence of a difference can be explained by

a policy to admit patients who already have a high level of agitation or wandering on less crowded units or units with an walking circuit. Since nursing homes in The Netherlands generally have more than one SCU, it is possible for patient or carers to choose between SCUs with different environmental features or to transfer patients from one SCU to another (e.g. when a patient shows excessive agitation or wandering).

In contrast to what was expected, the prevalence of neuropsychiatric symptoms in SCUs to which patients showing a high level of neuropsychiatric symptoms had been admitted was not higher than that found in regular SCUs (even after a correction for psychoactive medication use), with the exception of NPI–NH agitation. We hypothesize that other co-existing mechanisms (such as a higher use of physical restraints or a commitment to more specialized care aimed at reducing or even preventing neuropsychiatric symptoms) could have leveled off the expected differences between regular SCUs and specialized ones. The same may be true for the (lack of) association between staff size and symptom prevalence, as we found that staff size had a significant association only with apathy. Patients with apathy apparently benefit from a higher number of staff members, possibly due to an increased opportunity for stimulation.

To our knowledge, this is the first study that evaluates the complicated interaction between behavioural changes in dementia and Dutch nursing home features in a large patient sample. A major strength of the study is the rather substantial number of both patients and SCUs, which enabled us to achieve high statistical power to investigate both patient-related factors and the influence of differences between SCUs. In addition, the use of the multilevel analysis – a sophisticated statistical technique that has become popular over the past decade – enabled us to investigate differences between neuropsychiatric symptoms simultaneously at the patient and SCU level. By applying this technique, we were able to show that neuropsychiatric symptoms in different patients residing in the same SCU were related, which is suggestive of an interpersonal effect – i.e. the onset of neuropsychiatric symptoms depends in part on whether these symptoms are also present in other patients or on another common environmental factor related to the behaviour of all patients.

There are a number of limitations to this study. We did not categorize the dementia subtype, which is known to be a predictor of neuropsychiatric symptoms;[38–42] however, there is only limited evidence of this in nursing home patients.[43, 44] Another possible limitation is the choice of environmental correlates. For practical reasons, we selected environmental correlates that were easy to assess instead of more refined measurement scales for the quality of the physical and psychosocial environment, such as the Therapeutical Environmental Screening Scale (TESS)[15] or the Professional Environmental Assessment Procedure (PEAP),[45] as these two tools have not yet been translated and validated in the Dutch population. In addition to aspects related to the

quality of the physical or psychosocial environment used in these assessment scales, other factors may also have contributed to the substantial differences between SCUs (even after the correction for patient factors), such as the general attitude of the staff or the manner in which the staff members on a whole react to patients' behaviour. In community-dwelling patients, the personality and caregiver management strategies of the primary caregiver is known to affect the presence of neuropsychiatric symptoms.[46] However, a good theoretical psychological model or hypothesis of staff correlates – translated into valid assessment scales – is not available.

The results of this study contribute to an understanding of the importance of the environment on neuropsychiatric symptoms. However, the set of environmental correlates assessed in this study cannot explain the observed variation in neuropsychiatric symptom prevalence. We did not find any evidence for the hypothesis that small-scale housing is associated with a reduction in the prevalence of neuropsychiatric symptoms. Since the Dutch government supports a policy of patients residing in small living groups of about 6–12 persons,[47] there is urgent need for conclusive evidence on the alleged positive effects of small-scale housing on neuropsychiatric symptoms.

Future research should focus on the complex interactions between patients with dementia (with increased environmental susceptibility) and the physical and social environment (such as small-scale housing facilities). Further research on the influence of nursing home staff [13] – with respect to both attitude and management strategies – on neuropsychiatric symptoms is necessary. A better understanding of such interactions could be used for future staff training to reduce neuropsychiatric symptoms in nursing homes and for planning a building strategy so that future nursing homes will meet the needs of the patients with dementia.[48]

We conclude that there is a substantial variation in the level of neuropsychiatric symptoms among SCUs. Although we failed to predict neuropsychiatric symptoms by the environmental correlates used in this study, the large difference between SCUs – even when well-known patient factors (such as dementia stage) were corrected for – suggests that other factors associated with the physical or psychosocial environment may explain the variation of neuropsychiatric symptoms between SCUs in Dutch nursing homes.

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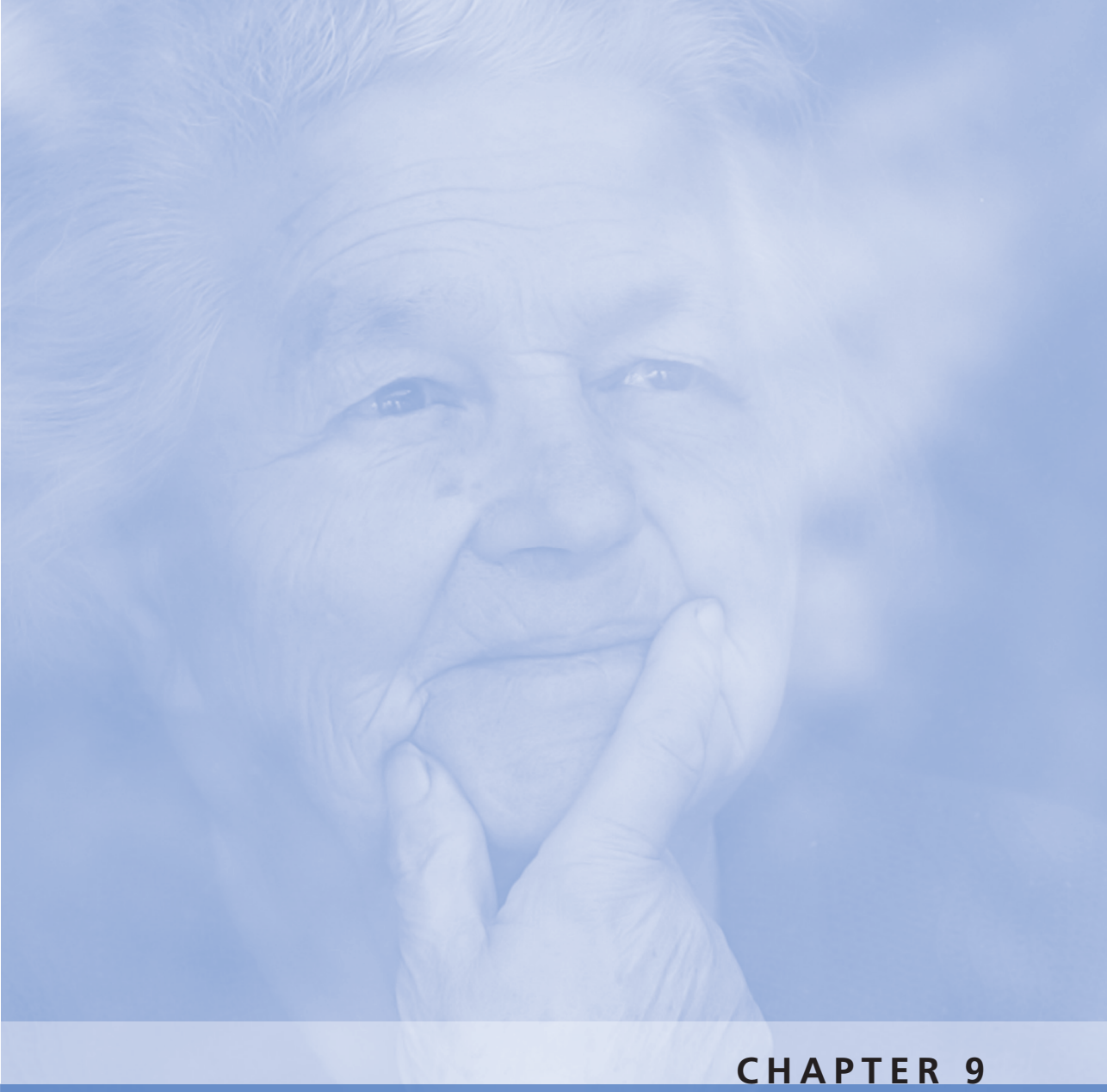

CHAPTER 9

General Discussion

Introduction

This chapter summarizes the main findings of this thesis by addressing the research questions. The methodological issues of the WAALBED study are discussed, followed by implications for researchers, physicians and psychologists, carers, architects and nursing home management, and policy makers. This chapter ends with suggestions for future research and a general conclusion.

Summary of present findings

1. *What is the prevalence of neuropsychiatric symptoms in dementia patients receiving nursing home care?*

Prevalences of neuropsychiatric symptoms in Dutch nursing home patients were high (Chapter 4). More than 80% of the patients had at least one clinically significant symptom. Agitation/aggression and apathy were the most frequently observed behaviours with prevalence of 30-35%.

Despite the fact that care for Dutch patients with dementia is provided in Dementia Special Care units by a multidisciplinary team, prevalence rates of neuropsychiatric symptoms were inside the range found in previous studies evaluating cognitively impaired nursing home patients in other countries (Chapter 2). Admission of patients with already high levels of symptoms, which are the main reason for institutionalization, and the policy of nursing homes not to transfer patients with high levels of neuropsychiatric symptoms to mental health services or hospitals in the Netherlands may explain why symptoms rates were not lower than in nursing homes in other countries.

Previous studies show a large variability in prevalence rates, which may be based on differences in patient population – i.e. cultural differences, variation in dementia type and severity –, as well as differences in assessment scales used (with different ratings or symptom definitions).

2. *What is the efficacy and adverse events of antipsychotic medication for neuropsychiatric symptoms in patients with dementia?*

Although antipsychotic medication was frequently described in nursing home patients with dementia in the Netherlands (Chapter 2), only limited evidence is available on the efficacy of these drugs, and growing concern has risen about the safety of these drugs, because of the alleged risk of stroke. In the systematic review described in chapter 3, we concluded that the efficacy of typical and atypical antipsychotics are comparable, but only low-dose risperidone seem to be associated with fewer (extrapyramidal) side effects and the evidence of increased risk of stroke for risperidone and olanzapine is too insufficient to confirm the warning of an increased risk of mortality. However, definitive conclusions on the issue of stroke associated mortality cannot be drawn out of the limited number of studies available, with a chance of selective reporting (publication bias).

3. *What is the factor structure of the NPI-NH and CMAI in Dutch nursing home patients with dementia?*

Three/four behavioural dimensions underlie neuropsychiatric symptoms in nursing home patients as measured with the Dutch version of the NPI-NH. This finding is consistent with the clinical taxonomy of symptoms often referred to as agitation/aggression, depression, psychosis, psychomotor agitation and apathy.[1] The factor structure was relatively stable across dementia stages, as was the case in drug-naive patients, and consistent with some of the previous literature. The findings may add to a better understanding of how symptoms are related. However, clusters found are too small to be used as subscales in every day clinical practice.

The factor structure of the CMAI was consistent with the taxonomy of symptoms referred to as physically aggressive, physically non-aggressive and verbally agitated behaviour. Due to the larger amount of symptoms per factor, CMAI factor based subscales can be constructed and used in clinical practice. It is interesting to note that our initial six-factor structure represents clusters referred to as hiding/hoarding (which is in some literature considered as the fourth behavioural dimension [2, 3]) and vocal agitation. These clusters represent behavioural dimensions that can clearly be distinguished from other agitation symptoms. However, the initial six factor solution may not be useful for constructing additional subscales because of the limited number of items per scale. Additional research into these other aspects of agitation in severely demented patients may be warranted.

4. *What is the influence of patient-related factors on the prevalence of neuropsychiatric symptoms in Dutch nursing home patients with dementia?*

Disease severity and gender were important predictors of neuropsychiatric symptoms. Some symptoms occurred more often in mild to moderate stages of dementia (depression, psychosis, agitation), while other symptoms were more prevalent in severe dementia (physical aggression, anxiety and apathy). With respect to gender, men showed more physically aggressive behaviour and apathy, while women showed more verbally agitated behaviour, depression and anxiety.

5. *What is the influence of factors associated with the physical and psychosocial environment in the special care units on the prevalence of neuropsychiatric symptoms in Dutch nursing home patients with dementia?*

The substantial variation found in the prevalence/severity of neuropsychiatric symptoms among SCUs, even after correcting for well-known patient factors (such as gender and dementia stage), suggests that factors associated with the physical and psychosocial environment may prove to be important in explaining neuropsychiatric symptoms. Less apathy was observed in SCUs with higher number of staff. The other environmental variables measured in this study, such as staff size, number of patients

per unit or per living room, the presence of an walking circuit did not predict neuropsychiatric symptoms. It is possible that important correlates of neuropsychiatric symptoms may have been overlooked and not measured. Alternatively, it is possible that not individual environmental correlates, but a combination of the present and other correlates would reveal a significant effect on neuropsychiatric symptoms.
The lack of a significant association between environmental correlates and neuropsychiatric symptoms might also be explained by the policy to admit or transfer patients with high level of agitation or wandering to a less crowded unit or a unit with an walking circuit. In conclusion, neuropsychiatric symptoms seem to be related to the environment of the dementia special care unit, but further research is necessary to explore what factors associated with the physical and psychosocial environment are responsible for the variation of neuropsychiatric symptoms between SCUs.

Methodological issues

Assessment instruments

Neuropsychiatric symptoms were measured in the WAALBED study using two different behavioural rating scales. The NPI-NH is a comprehensive neuropsychiatric rating scale and the CMAI is a specific rating scale for measuring agitation and aggression. The NPI-NH and CMAI are frequently used in nursing homes for both prevalence and intervention studies.[4, 5] Both scales have established validity and have been used in many different studies of neuropsychiatric symptoms in dementia. The combination of both scales made it possible to measure a wide range of important behavioural changes in dementia. However, other neuropsychiatric symptoms have been observed in dementia patients, such as self injurious behaviours, [6, 7] that are not measured in detail by the NPI-NH and CMAI. Secondly, the NPI-NH offers limited possibility to assess specific symptoms, such as visual or auditory hallucinations or certain types of delusions. Thirdly, the NPI-NH measures depressed mood as a symptom but not depression at a syndromic level. For further assessment of psychosis, depression and apathy other rating scales would be more appropriate, but this was outside the scope of this thesis. So, content validity of the results on prevalence rates of neuropsychiatric symptoms is limited by the behaviours sampled in the scales used in this thesis.
We spent much effort in training the nurse-assistants, to ensure reliability of the interviews. Assessments were preceded by a two-week observational period in which staff members not participating in the study were asked to report neuropsychiatric symptoms. Reliability of neuropsychiatric prevalence rates may depend on the quality of such reported data.
Apart from the technical aspects, other difficulties with regard to assessing neuropsychiatric symptoms may have occurred. In patients with severe dementia, communicative abilities decrease and symptoms can only be directly observed as overt

behaviour, such as aggressive behaviour or apathy. For that reason depression, delusions and verbally agitated behaviour were less often observed in these cases. Moreover, it is possible that the beliefs and attitudes of the nursing staff towards neuropsychiatric symptoms could introduce bias with regard to observation and interpretation of symptoms.

The NPI-NH and CMAI may be of limited use in evaluating individualized psychosocial treatment programs. Both scales measure the frequency and severity of certain symptoms, but do not assess the context in which the behaviours occur, i.e. the eliciting factors and consequences. These scales were designed and proven useful for evaluating (global) efficacy of pharmacological interventions. To study effectiveness of psychosocial interventions, much more information is needed. For that purpose other observation techniques (such as video taping caregiving activities) or dementia care mapping [8] would be more appropriate.

The Global Deterioration Scale (GDS) is used to reflect dementia severity. The GDS includes also neuropsychiatric symptom (delusions, anxiety and aggression) especially in severe cognitive deterioration (GDS 6). The consideration of neuropsychiatric symptoms in the GDS could be a possible source of bias when using the GDS to study the influence of dementia stage on the presence of neuropsychiatric symptoms. One might argue that a combination of the Mini Mental State Exam (MMSE) and functional assessments would have been superior.

The content validity of the measures of environmental correlates of neuropsychiatric symptom may be questioned. Some environmental factors were measured while other factors were perhaps not. The choice of the environmental correlates was driven by practical reasons, i.e. we used correlates that are easy to assess. More refined measurement scales for the quality of the physical and psychosocial environment, such as the Therapeutical Environmental Screening Scale (TESS) [9] or the Professional Environmental Assessment Procedure (PEAP), [10] have neither been translated nor validated for the Dutch population.

Selection bias

The WAALBED study was carried out in northern, eastern and southern parts of the Netherlands. Only the 72 nursing homes providing the specialist training program for nursing home physicians in cooperation with the Department of Nursing Home Medicine of the Radboud University Nijmegen Medical Centre were asked to participate. Twenty-five of them ultimately agreed to participate in the study. The managing director of these institutions selected the SCUs to be assessed. All these 'choices' may be a source of selection bias. However, participating SCUs did not differ with respect to admission policy towards patients with neuropsychiatric symptoms or dementia stage/ care level compared to non-participating SCUs. The age and gender distribution of our patient sample differed only slightly from that of the national nursing home population. Unfortunately we cannot compare the WAALBED

data with the national nursing home population with respect to dementia type and psychoactive medication use – both factors known to affect neuropsychiatric symptoms, since these data are not available. This unknown source of selection bias hampers extrapolation of the results to the Dutch national nursing home population. However, the large study sample – that comprised 4.4% of all demented nursing home patients in the Netherlands – makes large sampling errors improbable.

Type of dementia

No data were available on the type of dementia. The lack of an etiological diagnosis may obscure the results of how neuropsychiatric symptoms are interrelated and on the correlates of neuropsychiatric symptoms. Some neuropsychiatric symptoms are highly prevalent in certain types of dementia while they are observed less frequently in other dementias: e.g. hallucinations are prominent in Lewy Body Dementia and disinhibition is typical of Frontotemporal dementia. These differences are also clinically important in terms of treatment options and patient management. Thus an etiological diagnosis of the dementia syndrome is relevant. However, many Dutch dementia patients enter the nursing home without an etiological diagnosis established. In most instances the diagnosis of 'dementia' is all there is. We had to deal with this situation and considered that establishing and etiological diagnosis in this large patient sample was simply beyond the possibilities both in terms finances and available time. Moreover, in cases where an etiological diagnosis of dementia is feasible in the early stages of the disease, it becomes increasingly difficult in later stages. Our study sample included many severe dementia patients for whom it would be almost practically impossible to determine exact etiology of the dementia syndrome at the time they were included in the study. The patients in the longitudinal study on the course and predictors of neuropsychiatric symptoms (WAALBED-2) – also being conducted by the Radboud University Nijmegen Medical Centre – will be diagnosed with respect to their dementia type.

Generalizability

As nursing home care for patients with dementia in the Netherlands is mainly provided in dementia special care units, this study included patients residing in SCUs only. Dutch policy is to provide dementia care in the community, so that patients with dementia can stay at home as long as possible. Community dwelling patients with neuropsychiatric symptoms are more likely to be admitted to nursing homes compared to those without. Because of the high quality of the multidisciplinary treatment in the SCUs, patients are not often transferred to psychiatric hospitals when neuropsychiatric symptoms deteriorate. We therefore expect that the prevalence of neuropsychiatric symptoms in Dutch SCUs is higher than in nursing homes in other countries. Accordingly, this hampers generalizability of our results.

Implications for researchers

Conceptualization of neuropsychiatric symptoms

Our finding that disease related factors (Chapter 7) are associated with neuropsychiatric symptoms is in agreement with previous studies in community-dwelling patients in The Netherlands[11] and also with studies of community-residing and institutionalized dementia patients samples in other countries (see Chapter 2). Also, the way in which symptoms co-occur or cluster is consistent with previous findings (Chapter 5 and 6).

These robust trans-cultural findings strongly favour a biological origin of neuropsychiatric symptoms. The anatomical substrate of neuropsychiatric symptoms has been studied with Computer Tomography (CT), Magnetic Resonance Imaging (MRI) or Single Photon Emission Computer Tomography (SPECT) in dementia patients with vascular lesions. Relationships between regional anatomical lesions/hypoperfusions and neuropsychiatric symptoms have been shown for apathy as a syndrome (anterior cingulate),[12] apathy in Alzheimer's disease (anterior cingulate[13, 14] or thalamic areas [15] or frontal lobe [16]), apathy in frontotemporal dementia (frontal lobe),[17] major depression (orbitofrontal areas),[12] depression and apathy after stroke,[18] hallucinations in Alzheimer dementia (parietal lobes),[19] delusions in Alzheimer dementia or vascular dementia (frontal lobe),[19, 20] aggression in dementia (right medial temporal region[21] or left frontotemporal region[22]), disinhibition or stereotypic behaviour in frontotemporal dementia (temporal lobe).[17] Apparently, neuropsychiatric symptoms are related to the way in which the damaged human brain acts on stressors. Acute stress might in this respect be accompanied with confusion, disorientation and delirium, whereas chronic stress might result in exhaustion, depression or apathy. Apathy can be seen as extinction of behaviour due to brain damage in specific or global areas in the brain. The increasing prevalences of apathy during increasing cognitive deterioration (as a result of brain damage) is in line with this idea (Chapter 7). Alternatively, it is possible (although in our opinion less likely) that, regardless of time and location, dementia patients react in similar ways when confronted with cognitive deterioration or when admitted to a nursing home. Such a view would disfavour a common biological origin of neuropsychiatric symptoms.

However, neuropsychiatric symptoms were obviously influenced by other factors than biological factors only. Even after correction of disease related factors, prevalence rates of neuropsychiatric symptoms varied across SCUs in The Netherlands (Chapter 8) as is the case in SCUs in other countries (e.g. in Australia).[23] This variation in SCU symptom prevalence is likely to be associated with correlates of the physical and psychosocial environment (Chapter 8, see also implications for architects and nursing home management). Accordingly, the biopsychosocial model as an extension of the biological model, is not only valid in community-residing patients,[11] but is applicable to nursing home patients as well.

Classification of neuropsychiatric symptoms in general

The concept of BPSD, as originally proposed by the International Psychogeriatric Association (IPA), suggests clustering all behavioural (e.g. aggression and psychomotor agitation, psychosis) and psychological (e.g. depression) symptoms. In agreement with others, we showed that there is evidence for clustering symptoms into aggression, psychomotor agitation, psychosis, depression and apathy (Chapter 5).

The clinical relevance of classifying neuropsychiatric symptoms is recently acknowledged in an IPA consensus paper,[24] which stated that 'Agreement about the most appropriate differentiation and classification of neuropsychiatric symptoms into syndromic groupings is needed, and would be the best way to address the issue of symptoms overlap'. The classification of neuropsychiatric symptoms proposed in that paper differs from the one in the WAALBED study. The IPA consensus group proposed a hierarchical approach to differentiate neuropsychiatric symptoms into dementia-associated affective disorder (depressed or agitated) and dementia-associated psychotic disorder, that subscribes to the significance of treatable syndromes.

The dementia-associated affective disorder with agitation, however, suggests a co-occurrence of depression and agitation, which we have shown to be different behavioural dimensions. In the hierarchical approach of the IPA consensus paper, apathy is acknowledged as a syndrome distinct form depression, but – in contrast to our findings – this paper suggests a further differentiation into apathetic syndrome and executive syndrome. The latter syndrome includes disinhibited behaviours such as hoarding, pacing or hitting.[25] We feel that the clinical classification of symptoms – i.e. aggression, psychomotor agitation, psychosis, depression and apathy – of which we found supportive evidence, is more applicable in every-day clinical practice.

Classification of apathy and depression

Factor analysis of the NPI-NH (Chapter 5) supports the IPA proposal that apathy and depression should be viewed as separate entities. In this thesis, it is also shown that apathy and depression have different frequencies across gender and dementia severity (Chapter 7).

The finding that apathy was related to cognitive (i.e. executive) dysfunction (whereas depression is not) is also consistent with previous studies including patients with Alzheimer's disease[26] and other neurodegenerative diseases such as Parkinson Disease[27] and Progressive Supranuclear Palsy.[28] Apathy can be present in the absence of depression in dementia and in other diseases, such as Parkinson disease[29, 30] and stroke.[18] Apathy and depression may have different anatomical substrates[12] and revealed different outcomes in neuropsychological tests.[31] Depression and apathy can also overlap in both patients with dementia[26] and stroke.[18]

From a clinical point of view differentiating depression from apathy can be difficult,

because loss of interest and psychomotor retardation are features of both depression and apathy. These symptoms should not be considered sufficient core features of minor depression.[29, 32] This emphasizes the need to define diagnostic criteria for apathy as a syndrome (as is the case for depression) in neurodegenerative diseases such as Alzheimer disease and Parkinson disease.[33]
Differentiating depression from apathy, even in patients with severe dementia (Chapter 5), has important clinical consequences. Depression, by contrast to apathy, can be treated with antidepressants. We suggest that patients with executive dysfunction (apathy) with depressed mood should be treated with antidepressants, where apathetic patients without observable mood-disturbances should not. For apathy, there is no broadly accepted pharmacological or psychosocial intervention. There is some evidence favouring the use of cholinesterase inhibitors,[34] methylphenidate,[35] activity therapy/reminiscence,[36] snoezelen[37, 38] or music therapy.[39] Whatever intervention is chosen, the effects of apathy on quality of life are hardly investigated and additional research is warranted.

Classification of agitation

By contrast to the IPA consensus paper,[24] our results showed that agitation represents at least three underlying behavioural syndromes, i.e. physically aggressive, physically non-aggressive and verbally agitated behaviour (Chapter 6). The three clusters of agitation in the WAALBED study have also different frequencies across gender and severity, which supports the view that agitation is not a unitary concept but should be distinguished into three separate entities. This may have clinical consequences, for example because of the different efficacies for antipsychotics.[40]
Vocal agitation was also found as a distinct cluster – apart from the three other types of agitation. This type of agitated behaviour is acknowledged as a distinct phenomenon in the guideline about problem behaviour of the Dutch Association of Nursing Home Physicians (NVVA).[41] Vocal agitation may be more difficult to treat than other types of agitation, such as physical aggression or wandering. Verbally disruptive behaviour (screaming, vocal agitation) may be associated with cognitive deterioration, severe impairment, worse performance of activities of daily living, pain, depression, impaired social functioning.[42, 43] There may be different types of disruptive vocalizations with different aetiology.[44] Especially vocalization not related to pain or depression but to cognitive deterioration instead may be conceptualized as repetitive behaviour with a separate neurobiological etiology.[45] The CMAI only partially taps different types of disruptive vocalizations. We suggest that new assessment scales focussing on vocally disruptive behaviour should be developed.

Implications for physicians and psychologists

Antipsychotics and other psychotropic drugs are frequently used in Dutch nursing homes as we have shown (Chapter 4),[46] This is also the case in other nursing homes [47-52] and residential homes throughout the world.[53] Psychotropic drugs are used (too) frequently, despite guidelines[41, 54, 55] and Omnibus Budget Reconciliation Act (OBRA)-regulations that warn against excessive and long-term/ chronic use. Guidelines are not always adhered to[53] and patient factors, such as the presence of neuropsychiatric symptoms, are often not the only reason for prescribing psychotropic drugs. We noticed that prescriptions rates vary greatly among nursing homes [51] and may be associated with nursing home facility characteristics such as low level of staff.[52] Antipsychotics have only limited efficacy in agitation and psychosis and have considerable sides effects such as extrapyramidal symptoms, somnolence and an increased risk for stroke (i.e. olanzapine and risperidone)(Chapter 3). In a recent meta-analysis of published and unpublished randomized controlled trials atypical antipsychotics were found to be associated with a (small) increased risk of death compared to placebo.[56] The increased risk of death associated with atypical antipsychotic medication may also be true for conventional antipsychotics as well.[57] The evidence on the efficacy and adverse events of atypical antipsychotic drugs was increased by two recent publications: (1) The results of the CATIE-AD trial showed that time to discontinuation due to lack of efficacy favoured olanzapine, risperidone (but not quetiapine), but time to discontinuation due to intolerability favoured placebo;[58] (2) A Cochrane review showed that risperidone appeared to be efficacious for aggression and psychosis, and olanzapine for aggression only, but both drugs were associated with higher incidence of serious adverse cerebrovascular events and extrapyramidal symptoms. [59]

Psychotropic drugs, - especially antipsychotics -, may also be associated with lower quality of life.[60] Physicians should therefore be careful in prescribing antipsychotic drugs in frail elderly with dementia especially in the presence of cardiovascular risk factors. Psychotropic medication is often prescribed as long-term treatment.[51] However, the natural history of behavioural changes in Alzheimer's disease shows great individual variation [61] and some neuropsychiatric symptoms are intermittent [62, 63] or even may occur only once.[61] We advise physician to make regular attempts to taper or to discontinue psychotropic medication.

Caution on psychotropic drugs may not apply to antidepressants, since these drugs have fewer devastating side effects than antipsychotics and depression in nursing homes is often underdiagnosed and undertreated, at least in patients with no or mild cognitive disorders.[64] We feel that this is even more true in patients with severe dementia. Cholinesterase inhibitors are also thought to have fewer side effects, but are only registered for cognitive and global deterioration in patients with Alzheimer disease. The evidence of efficacy of cholinesterase inhibitors for neuropsychiatric

symptoms in both Lewy-body dementia [65, 66] and Alzheimer's disease [67] is weak and needs further study.

In our opinion, the use of psychosocial interventions as a first choice of treatment should be encouraged.[68] Unfortunately, the evidence of the effect of psychosocial interventions is limited and quality of the studies is moderate. There is insufficient evidence yet with regard to validation,[38, 69] aromatherapy,[70, 71] light therapy.[72] Other psychosocial interventions, such as reminiscence,[73] psychomotor therapy,[38] caregiver training,[74] cognitive stimulation therapy [74] are more efficacious. Music therapy only seems to work during treatment sessions, but may have no longer-term effects.[74, 75] Snoezelen/ sensory stimulation, previously thought to have only short term effects,[74] has positive effects on apathetic and aggressive behaviour and depression,[37] when integrated into 24-hour dementia care.

Significant other psychosocial factors in literature were the quality of staff-patient interaction,[76, 77] policy with regard to managing difficult behaviours [78] or the use of physical restraints[9] and concept of care (e.g. emotion-oriented care). Emotion-oriented care is a multifaceted care approach of different psychosocial interventions (i.e. validation, reminiscence, sensory stimulation) which can be applied by the nursing staff in routine care. Yet, the evidence of the effects of integrated emotion oriented care on neuropsychiatric symptoms in institutionalized patients is limited; in a randomized controlled trial in nursing home patients with dementia, emotion oriented care had a small positive effect on anxious behaviour compared to usual care, but only in patients less in need of assistance/care, but not on physically of verbally aggressive behaviour. [79] In a randomized controlled trial in cognitively impaired patients residing in homes for the aged, emotion-oriented care only has an effect on anxious behaviour and physically non-aggressive behaviour at 6 months after randomisation, but not at 12 months. [80]

The effect of psychosocial interventions may be more effective when individual psychosocial interventions are combined. A combination of didactic training and supervision, application of person centred care, positive care planning, awareness of environmental design issues, the use of behaviour therapy models, reminiscence techniques, was shown to be efficacious; in a recent randomized controlled trial comparing this enhanced psychosocial care with regular care provided to nursing home patients with severe dementia, enhanced psychosocial care – however not efficacious in reducing agitation levels and well-being – was able to reduce psychotropic drug use.[81] A second study on the effect of a combination of enhanced education and activities, and implementing guidelines for drug use, showed significant improvement in behaviour with a trend towards a reduction in neuroleptic use.[82]

In conclusion, we advocate a restricted and careful use of psychotropic drugs, especially antipsychotics, since a tailored psychosocial intervention or a combination of psychosocial interventions should be the first treatment option.

Implication for carers

The high prevalence rates of neuropsychiatric symptoms in general and agitation in particular (Chapter 2 and 4) is of major importance for accurate patient-oriented staff planning. This is not only true for aggressive and agitated behaviours, but also for apathy, a behaviour associated with deterioration of the disease resulting in patients being increasingly impaired in the basic activities of daily living and so resulting in high need of care.[83] The numbers of patients showing apathy or resistance to (morning) care and of those with wandering in the afternoon should be important factors to be taken into consideration when determining the number of staff to be employed during the day. Recent work of Cohen-Mansfield confirmed the steady increase of agitation throughout the day with a peak in the afternoon, due to fatigue of daytime nursing staff members and disruption during shift change.[84]
In this respect, we argue not only for a more patient-oriented staff planning, that meets the care needs of the individual patient. More attention should also be paid to 'care for the carers'. Perceived work-related stress and feeling of incompetence of nursing staff can be reduced by the introduction of patient oriented care.[79] Anne-Mei The, the writer of the book 'Living and Dying with Dementia',[85] launched an initiative to focus on the carers/ nursing staff, as satisfied staff is more able to care for the patients. This program encompasses education, supervision, and coaching of staff, that should be integrated into the care process.[86] This learning by practical experience or by other techniques such as role-playing or video-interaction techniques should provide tools for the nursing staff to deal adequately with patients with neuropsychiatric symptoms.

Implications for architects and nursing home management

The large variation of neuropsychiatric symptoms between SCUs in the WAALBED study highlights the importance of the nursing home environment. SCUs that had many staff members also had less patients with apathy. (Chapter 8) Staff in these SCUs may have had more opportunity to stimulate patients. This is in line with studies showing that patients with apathy benefited from getting attention from the activity therapist.[36] The author of this study noted that 'the mechanisms of action' by which activity may diminish apathy are unknown. It may work by overcoming the inability of apathetic patients to motivate themselves by providing an external motivator and general social stimulation. Or, it may work by providing a context and structure for patients who cannot provide these for themselves'.[36]
Other environmental correlates used in the WAALBED study did not explain the variation of neuropsychiatric symptoms between SCUs. The large variation of symptoms between SCUs may be explained by correlates that were not studied and there is a need for further study on this subject.

Significant physical environmental correlates of neuropsychiatric symptoms stated in literature are: SCU environment quality in general,[9, 87, 88] camouflaged exit doors,[89, 90] tapelines on the floor [91], mirrors [92] in front of an exit door, enhanced visibility of the toilet (as a cue for residents to use it),[93] personalized cues to enhance orientation to the bedroom,[94] environmental enhances such as large pictorial murals,[95] spatial density (more area per person) of a unit,[96] the amount of privacy,[90] gradation of space (i.e. the variety of spaces, such as quiet and stimulating rooms),[90, 97] the presence of central open areas,[98] the architectural design (shape) of the unit,[99] the presence of outdoor spaces (gardens or patio's), the presence of an ambient (residential) environment that residents can understand.[90] (For relevant psychosocial aspects see: implications for physicians and psychologists.)

The absence of the association between neuropsychiatric symptoms and unit size in the WAALBED study does not mean that 'small-scale housing' is ineffective. For the concept of small-scale housing is not so much determined by unit size, but rather by organisational features such as the integration of staff and patients forming one household living in a archetype 'house' and the policy to provide long-term care for patients until the end of their lives.[100] This concept is very similar to the ecologic model of care 'that is responsive to the unique interplay of each person and the environment' and that 'encompasses a vision of long-term care that is more comfortable, more like home, and offers more choice, meaningful activity, and privacy than traditional settings'.[101] A special care facility based on this model (small bungalows with 10 residents) showed to be effective in that residents with less decline in activities of daily living showed a more sustained interest in the environment and a less negative affect than cognitively-matched residents in traditional settings.[101] In The Netherlands, a large multi-centred trial has currently been conducted on the effect of small scale housing on neuropsychiatric symptoms. The results of this study are expected to be published soon.

Not all patients with dementia may benefit from this special facility [101] and it is questionable whether these facilities can give life-long care for residents. In Sweden, for instance, the small-scale housing facilities are intermediate care facilities as a pre-phase for admission in a nursing home. Awaiting the results of further studies on small scale housing, we advocate that individual attempts to enhance the quality of the physical and social environment should be used within an integrated concept of special care such as patient/emotion oriented care or the ecological model of care, to maximize its effect on the presence of neuropsychiatric symptoms and quality of life.

Implications for policy makers

The large variation of the SCU symptom prevalence independent of patient related factors (Chapter 8) suggests that other psychosocial and physical factors contribute to the frequency of neuropsychiatric symptoms, such as staff attitude and policy towards the use of pharmacological interventions, psychosocial interventions and the use of physical restraints. The proposed effect of SCU characteristics on neuropsychiatric symptoms might reflect differences in quality of care.

However, one should be cautious to use the level of neuropsychiatric symptoms as an indicator for the quality of nursing home care, since neuropsychiatric symptoms may not be the best indicator for quality of life. In cross-sectional studies both neuropsychiatric symptoms [102] and psychoactive drugs [60] were associated with low quality of life. Attempts to improve quality of life by enhancing psychosocial interventions were shown to reduce the amount of psychotropic drugs but did not change the prevalence of neuropsychiatric symptoms.[81] It is possible that the frequency of psychotropic medication (especially antipsychotic drug) use within SCUs would be a better indicator for the quality of nursing home care. The antipsychotic drug use should be corrected for the amount of demented patients with high levels of symptoms (e.g. due to concomitant psychiatric diseases). The general use of such an indicator should not be advocated on a larger scale until further research definitely decides on the relationship between psychoactive drugs and quality of care.

Suggestions for future research

This thesis provides answers to the prevalence and predictors of neuropsychiatric symptoms and gives an overview of the current evidence of the usefulness of antipsychotic medication. However, the WAALBED study had a cross-sectional design, which only revealed 'associations' between correlates and neuropsychiatric symptoms. Longitudinal studies are better designed for collecting evidence for 'causes' of neuropsychiatric symptoms. Currently a longitudinal study in Dutch nursing home patients with dementia (WAALBED-2) is now being conducted to investigate whether changes in quality of life are caused by changes of neuropsychiatric symptoms or by changes in antipsychotic drugs use.

Further studies on non-cognitive symptoms of dementia are necessary. Nursing home research should not focus on clusters of symptoms, such as agitation or psychosis, but on symptoms that are most distressful for carers, such as resistance to care or physical aggression or verbally disruptive behaviour. More sophisticated techniques, such as direct behavioural observation, video-taping care-giving activities or dementia care mapping should be used as appropriate assessment instruments, for they provide more specific information about the circumstances that initiate or exacerbate behaviour. Especially dementia care mapping is a valuable research tool that is more closely related to quality of life.[8]

More research is needed on the effect of psychosocial interventions and on care approaches to enhance quality of care or life in nursing home patients. Evidence on the efficacy of psychosocial interventions is insufficient and quality of life is very rarely used as a primary or secondary outcome in intervention studies in patients with dementia.[103] The insight in effective interventions on the physical and psychosocial environment provides valuable evidence for building the 'ideal nursing home' and for the combination of psychosocial interventions /care-strategies to be applied in daily practice. This insight is also helpful to develop guidelines on therapy for physicians, psychologists and nursing staff.[104]

General Conclusion

In this thesis on neuropsychiatric symptoms in Dutch nursing home patients with dementia prevalence rates are high and are influenced by disease related predictors and environmental factors. The findings of the WAALBED study indicate a biopsychosocial origin of neuropsychiatric symptoms. This model provides a better understanding of the etiology and the treatment possibilities than a biological model. As biological (pharmacological) interventions have only modest efficacy and considerable side effects, psychosocial interventions should be encouraged. We advocate a person-centred approach for the treatment of neuropsychiatric symptoms. This approach takes individual personality, coping strategies, history, dementia severity and co-morbidity into account when choosing the adequate therapeutic strategy. The person-centred approach provides a toolkit of interventions such as pharmacological interventions, validation, reminiscence, snoezelen, psychomotor therapy that can be tuned on the individual symptoms and needs of patients with dementia to reduce the burden of neuropsychiatric symptoms and increase the quality of life.

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SUMMARY

Dementia is an incurable disease with substantial effects on cognition, activities of daily living and behaviour. Neuropsychiatric symptoms, often referred to as agitation/aggression, psychosis, depression and apathy have major impact on both patient and caregiver, and are the main reasons for institutionalization. Also in nursing homes, patients with neuropsychiatric symptoms can be a serious burden on staff, leading to an increase of staff distress. The patients themselves are often subjected to high levels of physical restraints and to psychotropic medication which has considerable side-effects.
Earlier publications suggest that neuropsychiatric symptoms occur frequently and are related to dementia type and severity. There are also indications that neuropsychiatric symptoms are influenced by other factors associated with psychosocial interactions and the physical environment.
In the last decade more research has been conducted with regard to community-dwelling patients, but insufficient literature exists about nursing home patients. The typical environment of nursing homes with communal rooms in which patients –institutionalized because of their high levels of neuropsychiatric symptoms – spend their daytime provides an opportunity to study the value of the biopsychosocial model to explain the factors contributing to neuropsychiatric symptoms.

This thesis mainly describes the results of the Dutch WAAL BEhaviour in Dementia (WAALBED) study; a large study on neuropsychiatric symptoms in Dutch nursing home patients with dementia. In The Netherlands institutionalized care for people with dementia is provided in dementia Special Care Units (SCUs) by a multidisciplinary team of nurses, nursing home physicians, physical therapists, psychologists, activity therapists and other specialists, all of whom are employed by the nursing home. Such a team can also provide care for people with dementia in residential homes (outreaching nursing home care).
The aim of the thesis is to gain further insight in (1) the prevalence of neuropsychiatric symptoms in nursing home patients with dementia and (2) patient predictors and environmental correlates of neuropsychiatric symptoms.

Chapter 2 gives an overview of current literature on the prevalence of neuropsychiatric symptoms in cognitively impaired nursing home patients. Neuropsychiatric symptoms are found in more than 80% of the cognitively impaired patients. Prevalence rates of specific symptoms range considerably, from 3% to 54% for delusions, 1% to 39% for hallucinations, 8% to 74% for depressed mood, 7% to 69% for anxiety, 17% to 84% for apathy, 48% to 82% for aggression or agitation, and 11% to 44% for physical aggression. The large variation in prevalence rates may be based on differences in patient populations, as well as on differences in assessment scales used

(with different ratings or symptom definitions). Neuropsychiatric symptoms seem to be predicted not only by dementia type or severity but also by the psychosocial environment, the amount of psychoactive medication and physical restraints used.

Chapter 3 is a systematic review of the efficacy and adverse events of antipsychotic medication. Although antipsychotic medication is frequently prescribed to nursing home patients with dementia in The Netherlands (37% in the WAALBED study, see Chapter 4), limited evidence is available on the efficacy of these drugs and there is a growing concern about the safety of these drugs, because of the alleged risk of stroke. In literature only 14 studies could be found describing the efficacy of haloperidol, risperidone, olanzapine in more than one study (per drug) and quetiapine, tiapride, loxapine and perfenazine (in only one study per drug). It appears that the efficacy of typical and atypical antipsychotics are comparable, and only low-dose risperidone seems to be associated with fewer (extrapyramidal) side effects. Risperidone and olanzapine were shown in two studies to be associated with a higher risk of cerebrovascular adverse events. The profile of the adverse events of antipsychotic medication has been inadequately described in the published research and, consequently, the warnings for an increased mortality cannot be confirmed.

Chapter 4 describes the prevalence of neuropsychiatric symptoms in Dutch nursing home patients. Neuropsychiatric symptoms were measured with the Neuropsychiatric Inventory- Nursing Home version (NPI-NH) and the Cohen-Mansfield Agitation Inventory (CMAI). Overall, more than 80% of the nursing home patients of the WAALBED study suffered from at least one symptom. Delusions and hallucinations were present in 15% and 8% of the patients, respectively. Depressed mood and anxiety were present in 20% and 21% of the patients. Prevalence of aggressive/agitated behaviours were 31% for aggression/agitation, 20% for disinhibition, 34% for irritability and 29% for aberrant motor behaviour (measured with NPI-NH) and 44% for general restlessness, 33% for cursing or verbal aggression, 13% for hitting (measured with the CMAI). Apathy was present in 34% of the patients. We conclude that prevalence rates are high, a finding which has practical consequences for staff planning.

Chapter 5 describes the factor structure of the NPI-NH. Factor analysis was used to examine behavioural dimensions underlying neuropsychiatric symptoms. We described the factor structure in the WAALBED population across dementia stages (as assessed with the Global Deterioration Scale) and in patients with or without psychoactive medication. In three stages of dementia severity a four or five factor

solution was found, with factors referred to as agitation/aggression, depression, psychosis, psychomotor agitation and apathy. These symptom clusters were replicated in the group of drug-naïve patients, but only partially in the group of patients on psychoactive medication. The factor structure of the NPI-NH is consistent with the clinical taxonomy of symptoms, is relatively stable across dementia stages, and is only moderately influenced by psychoactive medication use. The clusters of symptoms were, however, too small to be used as subscales. The division of depression and apathy into separate behavioural dimensions – also in patients with severe dementia – may have important therapeutical consequences.

Chapter 6 describes the factor structure of the CMAI that was used to assess agitation or aggression in the WAALBED study population. A restricted 3-factor solution showed the factors associated with physically aggressive behaviour, physically non-aggressive behaviour and verbally agitated behaviour. The 3-factor solution is consistent with earlier findings in community-dwelling and nursing home patients with various dementia severity. The symptom clusters originated from these behavioural dimensions were used as subscales in Chapter 7 and 8. In addition, an unrestricted factor solution revealed three additional behavioural dimensions: hiding/ hoarding, vocal agitation and a factor of miscellaneous items (i.e. repetitious mannerisms and spitting). These addition factors are too small to be used as a subscale, but these findings may add to the taxonomy of agitation and aggression in dementia.

Chapter 7 describes the influence of gender and disease severity on neuropsychiatric symptoms in the sample of Dutch nursing home patients with dementia. Delusions, depression, physically non-aggressive behaviour, and verbally agitated behaviour were most common in moderately severe (GDS stage 5) and severe (GDS stage 6) cognitive deterioration with lower prevalences in very severe cognitive deterioration (GDS stage 7). Physically aggressive behaviour, apathy and anxiety showed highest prevalences in very severe cognitive deterioration (GDS stage 7). Physically aggressive behaviour and apathy were more prevalent in male patients, while depression and anxiety were more frequent in female patients with dementia. We conclude that both dementia severity and gender are important predictors of neuropsychiatric symptoms.

Chapter 8 describes the influence of correlates associated with the physical and psychosocial environment on neuropsychiatric symptoms. The nursing home population resided in 56 dementia special care units. The influence of both patient-related factors and SCU characteristics on symptom clusters of the CMAI and psychosis, depression/ anxiety, agitation and apathy was studied using multilevel

logistic regression analysis, a technique able to correct for the dependency of neuropsychiatric symptoms in patients in the same SCU. The results showed that there was a substantial variation of the level of symptom prevalence among SCUs, accounting for 4-14% of the total variance of neuropsychiatric symptoms. Significant patient related factors were dementia severity, gender, age, duration of institutionalization and psychoactive medication use, which accounted for another 7-21% of the total variance. The range of SCU symptom prevalence was considerably large even after correction for significant patient-related factors of each individual patient present in an SCU, highlighting the importance of nursing home environment contributing to neuropsychiatric symptoms. However, environmental correlates used in this study, i.e. the number of patients per unit or per living room, staff size/patient ratio, time spent by staff on care activities, presence of a walking circuit, had no significant association with most of the neuropsychiatric symptoms. Only at SCUs of which the staff spent more time on care activities did the patients show lower levels of apathy. We feel that other factors associated with the physical and psychosocial environment, such as other architectural characteristics, staff-patient or patient-patient interactions, staff attitude towards (patients with) neuropsychiatric symptoms, policy on using physically restraints and psychoactive medication, may explain the large variation of SCU symptom levels in Dutch nursing homes.

Chapter 9 gives an overview of the research questions that had been addressed in this thesis, discusses the methodological limitations, the implications for researchers, physicians and psychologists, carers, architects and policy makers and provides some recommendations for further research.

In conclusion, prevalence rates of neuropsychiatric symptoms in Dutch nursing home patients with dementia are high and are influenced by both disease related predictors and environmental factors. The findings of the WAALBED study indicate a biopsychosocial origin of neuropsychiatric symptoms. This model provides a better understanding of the etiology and the treatment possibilities than a biological model. As biological (pharmacological) interventions have only modest efficacy and considerable side effects, psychosocial interventions should be encouraged. We advocate a person-centred approach for the treatment of neuropsychiatric symptoms. This approach takes individual personality, coping strategies, history, dementia severity and co-morbidity into account when choosing the adequate therapeutic strategy. The person-centred approach provides a toolkit of interventions such as pharmacological interventions, validation, reminiscence, snoezelen, psychomotor therapy that can be tuned on the individual symptoms and needs of patients with dementia to reduce the burden of neuropsychiatric symptoms and increase the quality of life.

SAMENVATTING

Dementie is een ongeneeslijke aandoening met belangrijke effecten op cognitie, activiteiten van het dagelijks leven en gedrag. Neuropsychiatrische symptomen, vaak aangeduid als agitatie/agressie, psychose, depressie en apathie, hebben een grote invloed op patiënt en verzorger en zijn de belangrijkste reden voor opname in een instelling. Ook bij verpleeghuispatiënten vormen neuropsychiatrische symptomen een grote belasting voor het (verplegend) personeel, resulterend in een toename van werkbelasting en stress. Bij patiënten zelf worden voor neuropsychiatrische symptomen vrijheidsbeperkende maatregelen toegepast en psychofarmaca voorgeschreven met aanzienlijke bijwerkingen.
In eerdere literatuur wordt gesuggereerd dat neuropsychiatrische symptomen vaak voorkomen en gerelateerd zijn aan het type en de ernst van de dementie. Er zijn ook aanwijzingen dat neuropsychiatrische symptomen beïnvloed worden door andere factoren die te maken hebben met de psychosociale en fysieke leefomgeving.
In het laatste decennium is er meer onderzoek gedaan bij thuiswonende dementiepatiënten, maar er is slechts weinig literatuur beschikbaar over patiënten in verpleeghuizen. Deze specifieke omgeving van verpleeghuizen met huiskamers waarin patiënten met een hoge mate van neuropsychiatrische symptomen – deze zijn immers de reden van opname – hun dag doorbrengen, levert een geschikte setting om de waarde van het biopsychosociale model voor het verklaren van factoren die bijdragen neuropsychiatrische symptomen te bestuderen.
In dit proefschrift worden de resultaten beschreven van de Nederlandse 'WAAL BEhaviour in Dementia' (WAALBED) studie, een grote studie over neuropsychiatrische symptomen bij Nederlandse verpleeghuispatiënten met dementie. Zorg voor mensen met dementie in Nederlandse verpleeghuizen wordt gegeven op psychogeriatrische (PG) afdelingen door een multidisciplinair team van verpleegkundigen, verzorgenden, verpleeghuisartsen, fysiotherapeuten, psychologen, activiteitenbegeleiders etc, die allen in dienst zijn van het verpleeghuis zelf. Een dergelijk team kan ook zorg voor mensen met dementie in verzorgingshuizen leveren (substitutie zorg).
Het doel van dit proefschrift is verder inzicht te krijgen in (1) de mate waarin neuropsychiatrische symptomen voorkomen bij Nederlandse verpleeghuispatiënten met dementia (prevalentie) en (2) de invloed van patiënt- en omgevingsfactoren op deze neuropsychiatrische symptomen.

Hoofdstuk 2 geeft een overzicht van de huidige literatuur over de prevalentie van neuropsychiatrische symptomen bij verpleeghuispatiënten met een cognitieve beperking. Neuropsychiatrische symptomen komen voor bij meer dan 80% van de patiënten met zo'n cognitieve beperking. Prevalenties van specifieke symptomen lopen zeer uiteen, van 3% tot 54% voor wanen, van 1% tot 39% voor hallucinaties,

van 8% tot 74% voor depressieve stemming, van 7% tot 69% voor angst, van 17% tot 84% voor apathie, van 48% tot 82% voor agressie of agitatie en van 11% tot 44% voor fysieke agressie. De grote spreiding in prevalenties kan mogelijk worden veroorzaakt door een verschil in patiënten populaties, maar ook door gebruik van verschillende meetinstrumenten (met verschillende scores en definities van symptomen). Neuropsychiatrische symptomen lijken niet alleen voorspeld te worden door het type of de ernst van de dementie maar ook door de psychosociale omgeving, de hoeveelheid psychofarmaca en de mate waarin vrijheidsbeperkende maatregelen worden toegepast.

Hoofdstuk 3 is een systematische review over de werkzaamheid en bijwerkingen van antipsychotica. Hoewel antipsychotica vaak worden voorgeschreven aan verpleeghuispatiënten met dementie in Nederland (37% in de WAALBED studie, zie hoofdstuk 4), is er slechts beperkte bewijskracht voor de werkzaamheid en bestaat er toenemende ongerustheid over de veiligheid van deze geneesmiddelen, vanwege een vermeend risico op beroerte. In de literatuur werden slechts 14 studies gevonden over de werkzaamheid van haloperidol, risperidon, olanzapine (in meer dan één onderzoek per geneesmiddel) en van quetiapine, tiapride, loxapine en perfenazine (in slechts één onderzoek per geneesmiddel). De werkzaamheid van typische en atypische antipsychotica is vergelijkbaar, en alleen risperidon in een lage dosering wordt geassocieerd met minder (extrapyramidale) bijwerkingen. Risperidon en olanzapine lieten in twee onderzoeken een verhoogde kans op beroerte zien. In het gepubliceerde onderzoek is het bijwerkingenprofiel van antipsychotica niet goed omschreven en de waarschuwingen voor een verhoogde sterfte kunnen op basis hiervan niet worden bevestigd.

Hoofdstuk 4 beschrijft de prevalentie van neuropsychiatrische symptomen bij Nederlandse verpleeghuispatiënten. Neuropsychiatrische symptomen werden gemeten met behulp van de Neuropsychiatrische Vragenlijst – Verpleeghuisversie (NPI-NH) en de Cohen Mansfield Agitatie Vragenlijst (CMAI). Meer dan 80% van alle verpleeghuispatiënten in de WAALBED studie hebben een of meerdere symptomen. Wanen en hallucinaties zijn aanwezig bij respectievelijk 15% en 8% van de patiënten. Depressieve stemming en angst waren aanwezig bij 20% en 21% van deze patiënten. De prevalentie van agressief/geagiteerd gedragingen was 31% voor agressie/agitatie, 20% voor ontremd gedrag, 34% voor prikkelbaar gedrag en 29% voor doelloos herhalend gedrag (gemeten met de NPI-NH) en 44% voor algemene rusteloosheid, 33% voor vloeken of verbale agressie, 13% voor slaan (gemeten met de CMAI). Apathie was aanwezig bij 34% van de patiënten. Wij concluderen dat prevalenties hoog zijn, hetgeen praktische consequenties heeft voor planning van zorg.

Hoofdstuk 5 beschrijft de factorstructuur van de NPI-NH. Factoranalyse werd gebruikt om gedragsdimensies die aan neuropsychiatrische symptomen ten grondslag liggen te onderzoeken. We beschreven de factorstructuur in de WAALBED populatie over de verschillende stadia van dementie (zoals gemeten met de Global Deterioration Scale) and bij patiënten met en zonder psychofarmaca. In drie stadia van de ernst van de dementie werd een 4 tot 5 factoren oplossing gevonden, met factoren die aangeduid werden met agitatie/agressie, depressie, psychose, psychomotore agitatie en apathie. Dezelfde clustering van symptomen werd gevonden bij patiënten die geen psychofarmaca gebruikten, maar slechts ten dele bij patiënten met psychofarmaca. De factorstructuur van de NPI-NH is consistent met de klinische indeling van symptomen, is relatief stabiel over de verschillende stadia van dementie, en wordt slechts in beperkte mate beïnvloed door het gebruik van psychofarmaca. De symptoomclusters zijn echter te klein om te kunnen worden gebruikt als subschalen. Het onderscheid tussen depressie en apathie in aparte gedragsdimensies – ook bij patiënten met ernstige dementie – heeft mogelijk belangrijke therapeutische consequenties.

Hoofdstuk 6 beschrijft de factorstructuur van de CMAI, een meetinstrument dat werd gebruikt om agitatie en agressie in de WAALBED onderzoekspopulatie te meten. Er werd een beperkte 3-factoren oplossing gevonden, waarvan de symptomen bestonden uit fysiek agressief gedrag, fysiek niet agressief gedrag, en verbaal geagiteerd gedrag. Deze 3-factoren oplossing is consistent met eerder onderzoek bij zowel thuiswonende- als verpleeghuispatiënten met uiteenlopende stadia van dementie. De symptoomclusters die onderliggende gedragsdimensies vertegenwoordigen werden gebruikt als subschalen in hoofdstuk 7 en 8. Daarnaast werd een onbeperkte factor oplossing gevonden met drie extra gedragsdimensies: verstoppen/verzamelen, vocale agitatie en een factor met overige items (namelijk herhalende gedragingen en spugen). Deze extra factoren zijn te klein om te kunnen worden gebruikt als subschaal, maar deze bevinding voegt wel iets toe aan de bestaande kennis over de indeling van agitatie en agressie bij dementie.

Hoofdstuk 7 beschrijft de invloed van geslacht en ernst van de ziekte op de neuropsychiatrische symptomen in de populatie van Nederlandse verpleeghuis-patiënten met dementie. Wanen, depressie, fysiek niet-agressief gedrag en verbaal geagiteerd gedrag kwamen het meest voor in het stadium van matig-ernstige (GDS 5) en ernstige cognitieve achteruitgang (GDS 6) met lagere prevalenties in GDS 7. Fysiek agressief gedrag, apathie en angst lieten de hoogste prevalentie zien in het stadium van zeer ernstige cognitieve achteruitgang (GDS 7). Fysiek agressief gedrag en apathie kwam vaker voor bij mannen, terwijl depressie en angst vaker

voorkwamen bij vrouwen met dementie. Wij concluderen dat zowel het stadium van dementie als geslacht belangrijke predictoren zijn voor neuropsychiatrische symptomen.

Hoofdstuk 8 beschrijft de invloed van factoren geassocieerd met de fysieke en psychosociale omgeving op neuropsychiatrische symptomen. De verpleeghuispopulatie was verspreid over 56 PG afdelingen. De invloed van zowel patiëntfactoren als afdelingsgerelateerde factoren op de symptoomclusters van de CMAI en psychose, depressie/angst, agitatie en apathie werd onderzocht met behulp van multi-level logistische regressieanalyse, een techniek die het mogelijk maakt te corrigeren voor de statistische afhankelijkheid van neuropsychiatrische symptomen bij patiënten op eenzelfde PG afdeling. De resultaten lieten zien dat er een substantiële spreiding bestaat in de prevalenties van symptomen tussen verschillende PG afdelingen. Deze spreiding verklaarde 4-14% van de totale variantie van neuropsychiatrische symptomen. Significante patiënt factoren waren ernst van de dementie, geslacht, leeftijd, opname duur en psychofarmaca gebruik, die samen ook nog eens 7-21% van de totale variantie verklaarden. De spreiding in afdelingsprevalenties bleef aanzienlijk groot zelfs na correctie voor alle significante patiëntfactoren van iedere individuele patiënt op een bepaalde PG afdeling. Dit resultaat onderstreept het belang van verpleeghuiskenmerken als bijdragen aan de mate van neuropsychiatrische symptomen. Echter, de afdelingskenmerken die gebruikt werden in dit onderzoek (het aantal patiënten per afdeling of per huiskamer, het aantal verzorgenden per bewoner, het aantal uren dat werd besteed aan directe patiëntenzorg en de aanwezigheid van een loopcircuit), hadden geen significant verband met de meeste van de neuropsychiatrische symptomen. Alleen op PG afdelingen waarbij het verzorgend personeel meer tijd besteedde aan directe zorg waren patiënten minder apathisch. We denken dat andere factoren die geassocieerd worden met de fysieke en psychosociale omgeving, (zoals bouwkundige eigenschappen, interacties tussen verzorging en patiënt en tussen patiënten onderling, de attitude van de verzorging ten aanzien van patiënten met neuropsychiatrische symptomen, beleid ten aanzien van het gebruik van vrijheidsbeperkende maatregelen en psychofarmaca), de grote spreiding tussen afdelingsprevalenties in Nederlandse verpleeghuizen zouden kunnen verklaren.

Hoofdstuk 9 geeft een overzicht van de onderzoeksvragen die werden beantwoord in dit proefschrift, bediscussieert de methodologische beperkingen, de implicaties voor onderzoekers, artsen en psychologen, verzorgenden, architecten en beleidsmakers en geeft aanbevelingen voor verder onderzoek.

Concluderend kan gesteld worden dat de prevalenties van neuropsychiatrische symptomen bij Nederlandse verpleeghuispatiënten met dementia zeer hoog zijn en beïnvloed worden door ziekte-gerelateerde en omgevingsfactoren. De bevindingen van de WAALBED studie wijzen op de biopsychosociale grondslag van neuropsychiatrische symptomen.
Dit model levert een beter begrip van de therapeutische mogelijkheden dan het biologisch model. Omdat biologische (farmacologische) interventies slechts beperkt werkzaam zijn en belangrijke bijwerkingen hebben, moeten juist de psychosociale interventies worden gestimuleerd. We pleiten dan ook voor een patiënt-georiënteerde/belevingsgerichte benadering ten aanzien van de behandeling van neuropsychiatrische symptomen. Deze benadering houdt rekening met de individuele persoonlijkheid, copingsstrategieën, voorgeschiedenis, ernst van de dementie en co-morbiditeit voor het kiezen van een adequate behandelstrategie. Deze patiënt-georiënteerde/belevingsgerichte aanpak bestaat uit een scala aan interventies zoals farmacologische interventies, validatie, reminiscentie, snoezelen, psychomotore therapie die kan worden afgestemd op de individuele symptomen en behoeften van de patiënt met dementie om de belasting van neuropsychiatrische symptomen te verminderen en de kwaliteit van leven te verbeteren.

DANKWOORD

Een proefschrift wordt meestal achterstevoren gelezen, te beginnen bij het dankwoord, gevolgd door een samenvatting. Vaak worden daarna alleen nog de stellingen gelezen en blijft het daarbij. Toch hoop ik dat velen ook de rest van het proefschrift zullen lezen, omdat het onderwerp – neuropsychiatrische symptomen – zeer belangrijk is voor de zorg voor mensen met dementie. Ik hoop hiermee een bijdrage te hebben geleverd aan het dementie onderzoek. Dit onderzoek moet er uiteindelijk toe leiden dat de gevolgen van de ziekte beter hanteerbaar worden voor mensen met dementie, partners en verzorgenden. Verzorgenden hebben dagelijks te maken met neuropsychiatrische symptomen en zouden meer waardering moeten krijgen voor al de inspanningen die ze doen om het dagelijks leven van hun bewoners met dementie zo aangenaam mogelijk te maken.

Ik wil daarom eerst alle verzorgenden bedanken van de 59 psychogeriatrische afdelingen van verpleeghuizen en 13 'meerzorgafdelingen' van verzorgingshuizen, van Venlo tot Emmen, van Bergen op Zoom tot Enschede, die tijd hebben gereserveerd om de meetinstrumenten in te vullen. Zonder jullie en de bijdrage van verpleeghuisartsen en psychologen van al deze instellingen was een dergelijk grootschalig onderzoek niet mogelijk geweest.

Als tweede wil ik bedanken mijn promotor, Raymond Koopmans. Het was jouw idee om op de afdeling verpleeghuisgeneeskunde de 'pas geboren' onderzoekslijn over dementie te beginnen met dit onderzoek. In talloze besprekingen op je kamer op de afdeling, in de auto onderweg naar vergaderingen en in je omgebouwde garage annex studeerkamer, discussieerden we over de opzet en resultaten van het onderzoek en de vele conceptversies van artikelen. Je hebt me veel bijgebracht over het uitvoeren van wetenschappelijk onderzoek. Raymond, dank voor je vertrouwen dat ik ondanks mijn langdurige ziekte de promotie uiteindelijk wel zou afronden en dat je me in de gelegenheid stelt door te gaan als senior onderzoeker op de afdeling.

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Frans Verhey, ik was onder de indruk van de MAASBED studie over neuropsychiatrische symptomen bij thuiswonende dementiepatiënten. Omdat ik blij was dat we delen van je onderzoeksprotocol mochten gebruiken, is de WAALBED studie naar de MAASBED studie vernoemd. Ik heb veel geleerd van je deskundige inbreng in de begeleidingscommissie, waarvoor je vaak de dienstverlening van de Nederlandse Spoorwegen trotseerde om naar Nijmegen te komen. Een keer ben je halverwege gewoon teruggekeerd omdat de trein zoveel vertraging had dat de te verwachte aankomsttijd viel na het eindtijd van de begeleidingscommissie. Ik herinner me ook de gezellige etentjes in Maastricht en op congressen in Stockholm en Istanbul, waar ik met veel plezier aan terugdenk. Frans, ik ben blij dat de opgebouwde samenwerking tussen Maastricht en Nijmegen ook tot uiting komt in je bijdrage aan andere onderzoeken op de afdeling verpleeghuisgeneeskunde.
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Jos de Jonghe, de bijdrage van een psycholoog aan dit onderzoek op het grensvlak van de geneeskunde en de psychologie mocht natuurlijk niet ontbreken. Je had als psycholoog en als 'schaaldier' veel methodologische kennis over meetinstrumenten. Je gaf me de handreikingen om de statistische analyse zelf te doen. Dan hadden we vaak uitgebreide methodologische discussies waarbij Frans en Raymond ons maar lieten begaan. Hans Bor, je hebt daarom weinig hoeven doen, maar je was als statisticus wel een klankbord om te toetsen of ik wel de juiste analyse deed.

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Collegae op de afdeling verpleeghuisgeneeskunde en collegae verpleeghuisartsen van Kalorama, dank je wel voor jullie interesse en steun in de afgelopen jaren. Roland Wetzels, ik heb in jou als promovendus van de WAALBED-2 beloopstudie een waardig opvolger.

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Margje, als psycholoog in Kalorama heb je me het belang van de rol van de psycholoog in het omgaan met probleemgedrag bijgebracht en het leren kijken naar interacties tussen verzorgenden en bewoners. We hebben op 'onze' verpleegunit van zorgcentrum het Höfke, dwars door de gangbare gebruiken heen, samen de behandeling en begeleiding van cliënten met probleemgedrag op ons genomen. Ik ben blij dat ik je hierdoor beter heb leren kennen, niet alleen als collega, maar ook als vriendin en oppas voor Juan (en ik voor je zoon Thuur).

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CURRICULUM VITAE

Sytse Zuidema is op 6 oktober 1967 geboren in Sneek. In 1985 behaalde hij zijn VWO diploma aan het Christelijk Lyceum te Apeldoorn. Hij studeerde geneeskunde aan de Rijksuniversiteit Utrecht en verhuisde het laatste jaar van zijn studie naar Groningen voor het doen van wetenschappelijk onderzoek op het gebied van longziekten in het Academisch Ziekenhuis Groningen. Na zijn co-assistentschappen in het Medisch Spectrum Twente (MST) Enschede bleef hij ook na zijn artsexamen (1994) in dit ziekenhuis voor arts-assistentschappen longziekten voor zowel patiëntenzorg als wetenschappelijk onderzoek en was hij poortarts op de locatie van het MST in Oldenzaal. In de periode tussen 1998 en 2000 deed hij de vervolgopleiding tot verpleeghuisarts aan het UMC St Radboud te Nijmegen en werkte hij tot 2003 bij Stichting Zorgpalet te Enschede. Vanaf 2001 was hij tevens verpleeghuisarts-onderzoeker aan de afdeling Verpleeghuisgeneeskunde van het UMC St Radboud om de WAALBED studie naar probleemgedrag voor te bereiden. In 2003 verhuisde hij naar Nijmegen omdat Kalorama hem dankzij financiering door Stichting Joannes de Deo in de gelegenheid stelde om op dit onderwerp te promoveren. Hij is sindsdien als verpleeghuisarts in Kalorama werkzaam. Momenteel is hij ook werkzaam op de afdeling Verpleeghuisgeneeskunde/ Vervolgopleiding tot Verpleeghuisarts als senioronderzoeker en coördinator Kennis en Wetenschap. Daarnaast heeft hij meegewerkt aan de richtlijn 'gedragsproblemen bij dementie' voor verpleegkundigen en verzorgenden en aan de herziene richtlijn 'probleemgedrag' van de Nederlandse Vereniging van Verpleeghuisartsen (NVVA). Sytse is gehuwd met Nienke Zuidema-de Boer en ze hebben een dochter Juan.

Sytse Zuidema

Neuropsychiatrische symptomen, ook wel probleemgedrag genoemd, komen veel voor bij mensen met dementie. Het omgaan met dit apathisch, angstig, achterdochtig, agressief of dwaalgedrag maakt het zorgen thuis voor de naaste van de persoon met dementie extra zwaar. Vaak is dit gedrag een reden voor opname in verpleeg- en verzorgingshuizen. Verzorgend en verplegend personeel van deze instellingen hebben ook dagelijks te maken met probleemgedrag bij bewoners met dementie.
In dit proefschrift beschrijft Sytse Zuidema de resultaten van een grootschalig Nederlands onderzoek (WAALBED studie) in verpleeghuizen naar de aanwezigheid en oorzaken van probleemgedrag. Ook gaat hij in op de medicamenteuze behandelmogelijkheden en psychosociale interventies, om deze symptomen en de belasting die dit voor verzorgenden en verpleegkundigen met zich meebrengt te verminderen. Dit proefschrift is een aanrader voor verpleeghuisartsen, sociaal geriaters, psychologen, psychiaters, klinisch geriaters en zorgmanagers, die regelmatig te maken hebben met mensen met dementie.

Sytse Zuidema (1967) is als verpleeghuisarts-onderzoeker werkzaam op de afdeling Verpleeghuisgeneeskunde van het UMC St Radboud te Nijmegen en bij Stichting Kalorama te Beek-Ubbergen.

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