The neuropsychiatry of dementia : psychometrics, clinical implications and outcome

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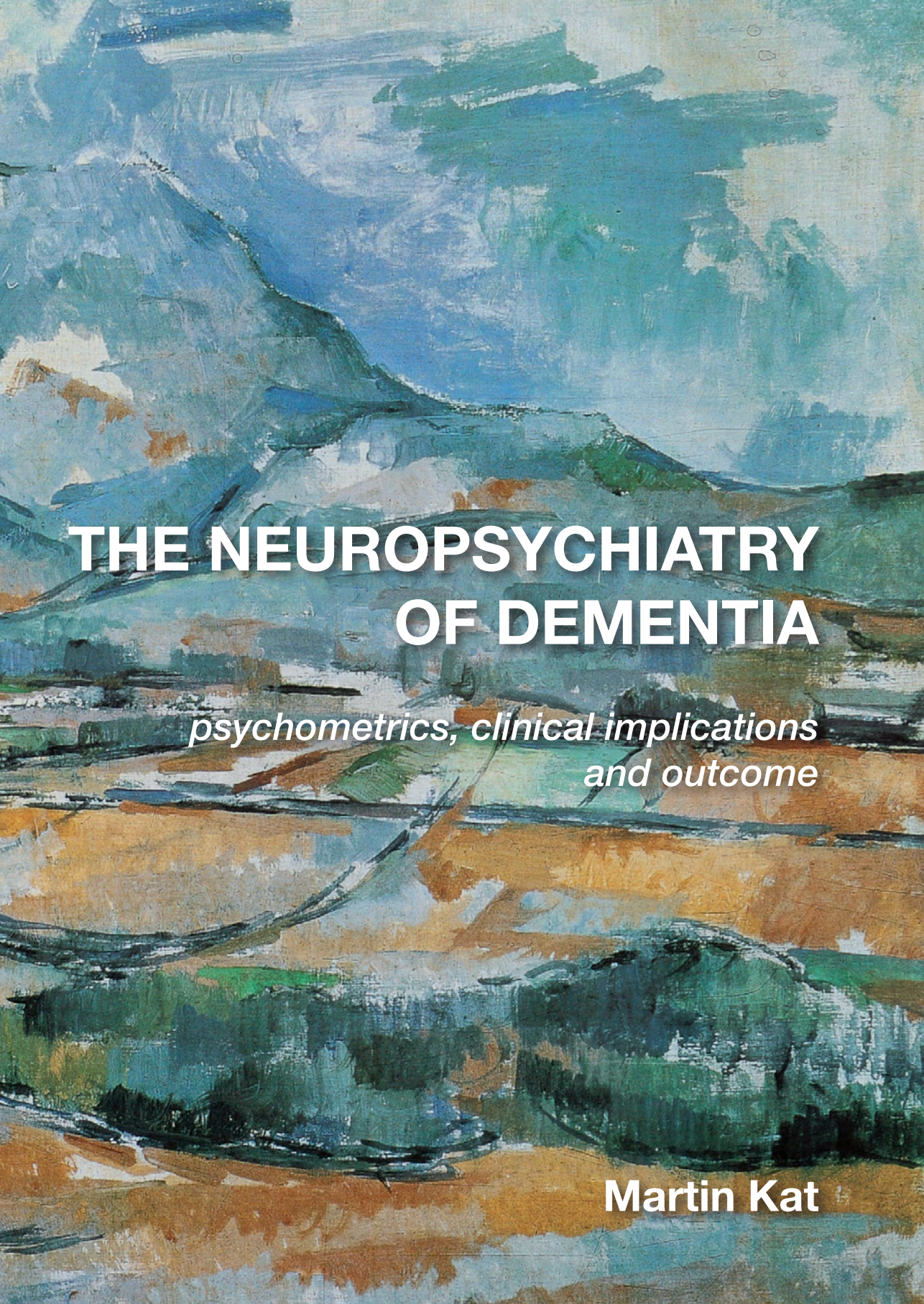
THE NEUROPSYCHIATRY OF DEMENTIA
psychometrics, clinical implications and outcome
Martin Kat

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Aan Paulien, Anne, Pam, Sophie
en mijn moeder (‘die jongen moet verder leren’)

CONTENTS

‘La nature n’est pas en surface; elle est en profondeur. Les couleurs sont l’expression, à cette surface, de cette profondeur. Elles montent des racines du monde’ (‘De natuur is niet aan de oppervlakte maar in de diepte. De kleuren zijn een uiting van deze diepte aan de oppervlakte; zij rijzen op vanuit de wortels van de wereld’)

Paul Cézanne

‘Dementia may result from anoxia, from trauma or from primary degenerative disease. It is therefore possible to extract important symptoms and syndromes which indicate the possibility of cerebral disorder whatever the basic pathology and despite the colouring lent by pathoplastic features. Such symptoms form the cornerstone of diagnosis in organic psychiatry and it is essential to recognise their earliest and most minor manifestations’

William Alwyn Lishman

CHAPTER 1

Introduction

Dementia is a syndrome in which impaired memory plays a key role. As long as this syndrome has been recognized, relatively little attention has been paid to psychiatric problems that may occur in association. This thesis is an attempt to answer the following questions:

1. How can neuropsychiatric symptoms of dementia be assessed in a valid and reliable manner?

2. How do certain neuropsychiatric symptoms of dementia relate to environmental variables? Which instrument is most suitable for studying these associations?

3. Is there a relation between delirium as a neuropsychiatric syndrome and dementia?

This introduction will first outline the historical framework that has led to these questions posed.

Dementia: historical aspects

Partly due to the influence of positivism, the nineteenth century shows the rise of a trend towards applied scientific psychiatry. Mental disorders are regarded diseases of the brain.[1] Researchers became increasingly interested into the relationship between clinical psychiatric disorders and the neuropathological substratum. This is also the age in which neurosurgery and neuropathology are introduced. Around 1850 microscopic techniques like specimen tissue staining are applied for the first time.

The view on dementia too changed in that period. Until 1880 approximately, dementia was a broad concept, still comprising many syndromes. Their denominator was manifested psychosocial incompetence as a result of a reduced capacity to judge adequately and reason logically. Defect conditions in psychosis and mood disorders too fell under this diagnostic category. Senile dementia e.g. was seen ‘as a final common pathway to a number of chronic psychoses and organic disorders’.[2]

With the rise of organically oriented psychiatry, a division in the originally widely defined concept of dementia came about in the second half of the 19th century. ‘Functional’ psychiatric syndromes disappeared from this diagnostic ‘entity’. Senile dementia became an ‘organic’ dementia, more focused on the irreversible nature of the disorders underlying this syndrome and the relation to age. Thus, amnesia became a key symptom and the multidimensional dementia syndrome primarily became a memory dysfunction.

This is also the time when the German physician Alois Alzheimer publishes his

findings. He was very much interested in clinicopathological research. In 1907 he describes the clinical picture and the neuropathological findings of his patient Auguste D. and tries to classify his diagnosis according to the brain disorder classification system current at that time. That did not quite work: 'Mein Fall Auguste D. bot schon klinisch ein so abweichendes Bild, dass er sich unter keine der bekannten Krankheiten einreihen liess'.[3] With this he implied to have discovered a new syndrome. In a number of aspects, the disorder did not resemble the criteria applying to dementia senilis at that time: the first symptoms arose at an early age already (50 years) and, in addition to the memory problems, psychotic symptoms and behavioural disorders were already present early onwards. Moreover, he detected temporal-parietal phenomena like aphasia, apraxia and agnosia early on in the course of the disease. Furthermore, he emphasized that Auguste 'zeigte als erste Krankheitserscheinung Eifersuchtsideen gegen den Mann'.[4] Apparently, the psychotic symptoms manifested themselves at a very early stage, even before memory dysfunctions were evident.

This patient, originally diagnosed by him with senile psychosis, later became known as the first Alzheimer patient. Based on their clinicopathological findings, Alzheimer and colleagues can not but conclude, from 1910 onwards, that the difference between pre-senile and senile forms of dementia can not be maintained. In 1911 Alzheimer submits: 'So scheint wirklich kein stichhaltiger Grund vorhanden diese Fälle als durch einem besondern Krankheitsprozes verursacht zu betrachten. Es sind seniele Psychosen, atypische Formen der senielen Demenz'.[5]

This equalization cleared the path for an 'organic' dementia concept, with emphasis on loss of memory and intellect, irreversible in course and apparently not exclusive to old age. The pre-senile phenomena Alzheimer found, like aphasia, apraxia and agnosia, were included in the process, but (remarkably so) psychiatric symptoms were not. Apparently, the latter did not fit the concept of dementia as a primarily 'organic' disorder, thus excluding 'functional' psychiatric phenomena.

This partly allowed the foundation to be laid for a view on dementia which would last until far into the 20th century and for many until today. Clinicopathological research into the relation between memory and intellectual disorders and the neuropathological substratum plays a key role in this.

From the Fifties until the Seventies, it is Roth and his co-workers[6] who define the psychiatric disorders in the (pre)senium more precisely, based on their clinical and neuropathological research. Next to the 'organic' dementias, which they call senile and arteriosclerotic psychoses, 'functional' psychiatric syndromes like affective psychosis and (late) paraphrenia (1955) are defined.[7] Blessed et al., linked dementia severity to the extent of pathological changes in the brain.[8] In a controlled study (non-demented

versus dementia patients) Tomlinson et al. showed that non-demented patients displayed no or hardly any Alzheimer pathology,[8-10] and it became clear that pre-senile and senile forms of dementia do not differ neuropathologically.

Like his British colleagues, it is dementia researcher Stam in the Netherlands at that time, who is making out a course for sharp boundaries between different psychiatric clinical pictures in the elderly. He too is working with a clearly clinicopathological perspective and he studies refined and sharpened definitions within the group of dementia disorders. Following Schneider, a renowned schizophrenia researcher at that time, Stam proposes to come to so-called 1st and 2nd order symptoms in clinical diagnostics.[11] Specific 1st order symptoms are memory disorders and/or loss of (other) acquired functions. Changes in personality, mood, reality testing and behaviour are considered to belong to the 2nd order.

Scientific research results in the period 1950-1980 led to further support for the hypothesis that senile dementia and Alzheimer's disease, based on clinical pictures and especially on the major neuropathological overlap, were actually synonyms for one dementia disorder, called Alzheimer's disease. It is noteworthy that most studies at that time were conducted among relatively young patients (< 75 years) with well defined dementia disorders and therefore not among the group with the highest dementia prevalence (75+). The result was that senile dementia was considered to overlap completely with the Alzheimer dementia concept.

This process was completed around 1980. The operationalized dementia criteria, resulting from clinicopathological research are reflected in the then existing, internationally recognized classification systems DSM-III[12] and NINCDS-ADRDA.[13] Symptoms concerning memory and (other) acquired functions belong to the core criteria.

The cognitive paradigm: the devaluation of neuropsychiatric symptoms

The result of this historical development was that the name Alzheimer was connected more and more to a form of dementia in which the irreversibility of cognitive disorders and the relation to (advanced) age play an important role. The highly characteristic other clinical phenomena that Alzheimer described in his original pre-senile case, like psychiatric symptoms and behavioural problems - in this thesis from here on referred to as **neuropsychiatric symptoms (np-symptoms)** – gradually vanished from the dementia scenario. This conceptual switch later became known as the 'cognitive paradigm', a term introduced by Berrios,[14] which he describes as follows:

'The current concept of dementia was constructed during the nineteenth and early

twentieth centuries. This process can be described as one of pruning down the heterogeneous clinical content of dementia. The process started before 1800 and culminated in the early 1900s in what I have called the 'cognitive paradigm', i.e. the view that dementia just consisted of an irreversible disorder of intellectual functions. Historical analysis shows that this view resulted more from ideology than clinical observation. For decades, the cognitive paradigm has prevented the adequate mapping of non-cognitive symptoms of dementia and hindered research.'

Now np-symptoms were considered non-cognitive symptoms, turning them into a rest group of a-specific clinical phenomena, playing a secondary role within the diagnostic criteria for dementia. One of the consequences was that diagnostic and neuropsychological instruments were developed, based on this hierarchic ranking in cognitive non-cognitive, so that these instruments detected what they were designed for, viz. memory and other 'cognitive' disorders. The cognitive paradigm became the leading principle in dementia diagnostics.

The term 'cognitive disorder' constitutes another illustration of the cognitive paradigm. Perception and thinking have fallen under the cognitive functions of psychiatric research since way back. Hallucinations and delusions are their psychopathological phenomena. By designating abnormalities of perception and thinking to the non-cognitive disorders, they resolutely disappeared from the cognitive domain of dementia research.

Dementia research primarily turned into memory research, exemplified also by the fact that care for patients with dementia is organized in 'Memory Clinics' throughout the world. Dementia became closely linked with 'cognitive' decline, as described in dementia senilis and in this sense hard to define, other than a gradual difference with progressing, 'regular' ageing. Where senile dementia as an 'organic' dementia was initially incorporated into Alzheimer's pre-senile dementia model, this changed later and AD was chiefly related to dementia syndromes occurring in the senium.

Neuropsychiatric assessment: scales and pathogenesis

The period after 1980 is the age of clinical epidemiological studies and psycho- and clinimetrics. It is the time when one starts to realize the scale of the disease and what consequences it has for patients, society, the economy and the health care system. There is also more awareness of how much impact dementia puts on the environment and that years of clinical neuropathological research have not yet produced an adequate solution to this problem. The focus in dementia research is on studying psychiatric and behavioural problems and the interventions necessary for these. In their book 'Dementia, a Clinical Approach' Cummings and Benson[15] say about the preceding period: 'The

results of this research have been valuable and exciting, but a considerable gap has opened between the new information and its application in the clinical management of demented patients.' Similar opinions were voiced in the Netherlands also, e.g. by Van Crevel[16] who underlined the importance of thorough anamnesis, adequate application of support examinations and the reliability of clinical diagnoses. He stressed the use of distinguishing between cortical and subcortical dementia syndromes.

This is also the time when it gradually becomes clear that behavioural problems and psychiatric disorders are highly prevalent in dementia (up to 90%) and should hold a prominent position in the diagnostic research and treatment.[17] It is also established that these problems draw heavily on the mental constitution of caregivers and cause early admissions to institutions. New instruments were developed to chart the psychiatric phenomenology. Examples are the CAMDEX,[18] BEHAVE-AD,[19] CUSPAD,[20] NPI,[21] and the MOUSEPAD.[22] Also in the Netherlands studies are published on the subject matter. At first, they were conducted at the level of validating scales[23,24] or surveying at symptom level, like depression[25] and apathy[26,27] or studying the mental impact of these symptoms on caregivers.[28,29] Along the way, studies of a factor analytic nature appear: among patients in different settings symptom clusters (syndromes) are distinguished within the spectrum of neuropsychiatric symptoms in dementia.[27,30-34] In many instances three factors are found time and again: a psychosis-, a depression- and a behavioural factor (too much: hyper, maniform; too little: hypo, apathetic).

So, since the Eighties and Nineties of the past century serious attention has been paid to the neuropsychiatric disorders of dementia. Initially this occurs at the levels of symptom- and syndrome diagnostics, while the classical hierarchic dementia concept, with memory disorders as key symptoms, is maintained. The past ten years shows a trend of attempts to explain these np-symptoms pathogenetically and to integrate it with defects of the memory and other (higher) cortical functions. Traditional hierarchical thinking in primary and secondary (reactive?) or cause and consequence is abandoned. The influence of the General Systems Theory is noticeable here. Alexander is the first to describe a number of brain circuits that connect (fronto)cortical with subcortical structures.[35] This allowed explaining, for instance, behaviour, motor- and cognitive aspects within one (functional) circuit. Neuropsychiatric, neurological and neurocognitive symptoms are now equally ranked pathological phenomena within one (or several) dysfunctioning fronto-subcortical circuit(s). The path was cleared for a new view on the pathogenesis of dementia, challenging the validity of the classical and hierarchical disease model (primary cognitive and secondary non-cognitive symptoms) as a product of mainly clinical neuropathological research.

One fine example of this development is the concept of dementia with Lewy

bodies (DLB),[36] described not so long ago. The clinical picture is characterized by impaired attention, memory, perception (hallucinations) and sleeping behaviour, next to possibly occurring motor symptoms (Parkinsonism) and behavioural disorders like agitation and apathy. This clinical unity of coordinated neuropsychiatric, neurocognitive and neurological symptoms was also pathogenetically related to deficiencies in the cholinergic system.[37]

The clinical picture of DLB resembles that of another neuropsychiatric syndrome, viz. delirium. Here too attention deficits, hallucinations, agitation, apathy and night time behavioural disturbances are found as important symptoms. There is a strong resemblance at syndrome level, while there may be differences in aetiology and impact on the brain (acute, chronic). Both syndromes show practically the same neuropsychiatric symptoms. To get a clearer view on the pathogenesis of np-symptoms of dementia, it might be useful to take delirium as an example and to study the relation between delirium and dementia more closely.

Aims and outline of this thesis

The development outlined above was the reason to study the neuropsychiatric aspects of dementia more closely and to try to integrate seriously these phenomena in the clinical diagnosis and pathogenesis of dementia. The studies carried out follow the chronology of the developments described earlier, starting off with the implementation of an adequate measure for neuropsychiatric disorders, its application in studies into np-disorders in various settings and, finally, the study into its possible meaning for the pathogenesis of dementia.

Introducing two neuropsychiatric instruments, chapters 2 and 3 deal with the first question to be answered: how can neuropsychiatric symptoms of dementia be assessed in a valid and reliable manner? The instruments are the NeuroPsychiatric Inventory (NPI) and the NeuroPsychiatric Inventory Questionnaire (NPI-Q). Psychometric research into the validity and reliability of the Dutch versions are at the centre of the discussion.

Chapters 4 and 5 try to answer the second research question of this thesis: how do certain neuropsychiatric symptoms of dementia relate to environment variables? To this purpose, the neuropsychiatric symptomatology of an ambulatory and an institutionalized population of dementia patients are classified according to the NPI domains. Chapter 4 studies both the relation between np-disorders in dementia and emotional stress experienced by caregivers and the question whether caregiver factors are of influence too. Subsequently disease related and caregiver related factors are compared. Chapter 5 is a consultation study. The NPI was used as a tool to classify referral reasons in case of psychiatric consultation. It assesses whether this scale is suitable to adequately

classify consultation questions and how neuropsychiatric disorders within the referred group relate to the prevalence of these disorders in the nursing home.

Finally, Chapters 6 and 7 describe the studies particularly focused on the relation between dementia and delirium, the third research question of this thesis. The pathogenetic aspects of neuropsychiatric symptoms of dementia are also further discussed. Both studies were conducted with a neuropsychiatric syndrome highly prevalent among the elderly, delirium. The study setting was a general hospital, the location where many elderly with delirium are found (up to 65%). We had the opportunity to follow a relatively homogeneous group of elderly, vulnerable to developing delirium. They were senior citizens admitted for hip surgery. The purpose of this first study (chapter 6) was to document the long-term course of post-operative delirium, based on the hypothesis that delirious patients would develop cognitive decline sooner than the elderly free from postoperative delirium, correcting for risk factors.

Chapter 7 reports on a second study on the course of delirium in a prospective case-control study of mortality among elderly developing postoperative delirium and its associated risk factors.

Chapter 8 summarizes the main findings of this thesis and contains a general discussion on the relevance of the results, some methodological considerations and the implications for daily clinical practice and future research.

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PART A

PSYCHOMETRICS

CHAPTER 2

Neuropsychiatric symptoms of dementia: psychometric aspects of the Dutch version of the Neuropsychiatric Inventory (NPI)

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ABSTRACT

Behavioural and psychological symptoms are highly prevalent in dementia. The Neuropsychiatric Inventory was constructed to measure these symptoms. Data from three studies are presented, concerning psychometric aspects of the NPI Dutch version.

The NPI was compared to the Revised Memory and Behavioral Problems Checklist (RMBPC) and the Mini Mental State Examination (MMSE) (n=24). In the three selected patient samples prevalence of behavioural or psychological symptoms was as high as 90%. Interrater agreement (n=19) was very high (kappa > .90). Factor analysis (n=199) supports NPI construct validity. The NPI correlated reasonably close (R = .42 - .63) with the relevant RMBPC subscales, but not with a cognitive measure (MMSE).

The NPI Dutch version can be scored objectively and it is a valid rating scale for measuring a wide range of behavioural and psychological symptoms of dementia.

Key words: dementia, rating scales, neuropsychiatric inventory (NPI), factor analysis

INTRODUCTION

Behavioural and psychological symptoms are highly prevalent in dementia. With Alzheimer's disease, prevalence of anxiety, depressive symptoms, delusions, hallucinations, apathy or agitation is at an estimated 80 – 100%.[1-4] Early recognition, accurate diagnostics and treatment, if possible, are important in clinical practice for several reasons. Both patients and their primary caregivers experience such symptoms as emotionally stressful. This might explain why psychiatric complications are associated with accelerated institutionalization of demented patients.[5,6]

Good instruments to register changes in the severity of symptoms are needed. Several behaviour observation scales have been developed to this purpose. In the Netherlands, there is a great deal of experience with the Beoordelingsschaal voor Oudere Patiënten (BOP, or Assessment scale for Elderly patients in translation)[7,8] and the Gedragsobservatieschaal voor de Intramurale Psychogeriatrie (GIP, or Behaviour observation scale for Intramural Psychogeriatrics).[9,10] In addition to assessment lists to be filled out by nursing staff, scales designed for relatives of patients living at home have been developed.[10-13] Examples of influential scales are, among others, the Behave-AD[14] and the Neuropsychiatric Inventory (NPI),[15] published relatively recently. Little is known on whether these questionnaires are usable in the Dutch situation.

Compared to many older scales, the NPI comprises a wide range of neuropsychiatric symptoms. Furthermore, the NPI uses screening- and in-depth questions, which sort of simulates a clinical interview, allowing it to be conducted relatively quick and easy. An additional advantage of this instrument is that the same interview can (optional) register emotional stress of caregivers.[16] Next to the original version for outpatients, there is one for nursing homes, with the informant being a nurse (NPI-Nursing Home version)[17] and a questionnaire version for relatives (NPI-Questionnaire).[16]

Meanwhile, the NPI has been translated and validated in many countries.[18-20] A Dutch version is available and is being applied in several locations. This article discusses various studies into the psychometric aspects of the Dutch translation of the NPI.

The Neuropsychiatric Inventory

The NPI was constructed to survey neuropsychiatric disorders in demented patients.[15] By now, studies have been carried out in various patient samples, which suggest that reliability and validity of the NPI seem likely.[21-25] The NPI was translated by the authors (JdJ, MK). As a check, the questionnaire was translated back into English (independently). The NPI is administered in a semi-structured interview setting with a partner or someone else highly familiar with the patient's daily functioning. After

the purpose of the interview and questionnaire have been explained, one screening question per behaviour domain is asked, after which approximately seven in-depth questions are possible. The behaviour domains are:

1. Delusions
2. Hallucinations
3. Agitation/Agression
4. Depression/Dysphoria
5. Anxiety
6. Euphoria
7. Apathy
8. Disinhibition
9. Irritability
10. Aberrant motor behavior
11. Nighttime behavior disturbances
12. Appetite and eating abnormalities

Cummings added the latter two subscales to the NPI at a later stage. Per domain, the relatives assess the frequency of the behaviour on a 4-point scale, the severity of the symptom (3-point scale) and the emotional stress for the caregiver (6-point scale). The NPI total score is calculated by multiplying the frequency and severity rates per domain (maximum score per domain is 12) and add them up. (total NPI-score minimum is 0 and maximum 144). The English NPI seems to represent 3 underlying factors; ‘frontal behaviour’, ’mood’ and ‘psychosis’.[25] A scale for caregivers’ emotional stress was developed separately,[16] the score does not count for the NPI-total score.

METHODS

Three studies into the Dutch translation successively focussed on interrater-agreement and generic- and construct validity of the NPI. In all studies, 'informed consents' were obtained from patients and their accompanying relatives before commencing.
SPSS software (version 10) was used for the analyses.

Study I

This study regarded NPI reliability. The extent to which the NPI is scored objectively was examined. The data were gathered by researchers of the Psychiatrics department of the VU Medisch Centrum in Amsterdam, within the framework of the so-called IMO-project (in translation, Conditions for the Implementation of the Model of Meeting Centres).[26] The data came from nineteen primary caregivers of patients with dementia syndromes, visiting different meeting centres in Amsterdam and Amstelveen for people with dementia and their caregivers.[27,28] The diagnosis of dementia syndrome was generally made by GPs, Riagg-physicians (Elderly department) or neurologists. All caregivers visiting the Amsterdam meeting centre in the period from May 2000 up to December 2000, and all caregivers first entering the support programme of the Amstelveen meeting centre were interviewed at home by trained interviewers (MK of RMD or the research-psychologist). A second, trained assessor (research assistants, psychology or medicine students), present during the interview, would also fill out an NPI. NPI-training took two (morning/afternoon) shifts, during which interviewers/assessors were trained in conducting the interview, how to score the NPI, how to handle complicated decision situations and answering frequently asked questions. Next to verbal instructions, a video in English on the backgrounds of administering the NPI was shown and there were role plays in pairs.

The average age of the caregivers interviewed was 66 years (sd 13.1), of which 73.7% were male and 26.3% were female. The majority (84.2%) were partners of the demented, the others (15.8%) were all daughters. The average age of the assessed patients was 72.9 years (sd 9.4), of which 31.6% were female. Treating physicians were asked to assess dementia severity based on the Global Deterioration Scale (GDS).[29,30] This scale distinguishes six stages of dementia: uncertain, mild, moderate, moderate-severe, severe and most severe. Of the demented one showed mild, six showed moderate, nine showed moderate-severe and three showed severe dementia.
Cohen's kappas were calculated for the separate NPI subscales scores and the Spearman rank correlation was determined for the total score.

Results study I

The average NPI-total score for this group was 26.9 (sd 18.4). One patient showed no abnormalities on the NPI (score 0). Interrater agreement for the separate NPI-subscales proved very high. (Kappa-coefficients: 0.91 – 1.0, $p<0.01$). Interrater agreement for the total score was correspondingly high (ranking correlation = 0.99, $p<0.01$).

Study II

The second study regarded NPI validity. Correlation was determined with self-rating questionnaires for caregivers and cognitive testing. A selection of Dutch data from a double blind, placebo controlled study, to be reported on elsewhere, were used to this purpose. Patients in that study were treated with an acetyl cholinesterase-inhibitor or a placebo. Readings regarded possible cognitive changes in the first place, behavioural ones in the second. Patients participating visited the geriatric outpatient clinic of the Medisch Centrum Alkmaar (n=20) or were treated elsewhere (n=4). In accordance with the research protocol they were assessed once or several times. This study used primary readings.

Clinical instruments

In addition to the NPI, the Revised Memory and Behavioural Problems Checklist (RMBPC)[31] and the Mini Mental State Examination (MMSE)[32] were administered. The RMBPC is a questionnaire for relatives of demented outpatients, validated for the Dutch situation.[33] This self-rating questionnaire (without accessory interview) consists of 24 questions (5-points scale), allocated to three subscales based on factor analysis: Depressed behaviour, Disturbing behaviour and Memory related behavioural changes. The RMBPC also has a scale per question rating the emotional stress for caregivers (4-points scale). The MMSE is a succinct, internationally well-known test to assess the presence and severity of cognitive disorders.

Results study II

The average age of the 16 women and 8 men was 74.3 years (sd 10.4). Twenty patients lived at home and four stayed in a (nursing) home. The informants interviewed were mostly partners,[18] in five cases it was a daughter or a son and in one case there was another relative. Regarding clinical diagnostics: there was one case of amnesic disorder, one case of fronto-temporal dementia and one case of mixed dementia, there were two cases of cerebro-vascular accidents and nineteen patients were diagnosed with (senile) dementia of the Alzheimer type.

The severity of the cognitive disorders in this group was relatively mild; the average

MMSE score was 21.5 (sd 4.6, range 12-29). The average NPI-total score was 12.9 (sd 9.9), which is lower than in experiment I (Mann-Whitney U 122.5, Z 2.58, p=0.01). One patient showed no abnormalities on the NPI (score 0). The average RMBPC total score was 24.3 (sd 11.1) and the average scores on the cognition, depression and disturbing behaviour parts were 15.2 (sd 7.1), 6.8 (sd 5.6) and 2.3 (sd 2.7) respectively. NPI-assessments were not associated with patients' age or sex. Table 1 shows the correlations between NPI, RMBPC and MMSE.

Table 1. Rank correlations NPI, RMBPC en MMSE (n=24).
'Spearman rank correlations NPI, RMBPC and MMSE (n=24).'

NPI subscales	RMBPC Total	RMBPC Cognitive dis.	RMBPC Depression	RMBPC Disinhibition	MMSE
Delusions	.51**	.53**	-	.47**	-.61**
Hallucinations	-	-	-	-	(-.31)
Agitation/agression	-	-	-	.36*	-
Depression/dysphoria	-	-	.60**	-.35*	-
Anxiety	.39*	-	-	-	(-.34)
Euphoria	-.38*	-	.35*	.36*	-
Apathy	.52**	-	.57**	-	-
Disinhibition	-	-	-	-	-
Irritability	-	-	-	.42*	-
Aberrant motor behavior	-	-	-	-	-.48**
Nighttime behavior disturbances	-	-	-	.47*	-
Appetite and eating abnormalities	-	.33*	-	(.32)	-
NPI total score	.57**	.35*	.49**	.45**	-

**: p < 0.05, **: p < 0.01 (unilateral check). Non-significant findings are not included in the table, nearly significant results are displayed between brackets.*

The NPI total score correlated with the RMBPC's. 'Depression' and 'Disinhibition' on the RMBPC showed relatively close correlation with the NPI-total score. Furthermore 'Delusions', 'Purposeless repetitive behaviour' and, to a lesser degree, 'Changed Appetite-/eating behaviour' on the NPI were positively associated with observed or tested

cognitive disorders. There was a (moderately) strong correlation between the NPI-and RMBPC depression subscales. Several NPI-subscales correlated with 'Disinhibition' on the RMBPC. Four of the twelve NPI-behavioural domains (Hallucinations, Anxiety, Disinhibited behaviour and purposeless, repetitive behaviour) proved not to be associated with the RMBPC depression- and disinhibition subscales.

The emotional stress experienced by primary caregivers increases with severer behavioural problems (correlation NPI total score and emotional stress score: $R = 0.69$, $p < 0.01$). The correlation with the RMBPC emotional stress scale supports the validity of the NPI emotional stress scale for primary caregivers ($R = 0.51$, $p < 0.01$).

Study III

The third study regards the factor structure of the NPI (construct-validity). Data were gathered from the MAAstricht Study of BEhaviour in Dementia (MAASBED), to be reported on elsewhere.[34] MAASBED focuses on course and risk factors of behavioural problems with dementia. The study consists of two parts: Firstly, the course of the behavioural problems and the patient's characteristics that influence it are assessed. Secondly, the characteristics of caregivers that influence the onset and course of the patients' behavioural problems are examined. It is a multidisciplinary study, resulting from a co-operation between the Hersenen en Gedrag (Brains and Behaviour) institute of the Universiteit Maastricht, the Geheugenpoli (Memory policlinic) of the Academisch Ziekenhuis Maastricht and the Ouderenzorg (Elderly care) department of the RIAGG Maastricht.[35]

Participating patients (n=199) met the DSM-IV criteria for the diagnosis of dementia: 146 patient with a dementia syndrome of the Alzheimer type, 32 vascular dementias, 3 frontal dementias, 5 Parkinson dementias, 2 Dementias with Lewy Bodies, 4 primary progressive aphasias, 1 alcohol dementia and 6 patients with both Alzheimer and vascular aetiology. Their average age was 76.4 years (sd 8.0) and 43 % were male patients. 71.4 % of the patients showed moderately severe dementia (Global Deterioration Scale, stages 3 and 4). Comparable to earlier research into thee English version, a Principal-components analysis (Varimax) of the NPI subscales scores was conducted for the construct validity study.

Results study III

One or more symptoms were shown on the NPI by 181 (91%) of the 199 patients. Apathy and depression were reported most frequently, euphoria, disinhibition and hallucinations least (table 2).

Table 2. Average NPI scores (frequency times severity; range 0-12) and percentage patients with symptoms (n=199).

NPI items	Average and SD	% patients with symptoms (score ≥ 1)
Factor Psychosis		36.7
Delusions	1.95 ± 3.41	34.7
Hallucinations	0.83 ± 2.52	13.1
Factor Hyperactivity		59.8
Agitation	1.50 ± 2.94	28.6
Euphoria	0.34 ± 1.54	7.0
Disinhibition	0.61 ± 2.12	12.6
Irritability	2.37 ± 3.83	39.7
Aberrant motor behavior	2.23 ± 3.73	34.7
Factor Mood /Apathy		80.4
Depression/Dysphoria	3.48 ± 4.22	57.3
Apathy	3.27 ± 3.72	59.3
Nighttime behavior dist.	1.22 ± 2.98	18.1
Appetite and eating abn.	1.73 ± 3.46	24.6
Anxiety	1.99 ± 3.53	39.2

Analysis shows three factors (55.1% explained variance). The first factor is a 'hyperactive' (or agitated) one, consisting of the symptoms agitation, euphoria, sensitiveness, disinhibition and motor agitation. The second one is a 'mood/apathy' factor, consisting of depression, apathy, sleeping and eating disorders. The third one is a psychosis factor, consisting of the symptoms delusions and hallucinations. Anxiety is considered a symptom on its own, which can occur separately or in combination with the three factors.

DISCUSSION

This study focuses on some psychometric aspects of the Dutch version of the NPI, an assessment scale increasingly used in international research into behavioural and psychological symptoms of dementia. The data of three selected patient samples confirm these symptoms occur in approximately 90% of the patients. The NPI-interview yields reliable, particularly objective results in that respect. The factor structure found, the correlations with other clinical instruments and even the lack of correlations with scales with other rating claims support NPI validity.

During the NPI-interview, two raters score almost exactly the same. The method is reliable in that respect and the results concur with the original American study.[15] This does not mean that two interviews, shortly after each other and by different raters, will produce the same. One might go on longer asking questions (or better) than the other. Such differences might lead to varying symptom assessments. However, the caregivers considered two interviews shortly after each other too big a burden. Such a reliability study needs to be done in the future. The preliminary conclusion is that the NPI produces reliable, objective results.

What makes the NPI a relatively unique, clinical instrument is what it strives to assess. Not many other scales pay as much and such specific attention to neuropsychiatric symptoms of dementia as the NPI.[11,12] From a validation point of view, the question is with which scale the NPI is best to be compared. The longer existing RMBPC has been translated and validated for the Dutch situation. With a relatively small number of patients in this study, some NPI symptoms showed correlation with the behavioural domains of the RMBPC. For a number of NPI-items, however, this is not the case. Small wonder, considering the items the RMBPC consists of; for instance, the scale has no items on hallucinations or euphoria. An additional explanation might be that a patient with relatively mild dementias (only 4 out of 24 scored under 18 points on the MMSE), shows behavioural and psychological symptoms in a milder form or less frequently, relatively speaking (the comparison between studies I and II supports this supposition). Subsequently, the restricted score range may have kept down the maximum correlation between both clinical instruments. Anyway, the comparison with the RMBPC does support NPI validity. The advantage of the RMBPC over the NPI is that it also rates the core, cognitive aspect of dementia, the advantage of the NPI is that it focuses more closely on behavioural-/psychological disorders. For accurate assessments the NPI is perhaps preferably to be used in combination with a cognitive measure like the MMSE.

On the NPI validity, it should furthermore be noted that – although the studied

samples were not exactly comparable – the results indicate that neuropsychiatric disorders occur more frequently in patients with more advanced dementia. Meanwhile, correlation with cognitive tests and cognitive decline assessments is very modest. Similar associations have repeatedly been demonstrated by others too.[10] In other words, the NPI does not merely assess the extent of cognitive decline with dementia, which supports the divergent validity of the clinical instrument.

Finally, the NPI-factor structure is virtually the same as found elsewhere.[25] This finding advocates construct validity of the instrument. Frisoni et al. also pointed out three factors in an earlier analysis: 'frontal behavior' (disinhibition and euphoria), 'mood' (depression and anxiety) and 'psychosis' (delusions, hallucinations, agitation and sensitiveness).[25] These highly concur with the factors found in MAASBED. The Frisoni study, however, could not link the NPI symptoms apathy and motor agitation to any of the factors. An earlier, 10-item version of the NPI, used in the Frisoni et al. study, might explain the differences found. This 10-item version – without the symptoms eating- and sleeping disorders- is hardly ever used anymore. Factor analysis of the 10-item version of the MAASBED-data resulted in the same factors as for the 12-item version.

The NPI is a relatively new, clinical instrument for assessing various, neuropsychiatric symptoms in dementia. Moreover, it allows for emotional stress to caregivers to be quantified. Considering the number of patients with behavioural and psychological symptoms, assessing these symptoms as a standard procedure in routine, dementia diagnostics and treatment evaluations deserves recommendation.

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CHAPTER 3

Neuropsychiatric Inventory Questionnaire (NPI-Q): A validity study of the Dutch form

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ABSTRACT

The Neuropsychiatric Inventory (NPI) is a clinical instrument for evaluating behavioural and psychological symptoms of dementia. It is based on an interview with a primary caregiver. A brief questionnaire form of the NPI, intended for use in routine, clinical practice (NPI-Q), has been developed. This study evaluates the validity of the Dutch NPI-Q form, comparing it to other questionnaires, i.e., the Revised Memory and Behavioural Problems Checklist (RMBPC), the short form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-N), the 15-item Geriatric Depression Scale (GDS-15) and the Cognitive Screening Test (CST-20). A data set of geriatric outpatients, referred for neuropsychological assessment (n=29), was used.
Correlations between the NPI-Q and the RMBPC's Depression- and Disruptive behaviour subscales were relatively high. No relationship was found between the NPI-Q and the RMBPC's Memory related behavioural changes subscale, nor with the IQCODE-N and the CST-20. Informant ratings on the NPI-Q depression-item were related to patient ratings on the GDS-15, especially when patients were relatively mildly, cognitively impaired. Caregiver distress was highly associated with NPI-Q symptom assessment.
Conclusion: the Dutch NPI-Q form seems promising as a valid, informant-based assessment of neuropsychiatric symptoms of dementia and associated caregiver distress in routine clinical practice.

Key words: Neuropsychiatric Inventory (NPI), NPI-Q, dementia, clinical assessment, validity

INTRODUCTION

The Neuropsychiatric Inventory (NPI)[1] is a frequently used clinical instrument in scientific studies of behavioural and psychological symptoms in dementia. Twelve symptom domains are assessed, based on interviews with patients' primary caregivers. A report on the Dutch version was published recently.[2] Meanwhile, the NPI has been adjusted for routine assessments in clinical practice; the so-called NPI-Questionnaire (NPI-Q).[3] This version comprises the same symptoms as the NPI. However, the questionnaire is filled out by patients' primary caregivers, which can save time. The NPI-Q's[3,4] reliability and validity were positively assessed in two foreign studies. Here, we will discuss some validity aspects of the Dutch version.

METHODS

This study regards correlations between the NPI-Q and other clinical instruments used in routine dementia assessments, specifically the Revised behavioural problems Checklist (RMBPC),[5,6] Cognitive Screening Test (CST-20),[7] the short form Informants' Questionnaire for Cognitive decline in the elderly (IQCODE-N)[8] and the 15-item geriatric Depression Scale (GDS)[9-11]. The hypothesis is that, in dementia study groups of elderly patients, the NPI-Q correlates more with the 'non-cognitive' items of the RMBPC and GDS than with the cognitive (sub)scales or tests.

The data were gathered from patients of the geriatric outpatient clinic of the Medisch Centrum Alkmaar, referred for neuropsychological assessment in the period of January – June 2001. Accompanying relatives filled out the NPI-Q and other questionnaires, while patients were neuropsychologically assessed and filled out the GDS elsewhere. Seriously cognitively impaired patients were assisted in filling out the GDS, i.e., when in doubt, assistance was offered by reading questions together and if necessary their essence was clarified. This happened in approximately one third of all cases. Only full protocols were analysed (n=29). Reasons to divert from standard testing protocols were, among others; patients of young age, patients coming in for re-assessment and only completing essential tasks again, patients with visual and hearing impairments or the occasional patient who was 'too ill'/'badly motivated'/'emotionally unsettled'. In these cases assessments were stopped.

In approximately 5 – 10% of all cases, the primary caregivers did not understand (one of the) questionnaires full well or we noticed too late that items had been skipped. Very rarely, primary caregivers found the questionnaires too big a burden. The average

age of the 17 male and 12 female patients was 74.8 years (sd 6.1, range 64-89).

Clinical instruments

The NPI-Q is a questionnaire completed by primary caregivers of dementia patients. It regards an assessment of the behaviour over the past month. The 12 NPI-Q items are similar to the screening questions of the NPI. The latter was translated by the authors (JdJ, MK) and, as a check, (independently) translated back into English.[2]

The symptoms to be assessed are shown in table 1.

Possible NPI-Q answers are; 'yes/no' (screening questions) and 'mild'' = score 1, 'moderate'= 2 and 'severe'= 3 (severity assessment). The minimum score is 0, the maximum 36. Unlike the NPI (maximum score 144), the NPI-Q does not assess symptom incidence. Furthermore, the NPI-Q includes the same emotional stress scale for primary caregivers as the NPI (6-point scale; 'not emotionally stressful – extremely stressful'). Completing the twelve NPI-Q questions takes about ten minutes. Foreign studies have shown that the NPI-Q is likely to produce reliable results and correlate strongly with the NPI.[3,4] Kaufer et al.[3] compared the NPI-Q and the NPI among 60 patients with dementia of the Alzheimer type. Fifteen primary caregivers filled out the NPI-Q a second time, shortly after the first time; the test-retest correlation was 0.80 for the NPI-Q total score and 0.94 for the emotional stress scale. The correlation between the NPI-Q and NPI total scores was 0.91 and it was 0.92 for the emotional stress scales of both versions. Correlations of the separate symptoms varied between 0.71 – 0.93. The differences in percentages of patients showing certain symptoms according to the NPI-Q or NPI ranged from 0% for 'Anxiety' to 10% for 'Appetite/eating behaviour' (average absolute difference was 5%).

The RMBPC is a questionnaire for relatives of dementia outpatients[6], which has been validated for the Dutch situation. It consists of 24 items (five-point scale), allocated to three subscales, based on factor analysis: Depressive behaviour, Disruptive behaviour and Memory related behavioural changes. With each question, the RMBPC also has a 4-point scale to assess primary caregivers' emotional stress.

The CST is a succinct, cognitive screening test for dementia, comprising 20 questions regarding orientation, recent memory and knowledge of historical events (score range 0-20).

Administering the CST yields accurate and valid results.[12]

The short form IQCODE-N is a self rating questionnaire for patients' primary caregivers, with which they compare patients' cognitive functioning to what it was 10 years ago. The list consists of 16 items (5-point scale). The study into the IQCODE showed close correlations between the informants' assessments, other measures

of cognitive decline and the clinical diagnosis of dementia.[13-15] The average item score internationally considered the limit value for dementia is 3.6. Considering the psychometric aspects, the Dutch short version strongly correlates with the long one, which differentiates between dementia and psychiatric patients.[8,16]

The GDS is a self-rating scale for patients, of which several (short) versions have been developed,[11] including a Dutch one.[10] The 15-item version strongly correlates with the original GDS (30 items, 'yes/no'-answers). A limit value > 4 on the 15-item version is a sensitive and rather specific reading for depression. The GDS validity among dementia patients is not undisputed.[17,18.]

The ranking correlations between the different questionnaires and cognitive tests were determined. SPSS software (version 10) was used in the analyses.

RESULTS

The NPI-Q total score averaged 7.6 (sd 7.1, range 0-28), the NPI-Q depression item 1.0 (sd 0.9, range 0-3) and the NPI-Q emotional stress scale 7.7 (sd 7.9, range 0-28). Two patients showed no neuropsychiatric symptoms on the NPI-Q (score 0) and twelve showed no depressiveness (table 1 shows a survey of all symptoms). Only 4 primary caregivers felt no emotional stress at all (score 0).

The average CST score was 15.3 (sd 3.6, range 4.5–20) and thirteen patients (41.4%) scored over 16.5, which turned out to be the optimum limit value for dementia.[19] The average GDS score was 4.1 (sd 3.2, range 0-11) and for the short form IQCODE-N it was 4.2 (sd 0.5, range 3-5). The score for the RMBPC Memory related behavioural changes scale was 11.1 (sd 4.0, range 0-18) and for the Depressed behaviour and Disruptive behaviour subscales it was 6.9 (sd 5.9, range 0-22) and 3.2 (sd 3.7, range 0-14) respectively.

Table 1. Patients with NPI-Q symptoms (n=29)

	N	%
1. Delusions	5	17
2. Hallucinations	2	7
3. Agitation/Agression	8	28
4. Depression/Dysphoria	17	59
5. Anxiety	9	31
6. Euphoria	4	14
7. Apathy	12	41
8. Disinhibition	9	31
9. Irritability	18	62
10. Aberrant motor behavior	7	24
11. Nighttime behavior disturbances	11	38
12. Appetite and eating abnormalities	14	48

Table 2. 'Spearman rank correlations NPI-Q and CST, GDS, IQCODE-N and RMBPC in elderly outpatients referred for neuropsychological assessment (n=29).'

	NPI-Q total	NPI-Q depression	NPI-Q emotional stress
CST	-0,23	-0,16	-0,08
GDS-15	0,38*	0,39*	0,36*
IQCODE-N 16	0,12	0,11	0,02
RMBPC-total	0,57**	0,46**	0,58**
RMBPC-'Cognition' (1)	0,10	0,09	0,10
RMBPC-'Depression' (2)	0,51**	0,63**	0,56**
RMBPC-'Disruptive behaviour' (3)	0,79**	0,36*	0,72**
RMBPC (2+3)	0,68**	0,60**	0,69**
NPI-Q total		0,66**	0,88**
NPI-Q depression			0,68**

**: Correlation is significant at 0.05 level, **: at 0.01 level (unilateral check).*

The biographical variables sex and age were not associated with the NPI-Q total- and depression scores, nor with the score on the emotional stress scale. The emotional stress as experienced by primary caregivers strongly correlates with their assessments of the severity of the neuropsychiatric symptoms. The NPI-Q shows a moderate to strong correlation with the RMBPC Depressed and Disruptive behaviour subscales (table 2). Of the three RMBPC subscales, the NPI-Q depression item correlates the strongest with the Depressed behaviour subscale. No correlation was found between the NPI-Q and the assessments of cognitive disorders, nor with the results of cognitive testing. A moderate, yet statistically relevant correlation was found between primary caregivers' assessments of depressive symptoms and patients' self-reporting (GDS). As GDS validity is considered to be decreasing as dementia severity increases, the correlations for two different groups were calculated: patients with a CST score under 14 ('more severe, cognitive disorders', n=12) and those scoring 14 or higher ('cognitively, relatively intact', n=17). The score matched the classic MMSE limit score 23/24 for cognitive disorders.[19] The ranking correlations between the GDS and the NPI-Q Depression in both groups were 0 (n.s.) and 0.48 (p=0.02) respectively.

DISCUSSION

This study was aimed at some validity aspects of the Dutch version of the NPI-Q, a new, succinct questionnaire for assessing neuropsychiatric symptoms in dementia. Nearly all outpatients assessed in this random sample survey showed neuropsychiatric symptoms. The correlations with other scales found support NPI-Q validity. Where the NPI-Q specifically correlates with the Depressed and Disruptive behaviour subscales of the RMBPC, it does not with the Memory related, behavioural changes subscale, nor with the short form IQCODE or the CST. These findings are an indication that, during routine outpatient assessments, valid impressions of neuropsychiatric symptoms possibly present can be obtained with the NPI-Q. One advantage over other assessment scales is that the NPI-Q might also register symptoms like hallucinations, delusions and euphoria.

The NPI-Q depression-item correlated moderately with patients' assessments on the GDS. The following explanations may play a role. It is conceivable that the two questionnaires measure something different, e.g., different aspects of depression (like 'mood' versus 'hopelessness'). Secondly, the relatively narrow scoring range (only one patient was assessed as severely depressed and 40% as not depressed) may have kept the maximum correlation low. A third explanation is that the GDS is less suitable for

measuring depressive symptoms in dementia patients.[17,18] The data seem to support this explanation: significant correlation between the NPI-Q Depression-item and the GDS was found in the patient group with relatively mild, cognitive disorders, but not in the group with severer, cognitive disorders. The patients first mentioned are probably more capable of understanding questionnaires and/or assessing how they have been feeling over the past few days. This may lead to a closer correlation with primary caregivers' assessments, compared to patients with severer, cognitive disorders. In this study, patients with severer, cognitive disorders were helped with reading and understanding the GDS questions, in an attempt to avoid comprehension problems. However, it is yet unclear whether this procedure actually boosts GDS- reliability and validity among patients cognitively more severely disturbed.

It should be noted that some psychometric aspects of the NPI-Q were assessed in a relatively small sample survey. Important other aspects, like the differentiation potential, reliability or correlation between the NPI-Q and NPI were not evaluated. Foreign studies have shown twice that the NPI-Q and NPI largely produce the same results. Ideally, the Dutch version of the NPI-Q should be compared to the NPI too. We collected data during the diagnostic phase of outpatient treatment. Repeatedly filling out several questionnaires at that moment was considered a burden. Studies for the English and Spanish versions have produced data indicating this method is likely to be reliable.[3,4.]

The NPI-Q is a new version of the NPI. Contrary to the latter, it requires no interview. The preliminary results of this study of the Dutch version indicate it is a practical, clinical instrument in getting a first impression of neuropsychiatric symptoms in dementia and the related emotional stress for primary caregivers. The NPI-Q can be obtained via the first author.

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PART B

CLINICAL IMPLICATIONS

CHAPTER 4

The emotional impact of psychiatric symptoms in dementia on partner carers. Do carer, patient and situation characteristics make a difference?

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ABSTRACT

This study aims to investigate the emotional impact of psychiatric symptoms of patients with dementia on their caregiving partners, and to explore if carer, patient and situation factors predict this emotional impact on carers.

A cross-sectional design was used. Partners of patients with slight to moderately severe dementia who live in the community (n=85) were interviewed. In a subgroup (n=58) potential predictors of emotional impact of psychiatric symptoms on carers were studied.

Agitation, irritability, apathy and disinhibition produced the highest mean emotional impact scores in carers. Besides by the neuropsychiatric symptoms themselves, the emotional impact of these symptoms on carers was predicted by sense of competence, degree of care needed by the patient and financial expenditure due to the caregiving situation.

The emotional impact of psychiatric symptoms on carers is predicted by several patient, carer and situation factors. Interventions aimed at decreasing the experienced burden of carers should therefore not only focus on the psychiatric symptoms of the patient, but also on the sense of competence of the carer and the financial burden due to the caregiving situation.

Keywords: burden, carer, dementia, emotional stress, predictors

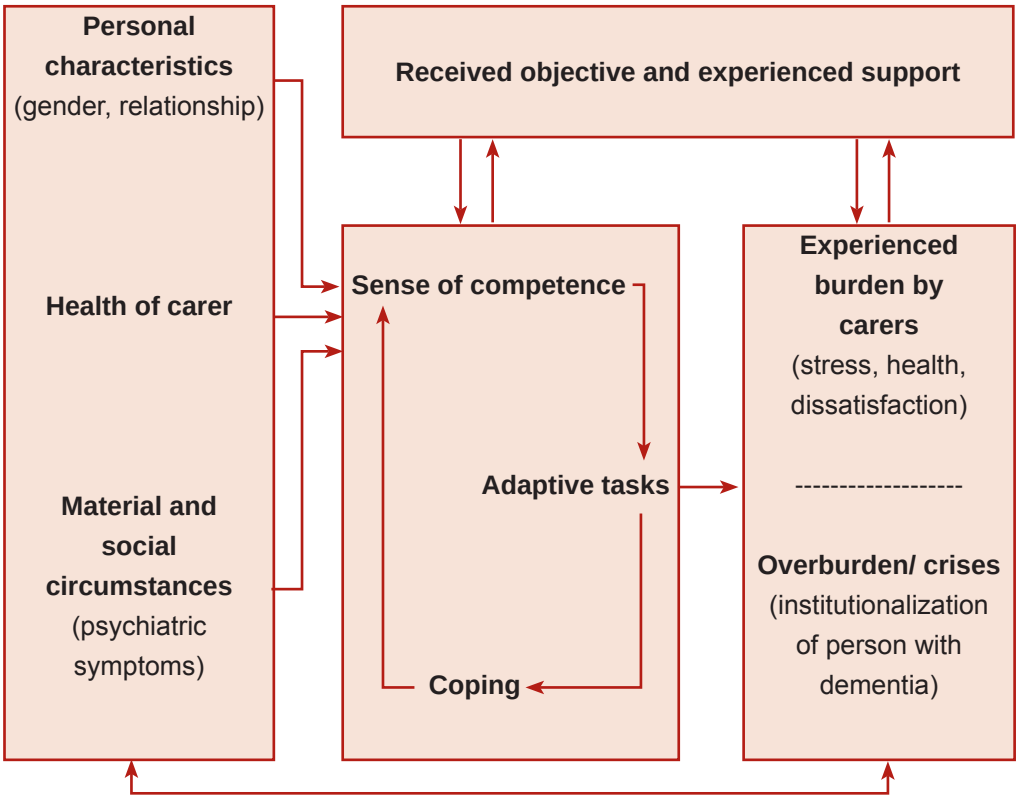
INTRODUCTION

Dementia is the most disabling psychiatric disorder in the elderly. In the Netherlands, two-thirds of the elderly people with dementia live at home and they are often cared for by spouses, children, other close relatives or acquaintances.[1] Despite the fact that many studies have reported on the negative physical, psychological and social consequences of caring for a person with dementia,[2-8] policy makers aim at keeping persons with dementia in the community as long as possible, and this is also often the wish of the patients and carers themselves. Since experiences of burden and depression in carers are major predictors of nursing home admission,[9] it would be interesting to know what specific factors determine carer burden. Insight into these determinants or predictors could be helpful in designing interventions aimed at diminishing the experienced burden by carers and could in that way perhaps lead to delayed nursing home admission. In the literature several models for carer burden are described.[10-14] In studying the factors that determine carer burden, several perspectives have been used in the literature. Some studies focus mainly on patient characteristics,[15-17] others focus on carer characteristics as well,[18-20] and some also take into account factors related to the caregiving situation.[9, 21, 22]

In this study we used the emotional impact of psychiatric symptoms of patients with dementia as a proxy marker for carer burden. The aim of this explorative study was to investigate the emotional impact of psychiatric symptoms of patients with dementia who live in the community on their caregiving partners, and to explore whether carer, patient and situation factors can predict this emotional impact on carers. As the theoretical basis of this study we used the 'Model of determinants of subjective burden of carers of persons with dementia' by Dröes c.s.[14] (see Figure 1). This model combines several aspects of determinant models with the general stress-appraisal-coping theory of Lazarus and Folkman[23] and the crisis model of Moos and Tsu.[24] Dröes et al. assume that both the person with dementia and their carer have to deal with general adaptive tasks as a consequence of the disease. Adaptive tasks for the carer are e.g.: Coping with the disabilities and psychiatric symptoms of the person with dementia, maintaining a positive self-image, an emotional balance, and social relationships. Whether these tasks lead to (over)burden, negative physical, psychological or social consequences depends mainly on the way individual carers cope with them (see also [5, 25-27]) and the sense of competence they experience as a result of this (see also [11]). The model also describes how factors such as personal characteristics, health, and material and social circumstances (including the need of the person with dementia for care, and psychiatric symptoms) (see also [5, 10, 11]), as well as received objective and experienced support

(see also [11, 21]), might influence the ways the carer copes with the adaptive tasks. In this manner individual differences in the emotional impact of dementia on carers are explained.

Figure 1. Model of deteminants of subjective burden of carers of persons with dementia by Dröes et al.[14]



METHODS

Design

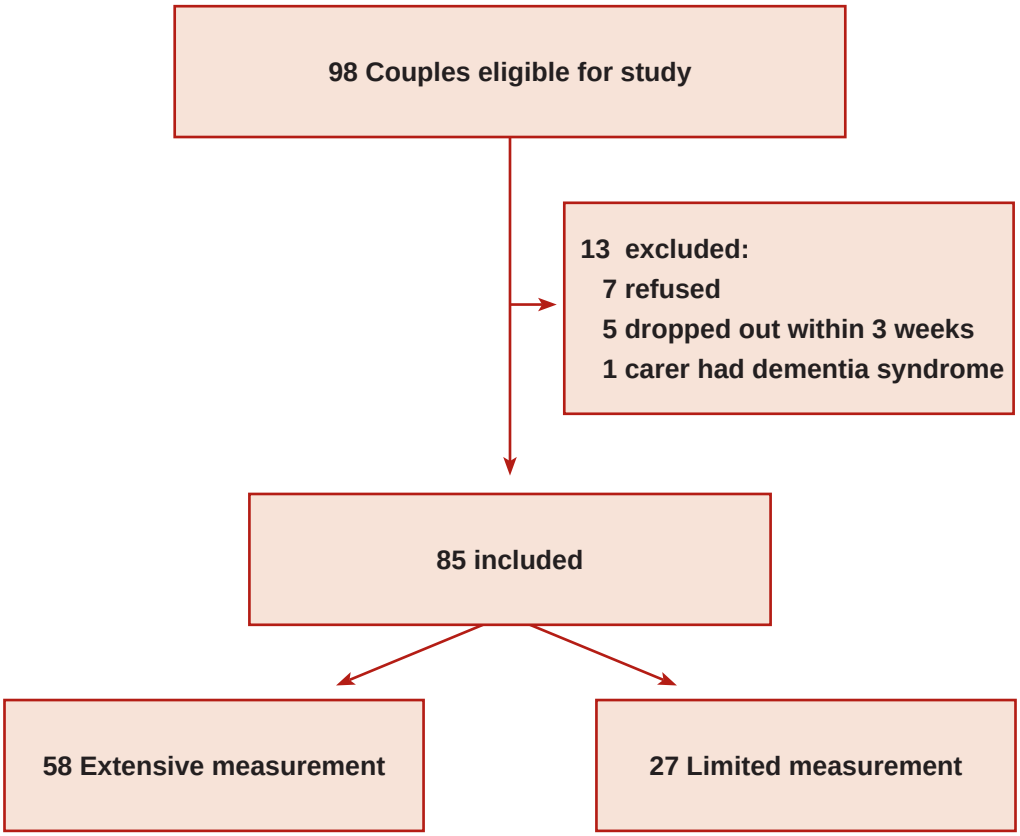
In this study we used a cross-sectional design. Between May 2000 and february 2002, partners of patients with dementia who participated in the Meeting Centres Support Programme (MCSP[28]) were interviewed at the start of the study or at the start of their participation in the programme. The interviews focused on the emotional impact they experienced from psychiatric symptoms of the person with dementia and on factors that might determine individual differences in this emotional impact on carers. In addition to carer characteristics (gender, age, education, work, coping, sense of competence), we also inventoried patient characteristics (gender, age, education, diagnosis, degree of needing care/assistance, and psychiatric symptoms) and situation characteristics (additional financial expenditure due to the caregiving situation, duration of caregiving, objective and experienced support).

Subjects

The study population was drawn from a large multicenter study on conditions for succesful implementation of Meeting Centres for persons with dementia and their carers in the Netherlands (IMO-project[29]). This study was conducted in ten meeting centres. In all recently started meeting centres (n=8) all clients that were admitted in the MCSP (patients with dementia and their carers) were asked to participate. In the two already existing meeting centres in Amsterdam new as well as current clients were asked. The reason for this was to increase the size of the study sample.

For the present study part of this study population was included, i.e. partners of persons with dementia and the persons with dementia they cared for. Of the 98 couples that were eligible, 13 (13%) were excluded (see Figure 2), while 85 (87%) participated in the study, after informed consent was obtained. In the new participating couples (n=58) all information was gathered as described above (see design). In the couples (n=27) that already participated in the MCSP only background features were collected and not the other potential determinants of burden (sense of competence, coping, objective and experienced support).

Figure 2. Flow chart of the study population (carers and the persons with dementia they care for).



Setting

All participants in the study (carers and patients) attended the MCSP. This is a comprehensive, combined programme for patients with dementia and their carers, that is organized in general community centres and centres for the elderly. It offers information and emotional, social and practical support to people with dementia and their informal carers by means of a social club for the person with dementia on three days a week, and eight to ten informative meetings and a bi-weekly long-term discussion group for the carers. Besides the support mentioned, both patient and carer can utilize the weekly consulting hour and participate in social festivities and excursions. Support and case-management are supplied by a small professional staff (f.i. a psychologist, an activity therapist and a nursing assistant) that cooperates according to a collaboration protocol with the local professional care and welfare services that are involved with persons with

dementia, f.i. the general practitioners, community work, home care, and the Regional Community Mental Health Care Organization.

The content of the programme, the applied support strategies and the research into the effectiveness of the support offered are described elsewhere in more detail.[28-31] Theoretically the program is based on the so-called Adaptation-coping model[32-34] (see also [23,24]) and the Model of determinants of subjective burden of carers of persons with dementia.[14] Both the patient with dementia and his carer are supported in coping with the adaptive tasks they encounter as a consequence of the dementia. Examples are: coping with disabilities, maintaining an emotional balance, preserving a positive self image, developing an adequate care relationship with professional carers, maintaining social relationships and preparing for an uncertain future.

Instruments and procedures

Carer measures

The emotional impact of psychiatric symptoms of the person with dementia on the carer was measured with the Dutch version of the NeuroPsychiatric Inventory Distress Scale or NPI-D[35] that is part of the NeuroPsychiatric Inventory or NPI. [36] In an interview the carers were asked to rate on a scale from 0 (not at all distressing) to 5 (extremely distressing), how distressing they consider each of the 12 psychiatric symptoms that are described in the NPI. The emotional impact of psychiatric symptoms is considered low when NPI-D score=0-1, medium when NPI-D score=2-3 and high when NPI-D score=4-5.[35] In this study all interviews were conducted by independent, trained graduate students. During the interviews also sociodemographic and situational variables (age, gender, education, duration of caregiving, etc.) were registered.

In a subgroup of carers (n=58) the interviews consisted of more elaborate measurements. As (potential) determinants of feelings of burden the following aspects were measured: sense of competence, coping strategies, and objective and experienced support. These were assessed by means of the modified version of the Sense of Competence Scale[37] (α= 0.79), the Jalowiec Coping Scale[38, 39] (α varies from 0.64 to 0.97), the Adapted Use of Services Checklist,[40, 41] and the Social Support List[42] (α=0.87) respectively.

As it is not inconceivable that a particular order in tests and questionnaires may cause a systematic (group) effect, all tests and questionnaires were carried out on the basis of a so-called balanced incomplete block design.[43]

Patient measures

Sociodemographic variables (age, gender, education) were registered during an interview with the carer. Information regarding the diagnosis and type of dementia was provided

according to the DSM-IV criteria[44] and the Standard of the Dutch Society of General Practitioners,[45] by the general practitioner or attending physician (f.i. a neurologist at the memory clinic). The severity of dementia was assessed with the Dutch version of Reisberg's Global Deterioration Scale[46, 47] (α=0.90). The 'degree of needing care/ assistance' was assessed with subscale 1 of the Assessment Scale for Elderly Patients[48] (α=0.94) by the supervisor of the meeting centre. Neuropsychiatric symptoms were measured with the Dutch version of the NeuroPsychiatric Inventory[36, 49, 50] (α=0.88) during the interview with the carer. The presence of 12 neuropsychiatric symptoms was assessed, and if present, the frequency (range 1 to 4) and severity (range 1 to 3) of the symptom was measured. For each symptom a NPI score was calculated by multiplying the frequency and severity scores (range 1 to 12). The total NPI score was calculated by adding the 12 symptom scores (range 0-144).

Data analysis

For the analysis of the data we used the SPSS-Windows 10.1 programme. To determine whether the ten meeting centres could be treated as one homogeneous group in the analysis, we first tested with the Kruskal Wallis test if they differed significantly on variables that, according to the literature, were likely to interfere with the relationship between psychiatric symptoms of the person with dementia and the emotional impact on the carer, i.e. severity of dementia and sense of competence of the carer.

The Cronbach's alpha coefficient was determined to assess the internal consistency of the NPI.

To inventory the prevalence of psychiatric symptoms in persons with dementia and their emotional impact on carers, mean scores and standard deviations were calculated (n=85) for each symptom.

Subsequently, the relationship between psychiatric symptoms (frequency, severity, frequency times severity) and their emotional impact on carers was tested with Pearson's correlation.

Hierarchical multiple lineair regression analyses (with a stepwise selection strategy, using the F-statistic with p=0.05 as the criterion for selection) were performed to identify which carer, patient and situation factors besides psychiatric symptoms, predict the emotional impact of the psychiatric symptoms on carers (n=58). Residual analyses were performed to search for violations of necessary assumptions.

All tests were two-tailed and we used a 5% significance level.

RESULTS

There were no significant differences between the different meeting centres with respect to severity of dementia (χ^2=8.47, df=9, p=0.48) and sense of competence (χ^2=6.05, df=7, p=0.53). We therefore treated the respondents as one homogeneous group.

Table 1 presents characteristics of the total group of carers and patients (n=85), and the subgroup who participated in the extensive measurement (n=58). These groups were comparable on most characteristics. As expected, the median of duration of caregiving was shorter in the extensive measurement group (which consisted of new clients). According to the general practitioner or attending physician, the diagnosis of dementia met the criteria of the DSM-IV or the Standard of the Dutch Society of General Practitioners in 82.4% of all patients, in 8.2% these criteria were not met (some of these patients had severe memory complaints but not a dementia syndrome, others had an amnestic syndrome or other diagnosis (f.i. depression)), and in 9.4% this information was missing. For the persons with other diagnosis than dementia at baseline, the diagnosis of dementia was confirmed during the experimental phase.

All but two patients showed psychiatric symptoms. Table 2 gives an overview of these symptoms that were observed by the carers in the patients (n=83) and their mean emotional impact on carers. Cronbach's α was calculated on data from all respondents and was 0.62 for NPI total score, 0.64 for NPI frequency, 0.64 for NPI severity, and 0.71 for NPI emotional impact.

Apathy and depression were the most common symptoms, being present in 63 and 52 patients respectively, and these symptoms have a high mean emotional impact on carers compared to other symptoms in our study as do agitation, irritability, and disinhibition.

The emotional impact of psychiatric symptoms on carers is significantly related to the NPI total score (r=0.83, $p < 0.01$), frequency of symptoms (r=0.83, $p < 0.01$), and severity of symptoms (r=0.89, $p < 0.01$).

Table 1. Carer and patient characteristics at baseline

Characteristics	Total group (n=85)	Extensive measurement group (n=58)
Carer		
Gender		
male	25 (29.4%)	17 (29.3%)
female	60 (70.6%)	41 (70.7%)
Age	71.1 (sd 8.8)	72.0 (sd 8,1)
Education		
lower (vocational) education	39 (45.9%)	29 (50.0%)
secondary education	34 (40.0%)	23 (39.7%)
higher (vocational) education	12 (14.1%)	6 (10.3%)
Work		
paid work	5 (5.9%)	3 (5.2%)
other	80 (94.1%)	55 (94.8%)
Duration caregiving (in months)	36 (median)	24 (median)
range	5-156	5-120
Additional financial expenditures		
yes	48 (56.5%)	31 (53.4%)
no	37 (43.5%)	27 (46.6%)
Limited in activities by this:	5 (5.9%)	3 (5.2%)
Patient		
Gender		
male	62 (72.9%)	42 (72.4%)
female	23 (27.1%)	16 (27.6%)
Age	73.9 (sd 7,6)	75.0 (sd 6,3)
Education		
lower (vocational) education	30 (35.3%)	24 (41.4%)
secondary education	40 (47.1%)	26 (44.8%)
higher (vocational) education	15 (17.6%)	8 (13.8%)
Diagnosis		
Alzheimer's disease/Vascular Dementia	60 (70.6%)	32 (55.2%)
Other types of dementia	14 (16.5%)	18 (31.0%)
Amnestic Syndrome*	1 (1.2%)	1 (1.7%)
Severe memory complaints*	2 (2.4%)	2 (3.5%)
Depression*	2 (2.4%)	1 (1.7%)
Unknown	6 (7.1%)	4 (6.9%)
Severity of dementia (GDS)		
Very mild cognitive decline	12 (14.1%)	9 (15.5%)
Mild cognitive decline	17 (20.0%)	15 (25.4%)
Moderate cognitive decline	25 (29.4%)	16 (27.6%)
Moderately severe decline	22 (25.9%)	15 (25.9%)
Severe cognitive decline	5 (5.9%)	3 (5.2%)
Unknown	4 (4.7%)	-
Degree of needing care/assistance (0-46)	NA	7.6 (sd 5.1)

** These persons were included despite different diagnoses at baseline because during the experimental phase the diagnosis of dementia was confirmed.*
NA: not available GDS = Global Deterioration Scale[46]

Table 2. Prevalence of psychiatric symptoms in persons with dementia (n=83) and their mean emotional impact on carers.

	n	Frequency Mean (SD)	Severity Mean (SD)	Severity x freq. Mean (SD)	Emotional impact Mean (SD)
Delusions	27	2.6 (1.2)	1.7 (0.8)	4.5 (3.2)	3.0 (1.4)
Hallucinations	11	2.7 (1.1)	1.6 (0.7)	4.7 (3.3)	2.4 (1.7)
Agitation/Aggression	41	2.5 (1.0)	1.9 (0.7)	4.9 (3.1)	3.3 (1.1)
Depression/Dysphoria	52	2.1 (1.1)	1.5 (0.7)	3.3 (2.6)	2.9 (1.3)
Anxiety	42	2.3 (1.1)	1.6 (0.7)	3.7 (2.7)	2.6 (1.4)
Euphoria	19	1.9 (1.1)	1.3 (0.6)	2.7 (2.5)	1.8 (1.5)
Apathy	63	3.4 (0.9)	1.8 (0.7)	6.2 (3.3)	3.1 (0.9)
Disinhibition	34	2.1 (1.1)	1.6 (0.7)	3.6 (3.3)	3.1 (1.4)
Irritability	38	2.6 (1.1)	1.6 (0.7)	4.4 (3.4)	3.3 (1.2)
Aberrant motor behavior	42	3.3 (0.9)	1.8 (0.7)	6.2 (3.1)	2.5 (1.3)
Nighttime behavior disturbances	15	3.0 (0.9)	1.5 (0.6)	4.5 (2.8)	2.9 (1.1)
Appetite and eating abnormalities	50	3.2 (1.1)	1.6 (0.7)	5.2 (3.1)	1.8 (1.6)
NPI total scores	83	14.0 (7.3)	8.6 (4.6)	24.4 (15.2)	14.4 (8.9)

NPI = NeuroPsychiatric Inventory

Table 3 contains the data on potential determinants of burden c.q. emotional impact of psychiatric symptoms, i.e. sense of competence, coping strategies, and objective and experienced support (n=58).

Table 3. Other potential determinants of emotional impact of psychiatric symptoms on carers.

	Mean (SD)
Sense of Competence (total) (28-108)	80.3 (11.0)
Coping (total) (0-180)	68.4 (16.9)
Objective support	
Number of institutions providing emotional support (0-14)	0.4 (0.7)
Number of institutions providing practical support (0-14)	1.1 (0.9)
Experienced support	
Satisfaction with support from institutions (0-2)	1.8 (0.4)
Social support (total) (4-48)	27.9 (5.6)

The results of the multiple regression analyses are presented in Table 4. Variables were entered in blocks following the model of determinants of carer burden of Dröes c.s.[14].

Table 4. Results of hierarchical multiple regression analyses: predictors of emotional impact of psychiatric symtoms on carers.

	Standardized Betas[a]
Block 1	
Neuropsychiatric symptoms (NPI total)	0.73 **
Block 2	
Characteristics and circumstances	
gender carer	ns
age carer	ns
education carer (1=low)	ns
paid work	ns
duration caregiving	ns
additional financial expenditures (1=yes)	0.21 *
Alzheimer's disease (1=yes)	ns
degree of needing care/assistance	-0.38 **
Block 3	
Competence and coping	
sense of competence	-0.29 *
coping total	ns
Block 4	
Objective and subjective support	
number of institutions providing emotional support	ns
number of institutions providing practical support	ns
satisfaction with support of institutes	ns
social support (SSL)	ns
Adjusted R^2	0.70

[a] *Standardized betas in final model*

** $p \leq 0.05$; ** $p \leq 0.01$*

The psychiatric symptoms observed by the carers in the persons with dementia proved a major predictor of the experienced emotional impact. It explained 52% of the variance. Other predictors of emotional impact of psychiatric symptoms were sense of competence of the carer, the amount of care needed by the patient and financial expenditure due to the caregiving situation. The emotional impact of psychiatric symptoms was higher in carers that had a low sense of competence or had more

financial expenditure or of whom the persons with dementia needed less care. The final regression model explained 70% of the variance in emotional impact of psychiatric symptoms on carers.

DISCUSSION

The emotional impact of psychiatric symptoms of people with dementia on their carers was the main interest in this study. Our study population consisted of partners of persons with (mainly) slight to moderately severe dementia. The most common psychiatric symptoms in the persons with dementia were apathy and depression, and carers experienced these symptoms, together with agitation and irritability, as the most distressing. This confirms what has been found in other (population) studies.[15, 35, 51-55]

Furthermore, our study examined predictors of the emotional impact of psychiatric symptoms on carers. As expected, the emotional impact was mainly predicted by the frequency and severity of the psychiatric symptoms themselves. However, almost 50 percent of the variance in emotional impact could not be explained by the psychiatric symptoms as such. This is in line with the outcome of a recent review in which the percentage of variance in carer burden scores that could be explained by behavioural and psychological symptoms varied from 5.6% to 71%.[56] Behavioural and psychological symptoms were the strongest predictors of burden in only half of the studies on which these analyses were based. Other predictors found in this review were caregiver factors (age, gender, education), patient factors (gender, functional impairment and attachment-style) and situation factors (social support).

In our explorative study, other predictors of emotional impact were characteristics of the carer (sense of competence) and patient and situation characteristics (degree of care needed by patient and financial expenditure due to the caregiving situation respectively).

The lower the sense of competence, the higher the emotional impact on carers. This is in line with our expectations based on the Model of determinants of subjective burden of carers.[14] The sense of competence reflects the perceived ability by the carer to cope with the task of caring for the person with dementia.

The degree of care needed by persons with dementia was inversely related to the emotional impact of psychiatric symptoms, which suggest that the emotional impact of behaviour changes is largest in the early phases of the disease (see also [57]). An earlier study found the same association.[7] Behaviour problems have often been found to be related to carer burden or institutionalization.[14, 16, 19, 21, 58, 59] Later stages of dementia may

also be associated with less emotional impact of psychiatric symptoms because carers may have learned to cope with the dementia over time.[60]

More financial expenditure due to caregiving, such as travelling costs and costs for the use of community-based services by the person with dementia, proved to be related to higher emotional impact on carers. More service use has been related to higher burden on carers in other studies as well.[7, 57, 61]

Though some of the determinants of carer burden in the model by Dröes et al[14] proved to be related to higher emotional impact on carers, that is material and social circumstances and sense of competence, we did not find evidence in our study that other potential determinants such as coping strategies or experienced support influence the emotional impact of psychiatric symptoms on carers.

Some limitations should be noted in interpreting the results of this explorative study. The carers involved in our study were all partners of patients with dementia who participated in the Meeting Centres Support Programme.[29] Although the patients they care for live in the community, this group is perhaps not representative of all partner carers in the community. This means that we should be cautious in generalizing the study outcome to all partner carers of persons with dementia living in the community.

Furthermore, because only partners of dementia patients were included this resulted in a reduction of the sample size. The reason to focus our study on partner carers was that several studies reported differences in (correlates with) burden and institutionalization between spouse carers and other carers.[5, 16, 19, 62, 63] As spouse carers were the main group in the MCSP we opted for this group.

A final limitation is the cross-sectional study design, which hampers firm conclusions on the causality of relations. Because of these limitations it must be emphasized that our findings need to be viewed with caution. In future studies, longitudinal research is recommended and also a larger and preferably random sample. The latter would allow studying predictors of the emotional impact of separate psychiatric symptoms such as agitation/aggression, irritability and apathy, that proved very distressing for the partners in our study and that other studies found to be very distressing for carers in general as well.[35, 64]

The results of our study support the importance of combined interventions for persons with dementia and their carers in reducing the emotional impact of psychiatric symptoms on carers. These interventions should not only be aimed at the psychiatric symptoms themselves f.i. by psychosocial or pharmacological therapies for the persons with dementia, but also at increasing the sense of competence of the carers. For example by providing them with timely support to cope with the consequences of dementia (see also [65]) and to use adapting management strategies (see [66]). The MCSP

has been proven successful in this respect.[28, 30, 31]

Also, situational factors such as financial burden due to the caregiving situation should not be forgotten in supporting carers and patients in the community, because they can increase the emotional burden of carers.

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CHAPTER 5

Reasons for psychiatric consultation referrals in Dutch nursing home patients with dementia. A comparison with normative data on prevalence of neuropsychiatric symptoms

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ABSTRACT

OBJECTIVE: To study psychiatric consultation referrals of nursing home patients with dementia and to compare referral reasons with normative data on prevalence of neuropsychiatric symptoms.

METHODS: This is part of a cross-sectional study of 787 patients residing in 14 nursing homes in the Netherlands. Nursing homes physicians (NHP) noted the primary reasons for psychiatric consultation according to the Neuropsychiatric Inventory items and two extra domains. Patients were subsequently assessed by an old-age psychiatrist. Eligible patients were those that had dementia. Reasons for referral were compared with independent data on prevalence of neuropsychiatric symptoms in nursing home patients with dementia.

RESULTS: A total of 325/787 (41.3%) patients had dementia. Agitation, disinhibition and aberrant motor behaviour were frequent reasons for referral (>25%). Psychotic symptoms, apathy and eating behaviour changes were infrequent reasons (< 10%) for seeking consultation. Agitation and disinhibition were more often primary reasons for consultation than would have been expected based on normative prevalence estimates of these symptoms. In contrast, delusions, euphoria, apathy, irritability and eating behaviour changes were less often reasons for referral compared with prevalence estimates.

CONCLUSIONS: This study is the first to examine psychiatric consultation for dementia patients in Dutch nursing home. Large differences exist between referral reasons and normative data on symptom prevalence. Specialized mental health service was provided for the agitated and disinhibited patient in particular. Chances are that this is at the expense of the apathetic, retarded and quietly 'not causing any trouble' patient.

Key Words: Neuropsychiatric symptoms, dementia, nursing home, psychiatric consultation

INTRODUCTION

Nursing home staff may seek psychiatric consultation for a variety of reasons. Usually, there is a need for receiving diagnostic and medication recommendations, advice on nonpharmacologic management techniques, staff support, and dealing with staff stress and family conflicts.[1] Reasons for consultation are distributed widely across diagnostic groups and may be relatively weak predictors of psychiatric diagnoses.[2,3] Up until now no study examined primary reasons for psychiatric consultation in nursing home patients with dementia and compared referrals to normative data on prevalence estimates of neuropsychiatric symptoms.

Prevalence estimates of psychiatric symptoms in nursing home patients with dementia range from 76-94%.[4,5,6] While age and impairment of Activities of Daily Living (ADL) predict not receiving treatment from a mental health professional,[7] depression, psychosis and agitation are positively associated with having received treatment.[2,7,8,3] Notably, nursing home staff often fails to recognize depression.[9,3]

There is no comprehensive classification system for liaison psychiatry. Formal diagnostic classification systems already have been used in some studies undertaken in the General Hospital.[10,11] However, these systems may not be useful for classifying nursing home referrals. Dementia patients referred to a mental health care specialist are very likely to have (neuro)psychiatric symptoms. Behavioural rating scales can be used for measuring these symptoms. One such a scale is the Neuropsychiatric Inventory (NPI),[12] a well-known and widely used measure of neuropsychiatric symptoms in dementia.

This study evaluates psychiatric consultation referrals of Dutch nursing home patients with dementia. To our knowledge this is the first time reasons for psychiatric consultation were compared with independent prevalence estimates of neuropsychiatric symptoms in a large sample of nursing home patients.

METHODS

Study Design

This is a cross-sectional study. Resident nursing home physicians (NHP) selected patients for whom they sought psychiatric consultation and systematically noted primary reasons for referral. Subsequently, an old-age psychiatrist clinically interviewed and diagnosed patients within the nursing home setting. Referral reasons for dementia patients were compared with patient characteristics and normative data on neuropsychiatric symptoms.

Participants

Fourteen nursing homes in the greater region of Amsterdam, The Netherlands were invited to participate. All accepted. The nursing homes had specialized psychogeriatric care units and somatic rehabilitation units. From June 1999 till September 2003 nursing homes were regularly visited once every 4 – 6 weeks by a senior old-age psychiatrist (MK) for routine psychiatric consultation services. NHP's were already familiar with the psychiatric consultation model during a couple of years prior to the study. Dutch nursing homes employ physicians who have completed a two year specialist training program, including some aspects of geriatric medicine and psychiatry, to become a qualified NHP.

Eligible patients were those receiving regular nursing home care and having a diagnosis of dementia established after clinical interview by the consulting psychiatrist.

Procedures and Assessment

NHP's were asked to state what the reasons for psychiatric referral were. Any of 12 neuropsychiatric symptoms as described in the NPI were used to elicit the referral reason. Several symptoms were allowed for. So, the NPI served as a checklist in this study and not as an interview based assessment. In addition, two optional items were included in the checklist based on our previous experience with the NPI in the nursing home setting: 'Demanding behaviour', defined as an inappropriate act (dependent, regressive behaviour) to get things done from the staff. The second item was 'Other indication', e.g. referral for neuropsychiatric assessment and advice on transferring patients from one setting to another. The original NPI requires an interview with a knowledgeable informant.[12,13] The scale consists of 12 symptom domains: Delusions, Hallucinations, Agitation/Aggression, Depression, Anxiety, Euphoria, Apathy, Disinhibition, Irritability, Aberrant motor behaviours, Abnormal sleep and Eating behaviours.

Psychiatric assessment consisted of a clinical interview by an experienced old age psychiatrist who made a diagnosis of dementia based on all available information. Diagnosis by the research psychiatrist was deemed important as some patients enter the nursing home without a proper psychiatric assessment of dementia, or as dementia develops in some patients during nursing home stay without being diagnosed. Dementia subtype classification was done according to the NINCDS-ADRDA criteria for Alzheimer's Disease (AD),[14] NINDS-AIREN criteria for Vascular Dementia (VaD), [15] criteria for Dementia with Lewy bodies and Dementia in Parkinson's Disease (DLB/PDD),[16] and criteria for Frontotemporal Dementia (FTD).[17] The subgroup of 'Other dementia' consisted of patients with mixed AD/VaD type dementias.

Neuropsychiatric symptoms reference data

The WAALBED study provides normative data on prevalence of neuropsychiatric symptoms in nursing home patients with dementia.[6] In short, the WAALBED study is set in the Eastern, Northern and Southern parts of the Netherlands. A total of 1322 resident patients aged 83 years (SD 8.1), male-female ratio 20/80, from 27 nursing homes were assessed with the NPI (Nursing Home version).[6] Standard NPI-NH procedures were used. In this study we compared consultation referrals with independent normative data using conservative prevalence estimates (WAALBED NPI scores > 3: e.g. frequency 1 x severity 3).

Statistical analysis

Parametric or nonparametric tests were used where deemed appropriate. Chi-square test was used to examine the associations between referral reasons, patients characteristics and prevalence of neuropsychiatric symptoms in nursing home dementia patients. A goodness of fit analysis was performed based on percentage scores from the WAALBED data. Percentages were compared with outcomes in this study (Chi-square test). Data were analyzed with SPSS, version 10.

RESULTS

A total of 825 patients were consecutively referred for consultation. Of these, 38 patients were excluded from the analyses because of missing data and 462 were ineligible as no dementia was diagnosed upon clinical examination. Of the remaining 325 patients 2% were day care patients. The majority of patients were female (59.7%). Male patients were slightly younger than female patients; average age 80.5 (SD 7.5) and 83.2 (SD 7.5) respectively, t-test 3.2, df: 318, P=.002.

Dementia typology

Of the patients with dementia, 33% had Alzheimer's disease, 20% Vascular Dementia, 6.5% Dementia with Lewy Bodies/Parkinson's Disease Dementia, 6% Fronto-temporal dementia syndromes and 34.5% Other dementias, mostly of mixed degenerative and vascular aetiology.

Referral reasons

NHP often sought psychiatric consultation for patients with troublesome behaviours as indicated by frequent referrals for Agitation, Disinhibition and Aberrant motor behaviour (>25%). Depressive symptoms and anxiety were often reason for referral too. Psychotic symptoms, Euphoria, Apathy, Eating behaviour changes and Demanding behaviours were infrequent reasons (< 10%) for seeking consultation.

Correlates of Referrals

Disinhibited behaviour was more often reason for referral in younger patients compared with older patients (Chi^2 10.0, df: 2, P = .007). Agitation was more often reason for referral in male patients compared with female patients OR 3.5 (CI: 2.2-5.6). Anxiety OR 1.9 (CI: 1.0-3.5), Aimless repetitive behaviour OR 2.9 (CI: 1.6-5.1) and Other indications OR 3.7 (CI: 1.5-9.1) were more often reason for referral in female patients compared with male patients.

Referrals and prevalence of neuropsychiatric symptoms in dementia

Reasons for referral were compared with independent prevalence data on neuropsychiatric symptoms in Dutch nursing home patients with dementia (table 1).[6] A total of 7/12 NPI based primary reasons for psychiatric consultation differed significantly from WAALBED data: Agitation and Disinhibition were more often primary reasons for consultation compared to prevalence estimates. On the other hand, Delusions, Euphoria, Apathy, Irritability and Eating behaviour changes were infrequent reasons for

consultation compared to prevalence estimates.

Table 1. Reasons for psychiatric consultation in dementia patients (n=325) compared to prevalence estimates of neuropsychiatric symptoms in dutch nursing home patients with dementia (n=1322)

NPI items	Reasons Psychiatric consultation	Prevalence NPI FxE score > 3	Chi²	P-value
Delusions	6.8	14.6	160	000
Hallucinations	7.4	7.6	0.0	.884
Agitation/Agression	38.3	31.4	6.9	.009
Depression	19.4	20.0	0.1	.782
Anxiety	18.5	20.7	1.0	.319
Euphoria	0.6	7.0	20.4	.000
Apathy	4.0	33.7	128.3	.000
Disinhibition	26.5	19.9	8.8	.003
Irritability	13.9	33.6	56.8	.000
Aberrant motor	25.6	29.0	1.9	.169
Abnorm. sleep	13.3	12.0	0.5	.495
Eating abnorm.	3.1	23.7	76.4	.000
Demand. beh.	4.0	NA	NA	NA
Other indic.	10.8	NA	NA	NA

(percentages are shown in table)

DISCUSSION

This study examined psychiatric consultation in Dutch nursing homes patients with dementia and compared reasons for referral with prevalence estimates of neuropsychiatric symptoms. Agitation was the primary reason for calling in a consulting psychiatrist in almost 40% of patients, while hallucinations, delusions and also apathy made up less than 10%. Hence, although dementia is characterized by different neuropsychiatric symptoms, chances are high psychiatric services are provided for 'difficult' behaviours but low for other behaviours that are generally considered less troublesome.

These data are relevant for gaining a better understanding of the discrepancies that exist between actual prevalence of neuropsychiatric symptoms in nursing home patients and reasons for calling in psychiatric services, thereby highlighting the risk of underdiagnosis of potentially important neuropsychiatric symptoms. Findings are of particular importance considering the fact that most Dutch nursing homes employ resident physicians and psychologists. Apparently, not all disturbing behaviours are successfully managed by nursing home staff, nor are less disturbing behavioural changes brought to the attention of a consulting psychiatrist. So, many patients that may need specialized mental health care do not get it. Educating staff about the wide range of behavioural changes in dementia and about the importance of psychiatric expertise in diagnosing and treating so-called less troublesome behaviours may be warranted.

Our findings are consistent with observations made in other countries.[2,7] In a study that included nursing home patients of which 36% had dementia, the most frequently observed reason for referral was behavioural problems (49%), followed by mood-related symptoms (35%), psychotic features (16%) and unexplained or problematic physical signs (12%).[2] That study did not specify apathy as a separate behavioural change category. An Italian study in residential care facilities showed that psychiatric referrals were associated with symptoms of depression (17.2%), psychosis (14%), agitation (34.8%), aggression (23.5%) and sleep disturbances (6.8%).[3] A large scale study showed that nursing home residents who stole, hurt themselves, exposed themselves or hallucinated were more likely to receiving specialist mental health services.[7] Behaviours considered less disruptive (e.g. forgetting events, being drowsy, dull) were related to lower treatment rates. All of the above mentioned studies used different registration methods for psychiatric referrals. Differences between settings and methodologies used limit direct comparisons between studies. Nevertheless, our findings show a referral pattern similar to that found by others. Contrary to previous

studies the procedures used in this study made it possible to compare referrals with independent prevalence estimates of neuropsychiatric symptoms in nursing home patients with dementia.

The pattern of referrals in this study was very different from the picture that emerges from the WAALBED neuropsychiatric symptoms prevalence study.[6] Differences between settings may explain diverging results to some extend. While our study included nursing home inpatients and a small percentage of day care patients, the WAALBED study included inpatients only. Though prevalence of neuropsychiatric symptoms may depend on the study sample, the inclusion of only a few day care patients in this study is unlikely to have had a major impact on results and can therefore not explain significant differences between studies. While in this study NHP's referred patients for psychiatric consultation, licensed vocational nurses assessed neuropsychiatric symptoms in the WAALBED study. WAALBED outcomes are considered valid estimates of neuropsychiatric symptoms in dementia. No data on NPI based psychiatric referrals are available in the Netherlands. We found that disturbing behaviours are the primary reason for psychiatric consultation. Very few patients with primarily delusions, apathy, euphoria and changes in eating behaviour were referred compared to prevalence estimates. Apathy may be considered a nondisturbing behaviour in the nursing home setting. However, others have highlighted the importance of apathy as a predictor of the quality of the (marital) relationship between patient and caregiver.[18] It is possible that nursing home staff interpret some behavioural changes as primary cognitive dysfunctions that do not need psychiatric treatment, e.g. delusions versus memory impairment and eating behaviour versus eating apraxia. Also, NHP's may treat mild hallucinations themselves, again without referring the patient. Dutch nursing home physicians have some specialist training in both geriatric medicine and psychiatry. The national association of NHP's published a 'problem behaviours' guideline. Therefore, referral patterns to consultant psychiatrists might differ importantly from referrals made by general practitioners in other countries. Overall, our results show that reasons for psychiatric referral and prevalence of neuropsychiatric symptoms differ. Future research should address the question why these differences exist.

This study has several limitations that need to be discussed. This is an observational study and it does not allow for conclusions on cause and effect. Secondly, selection bias may threaten validity of the results. Referring physicians used the NPI as a checklist and scored primary reasons for consultation. It means that they often chose symptoms that they felt needed attention most. It does not imply that other symptoms were not present at all. Although this procedure enabled us to mimic psychiatric consultation as it happens in everyday clinical practice, it also means that our data on referrals are

not exactly the same as estimates of actual symptom prevalence. Nevertheless, our findings are consistent with those of others,[2,3,7,9,19] which may imply that by and large validity is not challenged.

Strong points of this study are the large number of patients included, the use of a standardized checklist for referral reasons based on a validated neuropsychiatric rating scale and the clinical assessment of each patient by an experienced old age psychiatrist.

This study is the first to examine psychiatric referrals in Dutch nursing home patients with dementia. It offers a clear picture of the most important reasons to call in a consulting psychiatrist. Large differences exist between referral reasons and estimated symptom prevalence. Agitation and disinhibition are much more likely to be the primary reason for referral compared to other symptoms such as apathy. The latter is probably under diagnosed and not brought to the attention of the consulting psychiatrist. To put it another way: the consulting psychiatrist may see a lot of patients but he certainly does not see all with neuropsychiatric symptoms. Chances are that this situation continues at the expense of the apathetic, retarded and quietly ‘not causing any trouble’ patient.

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PART C

OUTCOME

CHAPTER 6

Long-term cognitive outcome of delirium in elderly hip-surgery patients. A 2.5 year prospective matched controlled study

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ABSTRACT

OBJECTIVE: To study outcome from delirium in elderly hip-surgery patients.
DESIGN: Prospective matched controlled cohort study. Hip-surgery patients (n=112) aged 70 and older who participated in a controlled clinical trial of haloperidol prophylaxis for delirium, were followed for an average of 30 months after discharge. Patients with a diagnosis of dementia or mild cognitive impairment (MCI) were identified based on psychiatric interviews. Proportions of patients with dementia/MCI were compared across patients who had postoperative delirium and selected control patients matched for preoperatively assessed risk factors who had not developed delirium during index hospitalization. Other outcomes were mortality rate and rate of institutionalization.
RESULTS: During the follow-up period 54.9% of delirium patients had died compared to 34.1% controls (relative risk = 1.6, CI: 1.0-2.6). Dementia or MCI was diagnosed in 77.8% of the surviving patients with postoperative delirium and in 40.9% of control patients (relative risk = 1.9, 95% CI = 1.1-3.3). Half the patients with delirium were institutionalized at follow-up compared to 28.6% controls (relative risk = 1.8, 95% CI = 0.9-3.4).
CONCLUSION: The risk of dementia or MCI at follow-up is almost doubled in elderly hip-surgery patients with postoperative delirium compared with at risk patients without delirium. Delirium may indicate underlying dementia.

Keywords: Delirium, Follow-up, Dementia, Mild Cognitive Impairment, Mortality

INTRODUCTION

Delirium is highly prevalent in elderly patients and it is associated with high morbidity and mortality, increased length of hospital stay and institutionalization following discharge.[1-8] Estimated incidence rates for delirium after orthopedic hip-surgery vary from 5 to 45%.[9-16] While several studies report high prevalence of cognitive impairment after delirium in heterogeneous patient samples,[4,6,17-21] few studies examined the risk of dementia associated with delirium in elderly hip-surgery patients after one year or more.

Two studies including general medical patients showed that in hospital delirium is associated with cognitive decline at follow-up,[17,18] whereas another study failed to show a similar association.[22] Medical illness, when it is associated with delirium, can significantly contribute to deterioration in cognitive performance.[20] Prevalence of incident dementia is higher at 2-3 year follow-up in medical patients with delirium on admission compared to patients without delirium.[4,19] Incident Vascular dementia at follow-up was significantly associated with baseline delirium in a study by Rahkonen et al. that included a population based cohort of 199 non-demented elderly aged 85+.[21] Dolan et al. studied geriatric patients with hip fractures excluding those with a medical chart diagnosis of dementia: Patients with delirium were twice as likely to have cognitive impairment at 2-year follow-up.[19] However, none of these studies examined the relative risk of dementia associated with delirium in a relatively homogeneous hip-surgery patient sample after controlling for important preoperatively assessed delirium risk factors. Also, few if any studies included independent baseline and follow-up clinical interviews by a geriatrician or old-age psychiatrist.

The aims of this study were to evaluate the effects of postoperative delirium on follow-up cognitive function in elderly hip-surgery patients; to evaluate the long-term effect of delirium on mortality and dependency, i.e. independent living or institutionalization; and to evaluate the MMSE as a delirium risk factor measure. To the best of our knowledge this is the first study that controlled for baseline differences in patient characteristics prior to the onset of delirium.

METHODS

Ethical Considerations

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. All patients or their relatives gave fully informed written consent.

Study Design and Objectives

This was a case-control study evaluating the long term outcome of post-operative delirium on cognitive decline in elderly hip-surgery patients. All study data were collected as part of a randomized trial to test whether low-dose haloperidol prophylactic treatment could prevent delirium after hip-surgery.[15] Briefly stated, the primary outcome of the clinical trial was delirium (DSM-IV and Confusion Assessment Method[23] criteria) occurring within a period of five postoperative days. No effect was found on incident delirium, but there was a beneficial effect both on severity and duration of delirium. Risk classification in the clinical trial was based on the presence of one or more predictive baseline risk factors as described by Inouye et al.[24]: Visual impairment, defined as binocular near vision worse than 20/70 after correction, Severe illness, measured by the Apache II (Acute Physiology Age and Chronicle Health Examination,[25] scale of 0 to 70), with a cut-off score of > 16 indicating increased severity, Cognitive impairment Mini Mental Status Examination[26] (MMSE score of <24 on a scale of 0 to 30) and Dehydration (ratio of blood urea nitrogen to creatinine of ≥18).[24] Only 5/132 patients who were at low risk (=0 risk points) developed post-operative delirium compared to 69/471 who were at intermediate (=1-2 risk points) or high risk (=3-4 risk points), supporting validity of the medical risk factor model in a hip-surgery patient sample.[27]

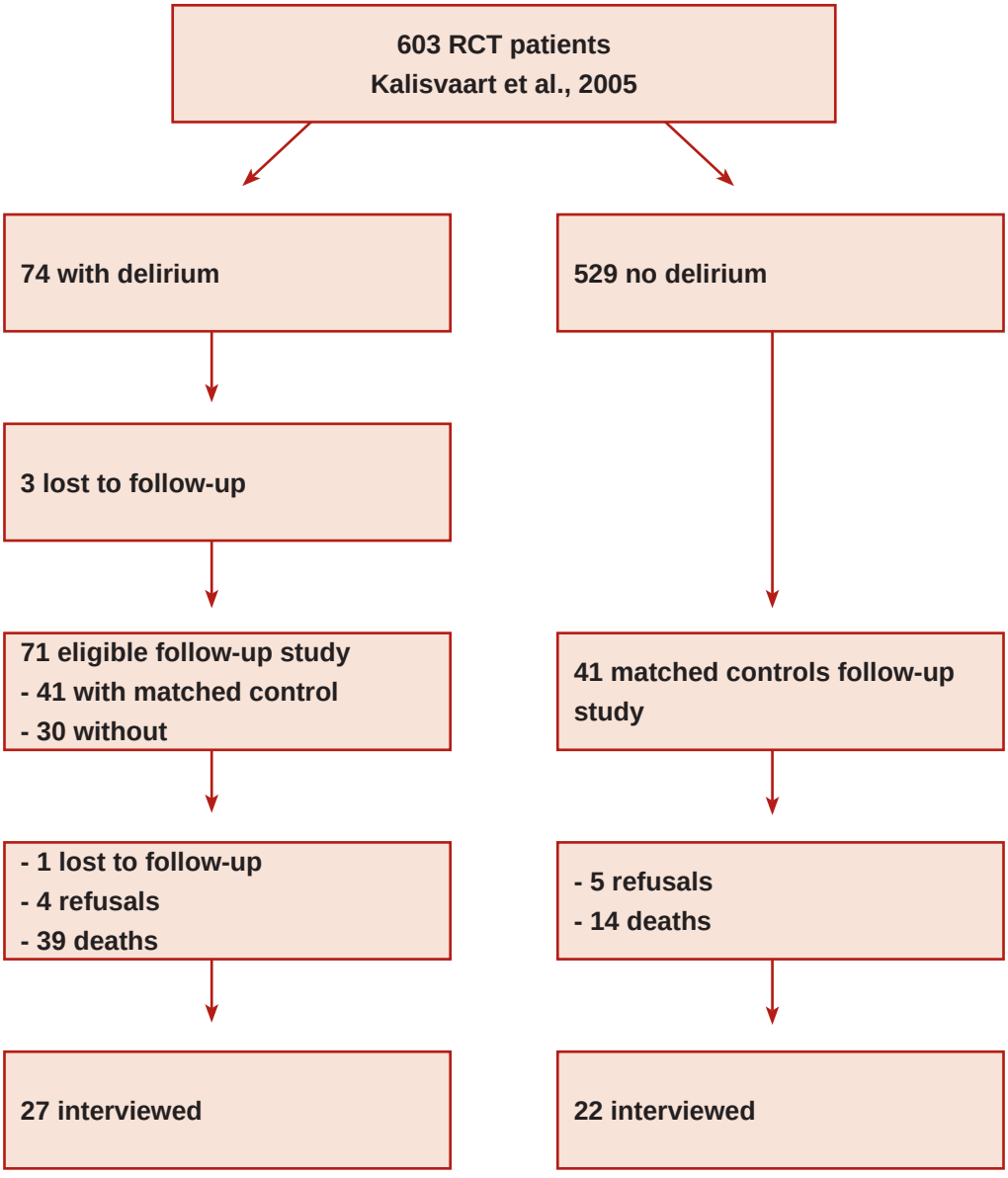
In the present study follow-up data on cognitive function and functional status were searched for and compared to incident delirium during hospital stay, predefined baseline risk factors used in the randomized clinical trial, and other potential risk factors.

Participants

The original study sample (n=603) has been described elsewhere.[15,27] All patients with post-operative delirium (n=74) including those without risk factors for delirium and who had not been randomized to receive study medication, were eligible to participate as cases in the follow-up part of the study. Also eligible to participate were control patients without delirium who had a similar risk factor profile as those with delirium (see patient Flow Chart). The risk factor profile has established predictive validity in hip-surgery patients.[27] A hierarchical method was used to match delirium cases and control. Age

and MMSE scores had the highest priority (max. age difference +/– 2 years: a maximum difference of 2 points on the MMSE was accepted unless it meant that a patient with a score of less than 24 was matched to a control patient with a score higher than 24. Secondary priority was given to the APACHE score (a maximum of +/- 2 points difference). Finally, the measure of Dehydration and gender had least priority.

Patient Flow Chart



Measurements and Procedures

Follow-up data on cognitive impairment and institutionalization of all participating patients were searched for. Eligible patients and a knowledgeable informant (spouse, other caregivers) were interviewed at follow-up by an experienced old-age psychiatrist (MK) who was blind to baseline diagnosis of delirium, risk factors and study medication. A research nurse (RV) who had been involved in baseline in-hospital patient assessments independently assessed cognition. Patients and informants filled out a depression rating scale and neuropsychiatric symptoms checklist.

Mortality data were retrieved from the Alkmaar hospital database. The hospital serves the region were all participating patients lived and any deaths to occur are reported back regularly. Data were checked by writing to the patients' general practitioners (GP) and requesting for any relevant information. If necessary, the GP was contacted directly by telephone.

Patient interviews were scheduled February 2003 – May 2004: the average post surgery follow-up period was 30 months (range 2-3 years) and interviews with delirium and control patients were evenly distributed over this time period. Available resources did not allow us to interview all 603 patients. Therefore, we invited all patients with post-operative delirium surviving the follow-up period to participate as well as the selected matched controls.

Follow-up assessments included standard clinical psychiatric interviews with the patient and (if possible) a knowledgeable informant, preferentially a spouse. The research nurse (RV) who was uninformed about psychiatric interview outcomes independently assessed cognitive/behavioral symptoms using the standardized MMSE (score range 0-30), modified Digit Span test of attention (score range 0-42),[28] the 15-items version of the Geriatric Depression Scale[29] (GDS-15, 0-15) and the Neuropsychiatric Inventory Questionnaire (NPI-Q, 0-36) a 12 item informant based screen for neuropsychiatric symptoms.[30,31] On average, interviews took 45 minutes per patient. Diagnosis of dementia or another mental disorder were defined based on the DSM-IV[32] criteria: for MCI the Peterson criteria were used.[33] The Cognitive Impairment Rating Scale (CIRS)[34] was used to clinically characterize the MCI type. The CIRS was constructed for the clinical and neuropsychological diagnosis of different cognitive impairments in MCI. It is a patient interview based global clinical impression of major cognitive domains (executive functions, memory, language, praxis). In this study the CIRS clinical diagnosis part was used only and no comprehensive neuropsychological test battery was used at follow-up. Predefined MCI categories were MCI amnestic, non-amnestic and multiple domain.

Care was taken to facilitate patient participation in the study. If patients were unable

to come to the hospital at follow-up they were visited at home by the two members of the research team (MK and RV). If patients had died during the follow-up period a family member and the patient's general practitioner were interviewed in order to gather demographic and medical information.

Outcomes

The primary outcome was the diagnosis of dementia or MCI. Secondary outcomes were mortality and institutionalization.

Statistical analysis

Means or proportions were used to describe demographic and clinical characteristics of the study sample at baseline and at follow-up. Relative risk of cognitive disorders, mortality and institutionalization associated with delirium was estimated using univariate analysis. Two-tailed p values of <0.05 were considered to indicate statistical significance. Subsequently, a logistic regression analysis approach was used to examine the association between baseline patient/clinical characteristics, delirium and primary outcome. Presence of delirium and potential other independent predictors that were significant in univariate analysis were entered in the regression model to calculate the odds (backward elimination) ($p < .10$). Statistical calculations were performed using SPSS for Windows, version 14 (SPSS, Inc. Chicago, IL).

RESULTS

Matching procedure

The planned analysis of primary and secondary outcomes is based on data of 71/74 patients with postoperative delirium: three delirium patients who had not been eligible for randomization to haloperidol or placebo in the RCT[15] were lost early to follow-up. The baseline risk factor profile of patients with delirium was considerably worse than that of the patients without. Of all 529 patients without delirium only 41 had a risk profile similar to that of patients with delirium. So, for 30/71 delirium patients no control patient was included.

Table 1: Average scores, mean ranks and average risk points at baseline for delirium (n=71) and control patients (n=41)

	Delirium (n= 71)		No delirium (n=41)			
Age	82.8 (SD 6.5)		82.6 (SD 6.9)		t-test = .31	p= .75
Male/female	23/48		7/34		chi^2 = 3.1	p= .08
Acute/elective	36/35		11/30		chi^2 = 6.1	p= .02
Placebo/ Haloperidol/ no medication	36/32/3		27/12/2		chi^2 = 2.7*	p= .10
Risk factors	M (SD)	Risk points y/n	M (SD)	Risk point y/n		
-MMSE	21.2 (4.6)	51/20	22.6 (4.5)	24/17	chi^2 = 2.1	p= .15
-APACHE score	15.1 (3.9)	31/40	14.2 (3.2)	16/25	chi^2 =.23	p= .63
-Dehydration index	12.1 (3.9)	53/18	13.1 (3.4)	24/17	chi^2 = 3.1	p= .08
-Visual impairment	0.34 (0.14)	15/56	0.37 (0.17)	11/30	chi^2 = 0.5	p= .49
-Total risk (1-4)		Mean= 2.1 (.98)		Mean= 1.9 (1.04)	Z = 1.3	p= .21
GDS	1.5 (1.5)		1.0 (1.4)		Z = 1.8	p= .07
Digit Span forward	13.8 (3.4)		14.8 (3.3)		Z = 1.3	p= .21
Digit Span backward	6.5 (2.7)		7.2 (2.2)		Z = 1.2	p= .23

*M = mean raw score (SD). p-value 2-sided; *: chi-square calculated for randomized patients only*

Matched delirium patients did better on the MMSE than unmatched delirium patients (p=.01). No other significant baseline differences between groups were demonstrated.

At baseline, there were no significant differences in age, sex and the four predefined risk factors between delirium patients and controls (table 1). Patients with delirium were more often acutely admitted to hospital than patients without delirium (p=.03). Also, their depression scores were somewhat higher, but average GDS scores were very low and not in the range of clinical depression. A larger proportion of patients with delirium had been assigned to haloperidol prophylaxis treatment condition than controls, although this difference did not reach statistical significance (p=.07).

Primary outcome

A total of 39/71 patients with postoperative delirium had died during the follow-up period. Twenty-seven survivors consented to be interviewed. The other patients refused (n=4) or were lost to follow for other reasons (n=1). A total of 22/41 control patients were interviewed: 14 had died and 5 refused. Baseline characteristics of remaining patients with or without delirium actually interviewed (n=22, n=27) were not significantly different, except for a significantly higher total number of risk points in delirium patients compared to No delirium patients: mean=1.9 (SD 1), vs mean=1.3 (SD .72), Z=2.2, p=.03; and higher number of acute admissions in the delirium group compared to No delirium: 9/27 vs 2/22, Chi^2 4.1, p=.04.

Postoperative delirium was associated with an increased risk of cognitive disorders at follow-up (table 2). Alzheimer dementia (AD) was diagnosed in 10/27 patients with postoperative delirium, 6/27 had Vascular dementia (VaD) or mixed VaD-AD, 4/27 had MCI amnestic type and 1/27 had MCI multi-domain type. Alzheimer dementia was diagnosed in 1/22 patients without postoperative delirium, 1/22 presented with the clinical picture of Frontotemporal dementia and 7/22 had MCI multi-domain type. No mood disorder was diagnosed in any of the patients.

An intermediate analysis including 28 patients with baseline MMSE >23 only, showed postoperative delirium was not associated with an increased risk of cognitive disorders at follow-up (RR=1.8, CI: 0.8-3.9), possibly due to the small number of patients included.

At follow-up, no group differences were found for self-rated depression, attention deficits (Digit span) and neuropsychiatric symptoms. There was a trend showing greater informant rated cognitive decline in patients with post-operative delirium than in those without (p=.06). At follow-up, patients with delirium had lower MMSE scores than those without (p=.02).

Notably, no effect was found for treatment condition on primary outcome; 11/17

haloperidol treated patients had dementia or MCI compared to 18/29 patients receiving placebo treatment (p=.86).

Multivariate analysis showed that delirium predicted dementia/MCI at follow-up and that baseline characteristics (i.e. type of admission) did not (Wald: 6.5, p=.011).

Secondary outcomes

Postoperative delirium was associated with an increased risk of death at follow-up (table 2). There was a trend showing higher institutionalization in patients with postoperative delirium than in those without. No effect was found for treatment condition (haloperidol - placebo) on secondary outcomes: 22/45 patients in the haloperidol treatment condition had died during the follow-up period and 30/62 patients in the placebo treatment condition (p=.95), and 7/22 were institutionalized, compared to 18/39 in the placebo group (p=.27).

Postoperative delirium was associated with an increased risk of death or dementia (i.e. combined primary and secondary outcomes cognitive status and mortality): 60/71 patients with postoperative delirium had died or had dementia/MCI compared to 23/41 controls, (RR=1.5, CI: 1.1-2.0).

Table 2. Cognitive status, mortality and institutionalization at follow-up for delirium and control patients

	Delirium		No delirium	N	Statistic
	Total	Matched			
Diagnosis - No cognitive impairment - MCI-dementia	6 21 (5-16)	5 15 (3-12)	13 9 (7-2)	 27/20/22	RR=1.9 (CI: 1.1-3.3)* RR=1.8 (CI: 1.05-3.2)**
Alive / deceased	32/39	21/20	27/14	71/41/41	RR=1.6 (CI: 1.01-2.6)* RR=1.4 (CI: 0.8-2.4)**
Independent living/ institutionalized	19/19	12/13	20/8	38/25/28	RR=1.8 (CI: 0.9-3.4)* RR=1.8 (CI: 0.9-3.7)**
ICQODE	3.8 (.97)	3.9 (.83)	3.3 (.58)	24/17/21	t-test 2.2, p=.03* t-test 2.3, p=.03**
GDS	2.2 (2.7)	2.4 (2.9)	1.2 (1.6)	20/7/21	t-test 1.5, p=.13* t-test 1.6, p=.13**
Digit Span forward	15.3 (4.1)	15.4 (4.4)	16.1 (2.6)	25/19/21	t-test .7, p=.46* t-test .6, p=.56**
Digit Span backward	7.4 (4.0)	8.1 (4.3)	8.7 (3.6)	25/19/21	t-test 1.1, p=.27* t-test .49, p=.63
MMSE	22.6 (6.5)	22.8 (6.8)	26.2 (3.9)	27/20/22	t-test 2.4, p=.02* t-test 2.0, p=.06**
NPI-Q total	5.7 (6.5)	6.4 (7.1)	4.1 (5.2)	26/19/20	t-test .9, p=.37* t-test 1.2, p=.25**
NPI-Q distress	5.9 (7.3)	6.6 (8.0)	4.6 (6.5)	26/19/20	t-test .6, p=.54* t-test .9, p=.38**

Delirium: Total delirium sample at follow-up including matched and unmatched delirium patients.

**: Total Delirium sample vs. Control comparisons,*

***: Matched delirium – Control comparisons IQCODE p=.03, MMSE p=.06.*

RR = Relative risk, CI = Confidence Interval. IQCODE, GDS, Digit Span, MMSE and NPI: mean (SD)

DISCUSSION

This study examined cognitive disorders at follow-up associated with postoperative delirium in elderly hip-surgery patients. Patients who developed delirium after surgery during hospital stay had a 170% increased risk of dementia or MCI in the 30 months follow-up period. Baseline differences between delirium patients and controls did not account for the effects found implying that delirium independently predicted long term adverse outcome. Secondly, significant higher proportions of patients with postoperative delirium had died at follow-up compared to those without delirium and institutionalization was similar for both groups.

The increased risk of cognitive disorders or death after delirium is impressive and our findings may have important prognostic implications for elderly patients who are at risk for postoperative delirium. Such high rates of cognitive impairment and mortality raises concern, particularly when one considers that delirium is often under diagnosed and in many instances preventable.

Four previous studies found an increased dementia risk associated with delirium at follow-up. Koponen followed-up 33 delirium patients of whom 29 were diagnosed with dementia at baseline and found significant decline in MMSE scores. Rockwood et al. studied geriatric patients from a general medical service over a 3-year period. They found that 60% of patients with delirium on admission but no dementia were diagnosed with dementia at follow-up (n=15) compared to only 18.5% of patients without delirium.[4] In a study by Rahkonen et al. acutely admitted older patients with delirium were included and followed-up for a 2-year period. During follow-up 55% of patients were diagnosed as being demented.[19] In another study by Rahkonen et al. an epidemiological cohort of 199 non-demented elderly aged 85+ were followed-up during a 3-years period.[21] Incident delirium in the follow-up period was retrospectively diagnosed in 20/199 patients. At the end of the follow-up period dementia was diagnosed in 13/20 cases with delirium and in 46/133 controls (p=.001). The relative risk of cognitive disorders found in our sample is comparable to those found in the earlier studies. However, none of these studies examined the relative risk of dementia associated with delirium in a homogeneous hip-surgery patient sample after controlling for important preoperatively assessed delirium risk factors or they did not include independent follow-up clinical assessments. The strengths of this study are the primary outcome data set; inclusion of a homogeneous hip-surgery patient sample; use of standardized and validated methods for diagnosing delirium based on clinical patient interviews; pre surgery and pre delirium measures of predefined baseline risk factors; psychiatric assessment at follow-up; and sub typing of cognitive outcome.

The underlying mechanism for the apparent association between delirium and cognitive decline is still largely unclear. It has been suggested that delirium and dementia share the same underlying pathology: delirium may serve as a marker of a subclinical dementing process.[4] Alternatively, it can be hypothesized that delirium itself triggers a whole range of metabolic and autonomic dysregulations and neurotransmitter changes that have neurotoxic effects on the brain and may ultimately lead to dementia. Yet another explanation may be that in some patients the somatic condition underlying delirium may not have fully remitted at the time of discharge from hospital. In turn, that may increase the risk of future dementia, especially in frail elderly patients. This hypothesis would be consistent with findings that delirium and its symptoms often persist for months after onset.[35;36] So, which hypothesis is supported by our data? To test the hypothesis that delirium exerts a toxic effect on the brain would at least have required a non demented patient sample at baseline. Absence of dementia prior to surgery was not ascertained in this study and no conclusions on causality can be drawn from that. As this study includes an orthopedic patient sample and delirium duration was carefully monitored in the RCT part of the project[15] results do not support the hypothesis that delirium symptoms persisted after discharge from hospital and perhaps confounded follow-up diagnosis of dementia. In this study care was taken no major cognitive differences existed between patients with delirium and controls prior to surgery. Nevertheless, we could not match 30/71 delirium patients to controls because of differences in the risk factor profile at baseline. Unmatched delirium patients did worse on the MMSE than matched delirium patients indicating more impairment. Moreover, a wide score range was observed for the MMSE (10–29). So, it is rather clear some patients already had dementia or MCI before entering the study. Although no conclusions on causality can be drawn from this study it further reinforces the finding that underlying dementia may be a contributor to inpatient delirium and that identification of underlying cognitive impairment may not be made until after an inciting event such as major orthopedic surgery.

Baseline MMSE was 22.5 in the no delirium group while follow-up MMSE was 26.2. What could account for this apparent transient cognitive impairment? Note that baseline and follow-up groups are not identical and healthy and cognitive intact patients may have survived the follow-up period while others did not. An intermediate paired observations analysis showed MMSE improved 1.2 points in the No Delirium group (n=22) (t-test: 2.2, p=.04), but no change was observed in the total group and in the delirium group. Dementia prevalence was higher in patients who had post-operative delirium as compared to those who did not. Though findings are based on relatively small numbers of patients and may be coincidental, we hypothesize that the (psychological) stress

associated with hospital admission may have caused some individuals to underachieve during baseline cognitive testing. During follow-up cognitive function may have returned to pre admission levels in patients without MCI or dementia. These findings imply that the MMSE not only measures stable or 'trait dependent' aspects of cognition, e.g. underlying dementia, but temporary or 'state dependent' changes as well. Therefore, cognitive dysfunction as measured with the MMSE in newly admitted hospital patients should be interpreted cautiously, as it may not be a symptom exclusively related to underlying dementia.

Treatment condition did not affect the long run outcome. Patients randomized to haloperidol or placebo had died or were cognitively impaired much the same way at follow-up. So, low-dose haloperidol prophylaxis at baseline did not protect against increased risk of mortality and cognitive decline. Vice versa, it did not have a negative effect on primary outcome. It would seem to us that where short term effects may be expected, the duration and dosage of the prophylactic treatment were too short or too low to really make a difference 2.5 years later.

Weaknesses of this study that need to be discussed are: 1. Baseline evaluations were aimed at excluding delirium, and not at diagnosing different neuropsychiatric syndromes. Delirium is associated with cognitive impairment. When evaluating the long term effects of delirium it is important to control for premorbid cognitive disorders. In this study patients were matched based on four risk factors, including the MMSE. No detailed neuropsychiatric assessment was used at baseline. A cognitive screening test does not provide the same diagnostic information as a clinical interview and cases with underlying cognitive disorders may have gone undetected. 2. The study is underpowered to evaluate the long term effects of postoperative delirium. Power calculations were based on the original intervention study. In the present follow-up study all delirium patients were included and a control sample. The baseline risk factor distribution did not permit us to sample any more control patients. 3. Patients were followed-up after 2.5 years. No intermediate assessments took place. Possible confounders of results occurring during this time interval may have gone undetected. Ideally, follow-up diagnosis and multiple assessments would have been preferred for all participating patients. These are preliminary findings on cognitive outcome from delirium. Future studies could focus on pre delirium clinical assessments, rigorous screening for pre delirium cognitive impairment, and repeated mid term and long term follow-up cognitive testing.

This controlled study evaluated the long term effects of postoperative delirium. It underlines the major impact of this neuropsychiatric syndrome on the well-being of elderly hip-surgery patients. More than half the patients with post operative delirium

die during 2 to 3 years after hospitalization; the vast majority of those surviving have a cognitive disorder. Although delirium is independently associated with cognitive impairment at follow-up, some patients with delirium may already have underlying dementia. Outcome from delirium is poor particularly for patients with dementia.[37] Our findings point to the imperative to screen for underlying impairment, since delirium may ensue and therefore, increase risk of morbidity and mortality. Monitoring at risk patients, not only during hospitalization but also following discharge, should be combined with delirium prevention strategies.

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CHAPTER 7

Mortality associated with delirium after hip-surgery. A 2-year prospective cohort study

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ABSTRACT

OBJECTIVES: To study the hazard risk associated with delirium in elderly hip-surgery patients at 2-year follow-up; and to explore risk factor stratification of poor outcome from delirium.

DESIGN: Prospective cohort study.

SETTING: Large medical school-affiliated general hospital in Alkmaar, The Netherlands.

METHODS: Participating patients (n=603) in a controlled clinical trial of haloperidol prophylaxis for delirium were followed-up for two years. Predefined risk factors and other potential risk factors for delirium were assessed prior to surgery. Primary outcome was time of death during the follow-up period. Cox proportional hazards were estimated and compared across patients who had postoperative delirium during hospitalization and those who did not.

RESULTS: A total of 90/603 patients (14.9%) died during the study period and 74/603 (12.3%) had postoperative delirium. Incidence of delirium was higher in patients who died (32.2%) compared with those who survived (8.8%). The effect of delirium on mortality was significant after adjusting for predefined delirium risk factors and other potential covariates including study intervention (adjusted Hazard risk=1.98, 95% CI 1.24-3.17). Ten percent of delirious patients at low risk of poor outcome (0-1 risk factors) died, 40.7% at intermediate risk (2-3 risk factors), and 59.3% at high risk (4-5 risk factors), compared to 6.1%, 13.5% and 43.1% of non-delirious patients.

CONCLUSIONS: Delirium independently predicts mortality at two-years follow-up in elderly hip-surgery patients. Outcome from delirium is particularly poor when other risk factors are present.

Keywords: delirium, long-term outcome, follow-up, risk factors, cognitive impairment, epidemiological, mortality, clinical prediction rule

INTRODUCTION

Delirium is highly prevalent in elderly hospital patients and it is associated with high morbidity and mortality, increased length of hospital stay and a high rate of institutionalization following discharge.[1-5] Incidence rates for delirium after orthopedic hip-surgery vary from 5 to 40.5%.[6-8] Of the investigations conducted to date, few have examined the mortality risk associated with delirium in elderly hip-surgery patients after one year or more.

The causal relationship between delirium and death at follow-up is largely still unclear and controversy exists whether delirium is independently associated with mortality at follow-up. Delirium and its symptoms often persist for months after onset.[9-12] It has been suggested that the protracted course of delirium may contribute to its long term adverse outcomes.[13] Some studies found that delirium in hip-surgery patients is associated with an increased risk of death at follow-up,[4,8,14,15] while other studies did not.[1,16-23] However, none of the positive studies examined the hazard risk associated with postoperative delirium after controlling for important delirium risk factors assessed preoperatively.

Prognosis of delirium is particularly poor when predisposing and precipitating risk factors for delirium are present. Several risk factors for delirium are independently associated with follow-up mortality.[13,24,25] Some of these factors are modifiable, such as comorbid disorders. Accurate risk stratification would be useful for identifying low-risk hip-surgery patients with delirium for whom hospitalization period may be relatively short; and intermediate or high risk delirium patients, who might require prolonged hospital stay, intensified treatment and special care programs, also during post acute care. To our knowledge no risk stratification for poor outcome from delirium studies have been published.

The primary aim of this study was to examine the effect of postoperative delirium in elderly hip-surgery patients on mortality at follow-up two years later, controlling for baseline risk factors present at admission before onset of delirium. The secondary objective was to explore risk stratification of poor outcome from delirium.

METHODS

Ethical Considerations

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. All patients or their relatives gave fully informed written consent.

Study Design and Objectives

This is a prospective cohort study evaluating the long term outcome of post-operative delirium on mortality in elderly hip-surgery patients. Study data on case mix variables were collected as part of a randomized, placebo-controlled, double-blind, clinical trial of low-dose haloperidol prophylaxis for postoperative delirium in elderly hip-surgery patients who were at intermediate or high risk for this complication. The aim of the RCT was to assess the effectiveness of 1.5 mg of haloperidol daily versus placebo on the primary (incident delirium) and secondary (deterioration of delirium) prevention of postoperative delirium in hip-surgery patients.[26] Men and women aged 70 and older admitted for acute or elective hip surgery were considered for inclusion in the haloperidol prophylaxis study. Risk classification was based on the presence of four predictive risk factors as described by Inouye et al.[27]: Visual impairment, defined as binocular near vision worse than 20/70 after correction, Severe illness, measured by the Apache II (Acute Physiology Age and Chronicle Health Examination,[28] scale of 0 to 70), with a cut-off score of > 16 indicating increased severity, Cognitive impairment Mini Mental Status Examination[29] (MMSE score of <24 on a scale of 0 to 30) and Dehydration (ratio of blood urea nitrogen to creatinine of ≥18).[27] Intermediate risk for postoperative delirium was defined as presence of one or two risk factors and high risk as presence of three or more risk factors. The low-risk patients were assessed daily according to the protocol for incident delirium but received no prophylactic medication.

Patients were ineligible if they had delirium at admission, or no risk factors for postoperative delirium present at baseline. Detailed ineligibility criteria, including medication use and comorbid conditions, are described elsewhere.[26] Eligible patients were sequentially randomly assigned to study treatment (placebo or haloperidol 0.5 mg three times daily).

Trial medication was started on admission and continued until 3 days after surgery. All patients were assessed daily for efficacy and safety evaluations. Experienced geriatric nurses and geriatricians provided proactive geriatric consultation to all patients. If postoperative delirium occurred, patients were treated according to standard procedures (haloperidol three times per day, lorazepam three times per day, or both

in increasing doses, depending on symptoms of delirium) and assessed for delirium severity and duration. A total of 430/603 had one or more risk factor for delirium and were randomized to haloperidol or placebo.

Primary outcome of the clinical trial was delirium as defined by Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) and Confusion Assessment Method[30] criteria. Secondary outcome variables were severity of delirium as measured with the Delirium Rating Scale Revised (DRS-R-98), delirium duration, and length of hospital stay. Daily patients assessments using the MMSE, DRS-R-98, and Digit Span test (assessment of attention) were used to make the DSM-IV and CAM diagnoses possible and to assess delirium severity. A total of 74/603 had postoperative delirium.

Briefly stated, no effect was found on incident delirium, but there was an effect on severity and duration of delirium. Incidence of delirium was higher in patients at intermediate or high risk of delirium as compared to those at low risk, supporting validity of the medical risk factor model in a hip-surgery patient sample. In addition to these predefined risk factors, other risk factors for delirium, particularly age and acute admission to hospital, were identified.[31]

In this study 2-years follow-up data on mortality were searched for and compared to incident delirium during hospital stay, controlling for demographical variables; predefined baseline risk factors used in the randomized clinical trial; and admission type.

Participants

The original study sample has been described elsewhere.[26;31] All 603 patients were eligible to participate in the follow-up part of the study.

Measurements and Procedures

Date of death data were retrieved from the Alkmaar hospital database and other sources. The hospital serves the region where all participating patients lived and any deaths to occur are reported back regularly. Great efforts were made to include data from all patients by writing to the patients' general practitioners (GP) and requesting for any relevant information. If necessary, e.g. when patients had moved out of the area, the GP, patients or patient's family members were contacted by telephone.

Outcomes

The primary outcome was time to death during 2-year follow-up.

Statistical analysis

Means or proportions were used to describe demographic and clinical characteristics of the study sample at baseline and during 2-year follow-up. Kaplan-Meier survival curves for delirium an no delirium cases were examined using the Log rank test. Inspection of the survival tables showed that more delirium patients died within the first 6 months than in next 18 months ($Chi^2 = 8.65$, P=.03), indicating that the Cox proportional hazards assumption was violated. Mortality risk associated with delirium was estimated using a time dependent Cox proportional hazards regression model; the outcome was time to death. Censoring event was 2-year follow-up survival. Presence of delirium and potential other independent predictors of time to death were entered in the regression models to calculate unadjusted and adjusted (backward elimination) hazard risks (P <.10). Age and predefined risk factors APACHE, MMSE, Vision and Dehydration were entered in the analysis as continuous variables and incident postoperative delirium, Admission type and Gender as dichotomous variables. A time by delirium interaction factor was added to the model.

To counteract a potential confounding effect of in-hospital deaths on outcomes an intermediate analysis included patients who survived index hospitalization period only. In a second intermediate analysis including randomized patients only (n=430) study intervention (haloperidol vs. placebo) was also entered in the statistical model. In a third intermediate analysis those patients not receiving the haloperidol intervention were included only.

Risk factor stratification for poor outcome from delirium was explored using a logistic regression approach: the outcome was 2-year follow-up survival status. Similar to the Cox proportional hazard model, delirium and other independent predictors of survival were entered in the regression models to calculate the odds (backward elimination) (P <.10). Contrary to the Cox analysis, dichotomous variables were used in the logistic regression analysis based on predefined cut-off points for delirium risk factors MMSE, APACHE, Vision impairment and Dehydration. Age was conveniently dichotomized (70-79 years and 80 or over). It was decided to construct a simple algorithm useful for clinical practice by assigning 1 point for each significant outcome predictor variable. The relative risk for poor outcome was calculated based on the number of predictor variables, comparing delirium patients with few if any, intermediate or many risk factors with the referent group without delirium. Statistical calculations were performed using SPSS for Windows, version 14 (SPSS, Inc. Chicago, IL).

Table 1: Characteristics of Hip-surgery Patients in the Sample

	Died during study period (n= 90)	Survived the study period (n=513)	Total cohort (n=603)
Age*	82.7 +/- 7.4	77.1 +/- 5.3	77.9 (6.0)
Male sex	26 (28.9)	112 (21.8)	138 (22.9)
Acute admission	47 (52.2)	88 (17.2)	135 (22.4)
Predefined delirium risk factors:			
MMSE*	22.1 +/- 5.6	25.8 +/- 3.6	25.2 +/- 4.2
APACHE score*	14.7 +/- 4.1	12.7 +/- 2.7	13.0 +/- 3.0
Dehydration index*	12.2 +/- 4.8	12.8 +/- 3.6	12.7 +/- 3.8
Visual impairment*	0.31 +/- 0.15	0.44 +/- 0.15	0.42 +/- 0.16
Study intervention:			
Placebo	33 (36.7)	185 (36.1)	218 (36.2)
Haloperidol	46 (51.1)	166 (32.4)	212 (35.2)
not randomized	11 (12.2)	162 (31.6)	173 (28.7)
Length of stay*†	26.4 (28.7)	19.0 (21.0)	20.4 (22.8)
Post-operative Delirium	29 (32.2)	45 (8.8)	74 (12.3)

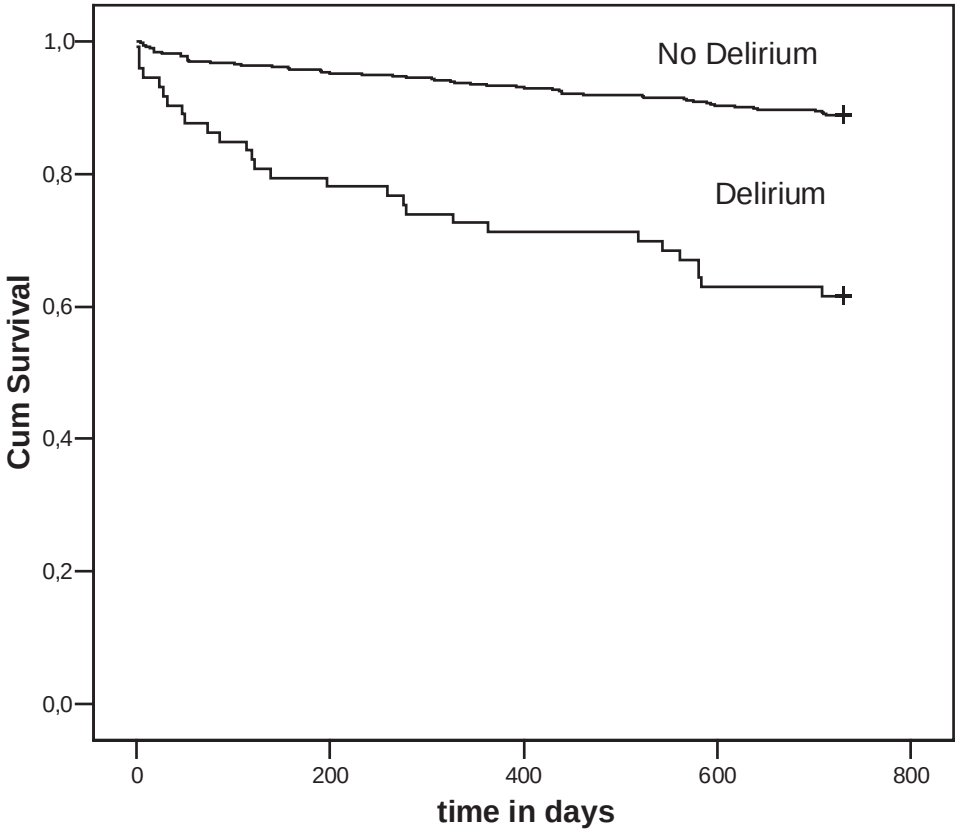
**: data are given as mean. †: data on length of in-hospital stay were available for randomized patients only.*

RESULTS

Descriptive findings and Cox proportional hazard analysis

A total of 90/603 patients (14.9%) died during the study period (table 1). For 4/90 patients the exact date of death could not be retrieved. The Kaplan-Meier survival curves for patients with or without delirium are plotted in Figure 1. The survival curve for patients with delirium decreases faster than the curve for patients without delirium (Log rank=46.35, df=1, P=<.001).

Fig. 1: Kaplan-Meier Survival Functions Patients with or without Delirium



Days	0	100	200	300	400	500	600	700
At risk*								
No Delirium	526	509	501	497	490	484	475	472
Delirium	73	62	57	54	52	52	46	46

**excluding cases with exact date of death*

Incidence of delirium was higher in patients who died compared with those who survived. Patients who died were also more often men, and were relatively old. They were more often at risk for delirium as indicated by higher rates of cognitive impairment and visual impairment. By contrast, illness severity and dehydration were not associated with time to death in multivariate analysis (table 2), nor was there a significant effect of the interaction between time and delirium.

Table 2: Univariate and Multivariate Analysis of Time to Death for Hip-surgery Patients (n=599)
During 2-Year Follow-up

	Unadjusted data		Adjusted data	
Predictors	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Age	1.14 (1.10-1.17)	<.001	1.09 (1.06-1.13)	<.001
Male sex	1.49 (0.95-2.37)	.09	2.19 (1.36-3.54)	.001
Acute admission	4.63 (3.03-7.08)	<.001	1.54 (0.89-2.65)	.12
Predefined risk factors:				
MMSE	.88 (.85-.90)	<.001	.95 (0.91-.99)	.02
APACHE	1.21 (1.14-1.28)	<.001	1.03 (0.96-1.11)	.40
Dehydration	.96 (0.90-1.02)	.16	1.0 (0.94-1.06)	.98
Visual impairment	.007 (.002-.027)	<.001	.03 (.006-.16)	<.001
Postoperative Delirium	.24 (.15-.37)	<.001	1.98 (1.24-3.17)	.004
Haloperidol Prophylaxis*	1.46 (0.93-2.30)	.10	NA	NA

**: data available for randomized patients (n=430) only.*

Intermediate Cox proportional hazard analyses

In three intermediate analyses hazard risks were examined for patients who died after the index hospitalization, those randomized to placebo or haloperidol, or those not receiving the intervention. A total of 14/90 were in-hospital deaths and 7/14 had delirium. When these 14 patients were excluded from the intermediate analysis, we found that incidence of delirium was higher in patients who died in the post hospitalization period compared with those who survived (adjusted Hazard Ratio 1.92, CI 1.13-2.70).

A total of 79/430 randomized patients died during the study period. A second intermediate analysis showed that incidence of delirium was higher in patients who died

compared with those who survived (adj. HR 1.80, CI 1.11-2.94). Notably, haloperidol prophylaxis was not associated with death at follow-up in multivariate analysis. In-hospital deaths were 2.4% in the haloperidol prophylaxis group and 4.1% in the placebo group.

A total of 391/603 were randomized to placebo or were not randomized. A third intermediate analysis including patients not having had the intervention showed that incidence of delirium was not higher in patients who died compared with those who survived (adj. HR 1.39, CI .64-3.03).

Risk Factor Stratification for Poor Outcome from Delirium

In logistic regression analysis, a significant statistical association with 2-year survival status was evident for Delirium (OR=2.4, 95% CI 1.3-4.6), Male gender (2.0, 95% CI 1.1-3.6), Age 80 years or over (OR=2.5, 95% CI 1.5-4.4), Acute admission type (OR=2.2 95% CI 1.2-4.0), Cognitive impairment (OR=1.7, 95% CI .9-3.0) and Visual impairment (OR=2.6, 95% CI 1.4-4.9).

Examining the risk factor stratification shows (table 3) that patients with incident delirium were at an increased risk for death after two years when intermediate levels of risk points were present, but no so when few if any risk factors were present, nor when many risk factors were present. However, many of the patients at high risk died (delirium 59.3% vs. No Delirium 43.1%), suggesting a potential significant group effect when larger patient samples are included.

Table 3: Risk Index Performance Predicting 2-Year Follow-up Survival Status

	Died during study period		Survived during study period		
	Delirium	No Delirium	Delirium	No Delirium	Relative Risk (95% CI)
Risk Factors*					
0-1	2 (10.0)	21 (6.1)	18 (90.0)	324 (93.9)	1.64 (.41-6.51)
2-3	11 (40.7)	18 (13.5)	16 (59.3)	115 (86.5)	3.01 (1.61-5.63)
4-5	16 (59.3)	22 (43.1)	11 (40.7)	29 (56.9)	1.37 (.88-2.14)

Mortality Risk Factors weighed equally (range 0-5).
( ): Percentages primary outcome within groups Delirium vs. No Delirium.

DISCUSSION

This study examined mortality at follow-up associated with delirium in elderly hip-surgery patients. Patients who developed delirium after surgery had an almost doubled increased risk of mortality in the 2 year follow-up period (table 2). In addition to baseline risk factors, delirium independently predicted the adverse long term outcome. The strengths of this study are the complete primary outcome data set; inclusion of a large sample hip-surgery patients; inclusion of patients who are at risk and who are not at risk for delirium; use of standardized and valid methods for diagnosing delirium; pre surgery and pre delirium measures of predefined baseline risk factors.

The association between delirium and risk of death is impressive. In this sample of 603 patients 29/74 with delirium died (39.2%) compared to the overall figure of 90/603 deaths (14.9%). Even when the 14 in-hospital deaths are left out from the equation, the odds still reflect a twofold risk of death. It goes without saying that such a high mortality rate raises concern, particularly when one considers that delirium is often under diagnosed and in many instances preventable.

One previous study found an increased mortality risk associated with delirium at 6 months of follow-up and three studies found increased risk at 12 months follow-up or more.[4,8,14,15] In the Nightingale et al. study hip-fracture patients were interviewed by a psychiatrist or psychiatric nurse between 2 and 5 days after surgery and an adjusted 2 year hazard ratio associated with delirium of 2.4 (CI 1.7-3.5) was found.[4] In the Edelstein et al. study 47/921 (5.1%) hip fracture patients had postoperative delirium and were more likely to have died at 1 year follow-up (unadjusted odds ratio 2.4, CI 1.1-4.9).[8] Lundstrom et al. found that 21/29 femoral neck fracture patients with postoperative delirium died within 5 years, compared to 17/49 who did not have delirium (P=.001).[15] The hazard ratio found in our sample is comparable to those found in the earlier studies. However, we clinically assessed patients on admission prior to surgery and included large numbers of patients many of whom were not at risk for delirium. By doing so we were able to examine both the effects of delirium and baseline risk factors on mortality. Thus, our method represents a rigorous approach to study the important problem of adverse long term outcomes associated with delirium.

Protracted delirium does not (fully) explain the relationship between delirium and long term mortality in this sample. Advanced age and pre-existing cognitive impairment, two of the risk factors for mortality found in this study, have been identified as two major risk factors for prolonged delirium.[32] Delirium may lead to different complications such as insufficient nutritional intake, falls associated accidents and exhaustion, all of which may increase the risk of death. Some found that delirium independently predicts in-

hospital mortality.[1] Other studies show that unresolved delirium at discharge is highly prevalent in general medical patients, and that it is associated with mortality at long term follow-up.[3,33] In this study 7 patients with delirium died during hospital stay, the other 22 delirium patients died during the post hospitalization period. Patients were participants in a RCT performed outside the U.S., Delirium severity and duration were measured in the RCT and none of the patients had delirium at discharge. Although some patients may have had (mild) delirium symptoms at discharge, we believe persistent delirium symptoms per se are not a likely explanation for excess mortality at follow-up. Alternatively, we hypothesize that vulnerability in delirium patients as expressed by presence of predisposing and precipitating factors explains, at least to some extend, excess mortality. Results from the risk factor stratification analysis seem to support this hypothesis.

Risk factor stratification for poor outcome was examined based on presence of delirium and other risk factors. Base rate mortality in the referent group at low risk was 6.1%. Prognosis of incident delirium was not significantly different when only few risk factors were present; all but two of the delirium patients with few risk factors survived. However, 40.7% of the delirium patients with two or three risk factors died; 59.3% died in case of four or five risk factors. So, prognosis of post hip-surgery delirium is reasonably good when you are relatively young and healthy. It is worse for cognitively impaired older men who are acutely admitted to hospital and who have poor vision. Unfortunately, many of the predictor variables that were identified are not amenable to treatment, but on the other hand risk factor stratification of low, intermediate and high risk is simple to use in everyday clinical practice. Practical consequences of the risk stratification may be that delirium patients who are at intermediate or high risk should not be transferred or discharged from hospital untimely; extra efforts should be made to identify and try to modify medical conditions associated with mortality; care programs should target the intermediate and high risk patients; post acute facilities should prepare treatment and care for those who need it most; patients and their families may want to be informed about delirium prognosis.

Validity of the risk stratification model was not tested in this study. Secondly, the small number of patients in the low and high risk groups may have reduced study power. Also, other risk factors for poor outcome from delirium after hip-surgery may exist, but they were not included in this study. We included risk factors that are robust predictors of delirium.[31] However, although dehydration was associated with delirium in general medical patients,[27] it was not in our hip surgery patient sample. Again, dehydration did not predict follow-up mortality in this study. So, risk factor selection may depend on the patient sample studied and different risk stratifications may be found in various patient

samples based on risk factors that are not necessarily the same as the ones used in this study. The risk factors for poor outcome found in this study need to be verified in future studies. In turn, this could result in a validated clinical prediction rule.

Treatment condition was not associated with study outcome. The apparent trend for excess mortality in patients randomized to haloperidol was not significant after controlling for covariates. Furthermore, in-hospital deaths were 2.4% in the intervention group and 4.1% in the placebo group. So, low-dose haloperidol prophylaxis did not protect against increased risk of mortality. Vice versa, it did not have a negative effect on primary outcomes. It would seem to us that where short term effects may be expected, the duration and dosage of the prophylactic treatment were too short or too low to really make a difference two years later. Nevertheless, possible detrimental effect of prophylactic treatment on survival warrants careful monitoring in future studies.

Study limitations that need to be discussed relate to generalizability of results and risk factor selection. This was a single site study and it was part of randomized trial not set up to evaluate the natural history of delirium and its outcomes. Nevertheless, patients enrolled in the study were selected from a large sample representative of hip-surgery patients. Secondly, chronic comorbid conditions were not included as a covariate. Instead, acute comorbid conditions were measured by the APACHE. Risk factor selection was based on a validated medical model.[27;31] We controlled for the intervention (haloperidol prophylaxis or placebo) and included non randomized patients. No independent effect of study medication on mortality was found. We conclude that the original randomized clinical trial design does not invalidate results and conclusions of this study.

This study shows that delirium among hip-surgery older patients is associated with mortality at follow-up. Our findings are consistent with the concept of delirium as a serious neuropsychiatric condition with adverse effects. Delirium outcome is most problematic in vulnerable patients. The symptoms that often persist for months may well be reflections of the unresolved underlying pathological conditions in these patients. Since we did not adjust for chronic comorbid conditions, delirium might be an exceptionally good marker for comorbid conditions. Our results suggest efforts should be made to investigate the causal mechanism(s) that explain for mortality associated with delirium and to develop prevention programs targeted at decreasing the risk of death after delirium. Such programs would probably include the use of a risk factor stratification; extra care for frail elderly that extends the hospitalization period; and monitoring of delirium symptoms for a prolonged period of time. The increased mortality risk associated with delirium warrants rigorous implementation of primary and secondary prevention strategies.

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CHAPTER 8

General Discussion

This chapter summarizes the main findings of this thesis and contains a general discussion on the relevance of the results, some methodological considerations and the implications for daily clinical practice and future research.

As discussed in the general introduction of this thesis, dementia is a clinical syndrome known for centuries. Whereas until 1900 approximately, many psychiatric disorders in the elderly were included under this heading, 'dementia' became a syndrome in which memory and intellectual impairment were key elements. This cognitive paradigm dominated scientific research until the '80s of the last century. Since that time psychiatric phenomenology has returned in the dementia concept, and the role of the emotional stress caused to patients and their environment, became subject of attention.

Experiences in daily psychogeriatric practice inspired the present studies based on a high prevalence of neuropsychiatric (np-)symptoms, also in the very early stages of AD.

Questions concerning the aetiology arose. Can np-symptoms be explained as a psychological reaction to developing a brain disorder or as 'cognitive' decline? Or are they part of the entire coordinated symptomatology related to the disease? We have been especially occupied with the latter question. The time was ripe for a dementia model considering neuropsychiatric, cognitive and behavioural symptoms as equally relevant.

The objective of this thesis is to fully integrate neuropsychiatric disorders into the dementia concept. To this end, we asked ourselves the following questions:

a. What is the most valid and reliable method that can measure neuropsychiatric symptoms of dementia?
b. How do certain neuropsychiatric symptoms of dementia relate to environment variables?
c. What is the pathogenesis of the neuropsychiatric symptoms of dementia in reference to delirium as a highly prevalent neuropsychiatric disorder in the elderly?

The first question is answered in chapters 2 and 3.

First of all, to measure neuropsychiatric disorders in dementia, we needed a valid instrument. Moreover, we preferred using a Dutch scale. In our preliminary research we came across a number of recognized English scales, frequently used already. In **Chapter 2** we describe our research into psychometric aspects (interrater reliability,

convergent validity and construct validity) of the Dutch version of the Neuropsychiatric Inventory (NPI). The NPI was published in 1994 by Cummings, then still comprising 10 items.[1] The validated 12-item version appeared in 1997, including neurovegetative abnormalities affecting appetite and sleep.[2] We started our research in 1997 with the 12 item version. No validated Dutch version was available then. We made and validated a new translation, including (independent) back translation into English. Interrater agreement was very high for the separate as well as the sum scores (kappa >.90). The translated NPI was compared to the translated and validated versions of the RMBPC (subscales) and the MMSE.[3,4] The RMBPC has a different setup. Besides (a limited number of) psychiatric symptoms, it also rates memory impairment. To be certain about a possible bias due to memory disorders we also checked with the Dutch, validated MMSE. The items showed fairly high correlations with the relevant subscales of the RMBPC. Correlation with the RMBPC's emotional stress scale also supported validity of the NPI's emotional stress scale for caregivers. The instrument was proven to have construct-validity. Moreover, correlations with cognitive tests and assessments of 'cognitive' decline were modest at best, an argument in favour of the scales' divergent validity. The conclusion of this study is that the Dutch version of the NPI categorizes data objectively and that it is a valid instrument to survey a wide scale of neuropsychiatric symptoms of dementia.

Our study was carried out in a time when a number of measures had already been developed to systematically register a wide range of neuropsychiatric symptoms of dementia.[5-8] We opted for the NPI because it had the best universal (and value free) design: it allowed the most widely differentiated spectrum of neuropsychiatric symptoms to be registered, and it was designed for a broad inclusion of dementia syndromes and therefore applicable with the elderly, without limitations. Most other behaviour scales of that time were developed based on the 'classic' Alzheimer dementia concept.[5,8-11]

As an informant-based interview the NPI can be conducted relatively quickly and it is the only one with a process of main and in-depth questions. During the neuropsychiatric interview, the instrument follows the diagnostic process in a natural manner. Moreover, per domain serious, systematic attention is paid to the emotional distress the phenomenon at hand causes caregivers. The NPI therefore produces the most accurate caregiver distress picture, because, unlike the other scales, it has a 'frequency x severity'-score per item. This renders the instrument a better predictor of distress relatedness.

Before our research started, it was already known that the (American) NPI had been tested and proven valid with a number of other brain disorders like Progressive Supranuclear Palsy,[12] Huntington's disease[13] and Frontotemporal dementia.[14] Later

studies into Parkinson's disease with dementia,[15] Dementia with Lewy Bodies[16] and Cortical Basal Degeneration[17] were published. Now, the instrument is an international standard for medication trials, caregiver distress[18] evaluation and epidemiological and factor analytical studies.[19-22] The NPI has been widely used, with the advantage that now there is a considerable body of normative data for different dementia groups.[23]

The conclusion of chapter 2: the Dutch version of the NPI is a valid and reliable instrument to register and evaluate neuropsychiatric symptoms of dementia. It is easily applicable in practice and has a wide range setup.

As a diagnostic interview, the NPI can take a long time, especially when problems are complex (up to 45 minutes). This is not always an advantage in daily practice. Therefore we looked for an instrument approaching the NPI's psychometric qualities as closely as possible, but with a practical setup. Our needs were met by the American NPI-Q.[24] This scale is directly derived from the NPI that we had used already in studies. **Chapter 3** discusses the findings on a few validity aspects of the Dutch NPI-Q. This variant of the NPI comprises the same 12 domains. We used the psychometric results found with the NPI version (chapter 2). The NPI-Q is a shortened version of the NPI; it is a self-rating scale for caregivers, instead of an interview with them. The scale is meant to be more like a screening instrument, with abridged main questions and no in-depth questions to objectify item presence. Furthermore, it lacks a frequency measure. This renders the NPI-Q more vulnerable, with an elevated risk on unreliable answers, since symptoms are present: yes or no. In case of doubt, therefore, it is wise to ask caregivers extra questions and give further explanation, if necessary. Rating the emotional distress of caregivers is possible.

Our research focused on several validity aspects of the Dutch version of the NPI-Q. The study was done among outpatients with dementia, almost all showing np-symptoms. Correlations found with other measures supported NPI-Q validity. Behavioural and psychiatric symptoms showed relatively high correlations with equivalent (sub)scales of other instruments,[4,25,26] while there turned out to be no correlation between memory and other 'cognitive' domains.[4,27-29] Caregiver distress was strongly associated with NPI-Q symptom assessment.

In conclusion: our preliminary results support validity of the NPI-Q Dutch form. It is a practical rating scale for assessing neuropsychiatric symptoms in dementia and associated caregiver distress. The instrument does not take much time to administer.

To our knowledge, no shortened screening versions of other broadly designed measures known at that time, like BEHAVE-AD,[5] PBE,[6] BRSD,[7] MOUSEPAD,[8] were circulating when Kaufer introduced the NPI-Q in 2000. In this sense the NPI-Q was

the obvious option. Studies on more recent measures provided no new points of view. Besides, here too it holds that the universal character of the NPI strongly favoured opting for its shortened version. As a result, the NPI-Q too could be used with many dementia types, to the (economic?) benefit of elderly psychiatry and behavioural neurology practice. The argument of better predicted stress relatedness does not hold for the NPI-Q. Unlike with the original NPI, there is no frequency measure either. The NPI-Q too is an internationally, frequently used scale by now, making study comparisons easier. Moreover, a large quantity of normative data is available as a result.

The conclusion drawn from the findings described in chapter 3 is that the Dutch version of the NPI-Q is sufficiently valid, well supplementary to the Dutch NPI. It is particularly intended as a screening instrument, highly suitable for e.g. evaluating treatments in daily practice. The assessment takes a relatively short time. There is a slightly higher risk on false answers than with the NPI, which should be taken into account.

Chapters 4 and 5 answer the second question concerning the correlation between neuropsychiatric symptoms of dementia and environment variables. We used the NPI to this purpose. Chapter 4 reports on the study among a group of dementia outpatients and their caregivers. Chapter 5 describes the study we carried out among dementia patients admitted to a nursing home.

In a study among a group of elderly with dementia living at home, we studied a possible correlation between the presence of np-symptoms and a number of caregiver- and environment factors (**chapter 4**). We were especially interested in the relation between np-symptoms and the emotional distress experienced by caregivers (primary outcome) and whether other factors influence this too. Our study showed that 52% of the emotional impact variance could be explained by the neuropsychiatric symptoms as such. Other factors playing a role were sense of competence, care level required and its costs. It was concluded that emotional distress experienced by caregivers is, to a major extent, due to np-symptoms present in dementia, but that other factors too play a role.

This out-patient population consisted of patients with (very) mild to moderate stages of dementia. 83 of the 85 (98%) examined showed np-symptoms, measured/rated with the Dutch NPI version (interview). Depression and apathy had the highest prevalence rates, concurring with the findings of other studies.[30-32] Together with agitation and irritability, caregivers experienced these symptoms as distressing the most, confirming what has been found in other (population) based studies.[33-39] In a review Ballard et al. concluded that there was a pattern, despite the lack of a good comparison due

to the different designs that were used.[40] Withdrawal, apathy,[33,41] mood disturbance,[42] aggression,[43] and restlessness[44] were the most important np-symptoms associated with caregiver burden.

Next to the NPI, we also used the Model of Determinants of Subjective Burden of Carers of Persons with Dementia by Dröes,[45] which is based on the assumption that dementia patients as well as caregivers have to deal with general adaptive tasks as a consequence of the disease. A relatively great deal of attention is paid to the adaptive tasks of caregivers. Whether these tasks lead to (too much) distress or negative physical, psychological or social consequences depends mainly on the way individual caregivers cope with them,[46-51] and the sense of competence they experience as a result of this.[52] The latter is the perceived caregiver ability to cope with the task of caring for a dementia patient.

Using this model, our study showed that 48% of the variance in experienced emotional distress was explained by other factors than np-symptoms as such. A low sense of competence was related to greater emotional impact on caregivers. Other studies too show that the individual experienced distress in the adaptation process is an important factor and call for this to be taken into account during treatment.[53-59] A second factor was the degree of care needed by persons with dementia, which was inversely related to the emotional burden of np-symptoms, suggesting the emotional distress is largest in the early phases of the disease.[60] An earlier study found the same association.[61] Thirdly, we found additional financial expenditure due to care giving, such as travelling costs and costs for the use of community-based services by the person with dementia, proved to be related to a higher emotional impact on caregivers. High caregiver distress has been associated with more use of services in other studies as well.[60-62]

The study discussed in this chapter showed that caregiver distress is determined by patient, caregiver and environmental factors. The results of more recent research too suggest a multifactorial influence.[63-65] Furthermore, if dementia results in apathy, agitation and mood disturbances, these are important factors of caregiver burden. This finding too is supported by other research among dementia outpatients.

Measuring with the NPI gives the advantages of covering a wide range of np-symptoms and allowing caregiver distress to be rated per sub-item. Thus we could distinguish between apathy and depression and its specifically associated emotional reactions. A recent study shows that the distress associated with np-symptoms does not always depend on the frequency and severity of symptoms. Low frequencies and severity too can cause major distress.[66] The NPI allows this differentiation.

Concluding from chapter 4: the validated Dutch NPI is an adequate instrument

for detailed registration of caregiver distress related to np-symptoms of dementia. Moreover, it appears that caregivers overall burden is only partly determined by np-symptoms. Other factors too should be taken into consideration. As far as we know, our study is the first to examine caregiver burden by np-symptoms with the validated Dutch version of the NPI distress scale.

Demented outpatients often rely on support by partners or other relatives. These are generally patients with mildly to moderately severe stages of the disease. Patients with more severe stages of the disease live in nursing homes and get care from professional caregivers. **Chapter 5** discusses the findings of a consultation study we did among dementia patients admitted to nursing homes (n=325). We were interested in the reasons why consultation was sought (at symptom level) and how nature and frequency of the symptoms in the referred group related to prevalence data of the np-symptoms of dementia in nursing homes. To answer the second question, we used prevalence data from another Dutch study.[67] As we suspected that dementia patients referred to mental health care specialists are very likely to have np-symptoms, we also wanted to know to what extent referral reasons could be adequately classified according to np-domains of the NPI.

Agitation, disinhibition and aberrant motor behaviour were frequent reasons for referrals (>25%). Apathy, psychotic symptoms and changed eating behaviour were infrequent reasons (<10%) for seeking consultation. Agitation and disinhibition were more often primary reasons for consultation than was expected based on normative prevalence estimates of these symptoms. In contrast, delusions, euphoria, apathy, irritability and changed eating behaviour were less often reasons for referral compared to prevalence estimates.

We concluded that there are large differences between referral reasons and normative data on symptom prevalence. Specialized mental health service was provided for agitated and disinhibited patients in particular. Chances are that this was at the expense of the apathetic, retarded and quiet patients, ‘not causing any trouble’. Using the NPI domains it was possible to classify more than 85% of the reasons for consultation. So, the NPI subdomains encompassed all referrals for consultation in this dementia population. The remaining 10-15% mostly concerned (other) diagnostic questions or indication consultations.

To our knowledge this is the first time that reasons for psychiatric consultation were compared to independent prevalence estimates of np-symptoms in a large sample of nursing home patients with dementia. Therefore it is hard to comment on the generalizability of our results. However, our findings are consistent with observations

made in other countries[68-71] focused on subtype and frequency of referrals, which were evaluated but lacked comparisons to prevalence estimates. The results of these studies are not entirely comparable due to differences in design, instruments used, populations selected, settings and countries where the studies were done. However, some trends concurring with our findings can be identified. The most frequently observed reasons for referral were behavioural problems (agitation/aggression, mostly followed by mood-related symptoms and psychotic features), whereas behaviours that may be considered non-disturbing, like apathy (if measured as a separate item) or retarded depressed behaviour, led to hardly any consultation request.

Nursing home staff often fail to recognize depression.[71,72] Particularly quiet or retarded depressed residents may be overlooked.[70] Also age and impairment of Activities of Daily Living predict not receiving treatment from a mental health professional.[69] There may be other factors influencing referral patterns, like knowledge levels and availability of staff and other professionals, like psychologists, in these settings. Cohen-Mansfield et al. conclude that physicians are not always sufficiently informed about nonpharmacological interventions, leaving consultations undone and staff tempted quicker to prescribe medication themselves.[73] Whether this also applies to Dutch nursing home physicians, who have had some specialist training in both geriatric medicine and psychiatry, is debatable.

Apart from the methodological limitations mentioned, our findings are consistent with those of others, which support the validity of our observations.

We conclude from chapter 5: This is the first study in which reasons for referral for Dutch nursing home patients with dementia were compared with normative data on prevalence of np-symptoms. Reasons for psychiatric referral and prevalence rates of np-symptoms differ. Symptom domains characterized as troublesome ('hyper-behaviours') were over reported, while symptoms like apathy and retarded depressive behaviour ('hypo-behaviours'), were underrated. The NPI domains proved good tools to characterize problems requiring consultation in this patient population. More research into the generalizability of our findings and the factors influencing the discrepancies that we found is needed. Especially the finding that 'hypo-behaviours' seem a minor problem in nursing homes, while they can be experienced as a heavy burden in the outpatient population (see our findings in chapter 4), is worth to be analysed further.

Chapters 6 and 7 discuss the studies related to the last question of this thesis, the question of the pathogenesis and outcome of np-symptoms of dementia. A cohort of delirious patients was monitored prospectively and tested on a number of cognitive functions (chapter 6) and the pattern of mortality was described (chapter 7). Delirium

is a well defined np-syndrome, much studied over the last decade. There is growing evidence for the hypothesis that dementia and delirium represent a continuum of cognitive disorders, rather than as two entirely separate conditions.[74,75] Prevalence of delirium among the elderly is high, especially among elderly patients admitted to general hospitals (up to 65%). The cohort monitored by us was also a fairly homogenous research population with relatively little comorbidity. We studied elderly subjected to hip surgery, who developed delirium postoperatively. Patients were recruited from a patient population (n=603) of a delirium prevention study,[76] a randomized placebo-controlled study for patients at risk for delirium. In this study, patients were tested on admission in the pre-delirium stage (T=0) on cognitive functioning, among other things. All patients with postoperative delirium (n=74) were eligible to participate in the follow-up studies.

Chapter 6 discusses the study on predictors for cognitive decline after 2.5 years on average. In the end, 71 postoperatively delirious patients could be included, 41 of which could be matched with patients who did not develop delirium, but having the same number of risk factors (preoperative at T=0). In the follow-up measurements after 2.5 years, patients were assessed for the same tests as on T=0, independently by a standard, neuropsychiatric, clinical interview with patients and knowledgeable informants. During the follow-up period, 54.9% of the delirium patients had died compared to 34.1% of the controls (relative risk = 1.6, 95% CI = 1.0 - 2.6). Dementia or MCI was diagnosed in 77.8% of the surviving patients with postoperative delirium and in 40.9% of the control patients (relative risk = 1.9, 95% CI = 1.1 - 3.3). Half the patients with delirium were institutionalized at follow-up, compared to 28.6% of the controls (relative risk = 1.8, 95% CI = 0.9 - 3.4). We concluded that the risk of dementia or MCI at follow-up for elderly hip surgery patients with postoperative delirium is almost doubled in comparison to patients with a similar risk profile but without delirium. Delirium may indicate underlying incipient dementia.

Our study shows that baseline differences between delirium patients and controls did not account for the effects found, implying that delirium independently predicts long-term adverse outcome. Six other studies also found an increased dementia risk associated with delirium at follow-up.[77-82] The relative risk of cognitive disorders found in our sample is comparable to those found in the other studies. However, none of these studies, except two,[81,82] examined the relative risk of dementia associated with delirium in a homogeneous, hip surgery, patient sample after checking for important, preoperatively assessed, delirium risk factors, or they did not include independent, clinical, follow-up assessments.

The strengths of our study are the primary outcome data set, inclusion of a homogeneous, hip surgery, patient sample, and use of standardized and validated

methods for diagnosing delirium, based on clinical patient interviews, pre-surgery and pre-delirium measures of predefined baseline risk factors, clinical, neuropsychiatric assessment at follow-up and subtyping of cognitive outcome.

In our study, care was taken that, prior to surgery, no major differences with respect to cognitive function existed between patients with delirium and controls. Nevertheless, we could not match 30/71 delirium patients to controls because of differences in risk factor profiles at baseline (T=0). Unmatched delirium patients did worse on the MMSE than those matched, indicating more cognitive impairment. Moreover, a wide score range was observed for the MMSE (10-29). So, it is clear that some patients already had dementia or MCI before inclusion in the study. Although no conclusions on causality can be drawn from this study, it further reinforces the finding that underlying processes associated with dementia may be a contributor to inpatient delirium, and that identification of underlying cognitive impairment may not be made until after an inciting event, such as major orthopaedic surgery.

Our findings are supported by others. Elie et al. conclude that dementia is the strongest risk factor for delirium among older patients.[83] Bickel et al. found that long-term cognitive impairment was observed primarily in patients with delirium who were advanced in age and had pre-existing mild cognitive deficits.[82] Cole et al. submit that one explanation for the poor prognosis of delirium among older hospital patients may be that many of these patients do not recover from delirium, also not after discharge from hospital.[84] Our results do not support this hypothesis. For our study, we recruited patients from a relatively healthy population of elderly, participating in an RCT with haloperidol to prevent postoperative delirium. Delirium duration was carefully monitored in the trial and patients did not leave hospital until their delirium was over. In the fact the average stay of patients with delirium was longer than that of the patient group that did not develop delirium postoperatively. Moreover, the clinical neuropsychiatric examination at follow-up showed no delirium in any of the patients studied.

We conclude from chapter 6 that our study was carefully controlled in order to evaluate the relationship between the occurrence of postoperative delirium and long-term cognitive impairment. Dementia or MCI at follow-up is almost doubled in elderly hip surgery patients with postoperative delirium compared with at-risk patients without delirium. Delirium may indicate underlying dementia. Under specific conditions, like undergoing surgical procedures, delirium, as a neuropsychiatric syndrome highly prevalent among the elderly, can be the manifestation of cognitive decline already present. The relation between dementia and delirium can best be seen ‘along a

continuum of cognitive disorders, rather than two entirely separate conditions'.

The aim of our second delirium follow-up study was to examine delirium and delirium risk factors predicting mortality at two-years follow-up in elderly hip-surgery patients (n=603) (**chapter 7**). Primary outcome was death during the 2 years follow-up period. Cox proportional hazards were estimated and compared between patients who had postoperative delirium during hospitalization and those who did not. A total of 90/603 patients (14.9%) died during the study period and 74/603 (12.3%) had postoperative delirium. Incidence of delirium was higher in patients who died (32.2%) compared with those who survived (8.8%). The effect of delirium on mortality was significant after adjusting for predefined delirium risk factors and other potential co-variates, including study intervention (adjusted Hazard risk = 1.98, 95% CI 1.24-3.17). Risk factor stratification showed that 10% of patients with delirium and 0-1 risk factors had died, 40.7% of those with 2-3 risk factors and 59.3% with 4-5 risk factors compared to 6.1%, 13.5% and 43,1% of patients without delirium at low, intermediate and high risk of poor outcome. We conclude that delirium independently predicts mortality at two-year follow-up in elderly hip-surgery patients. Outcome for delirium is particularly poor when other risk factors are present.

One previous study found an increased mortality risk associated with delirium at 6 months follow-up and three studies found increased risk at 12 months follow-up or longer.[81,85-87] In the Nightingale et al. study, hip-fracture patients were interviewed by a psychiatrist or psychiatric nurse between 2 and 5 days after surgery and an adjusted 2 year hazard ratio of 2.4 was found associated with delirium (CI 1.7-3.5).[86] In the Edelstein et al. study 47/921 (5.1%), hip fracture patients had postoperative delirium and were more likely to have died at 1 year follow-up (unadjusted odds ratio 2.4, CI 1.1-4.9).[87] Lundström et al. found that 21/29 femoral neck fracture patients with postoperative delirium died within 5 years, compared to 17/49 of those who did not have delirium (P=.001).[81] The hazard ratio found in our sample is comparable to those found in the earlier studies. However, we clinically assessed patients on admission, prior to surgery, and included large numbers of patients, many of whom were not at risk for delirium. In doing so, we were able to examine the effects of delirium as well as baseline risk factors on mortality. Thus, our method represents a rigorous approach to studying the important problem of adverse, long term outcomes associated with delirium.

Advanced age and pre-existing cognitive impairment, two of the risk factors for mortality found in this study, have been identified as 2 major risk factors for prolonged delirium.[88] Although some patients may have had (mild) delirium symptoms at discharge, we believe persistent delirium symptoms per se, as Cole concludes,[84] are not a likely

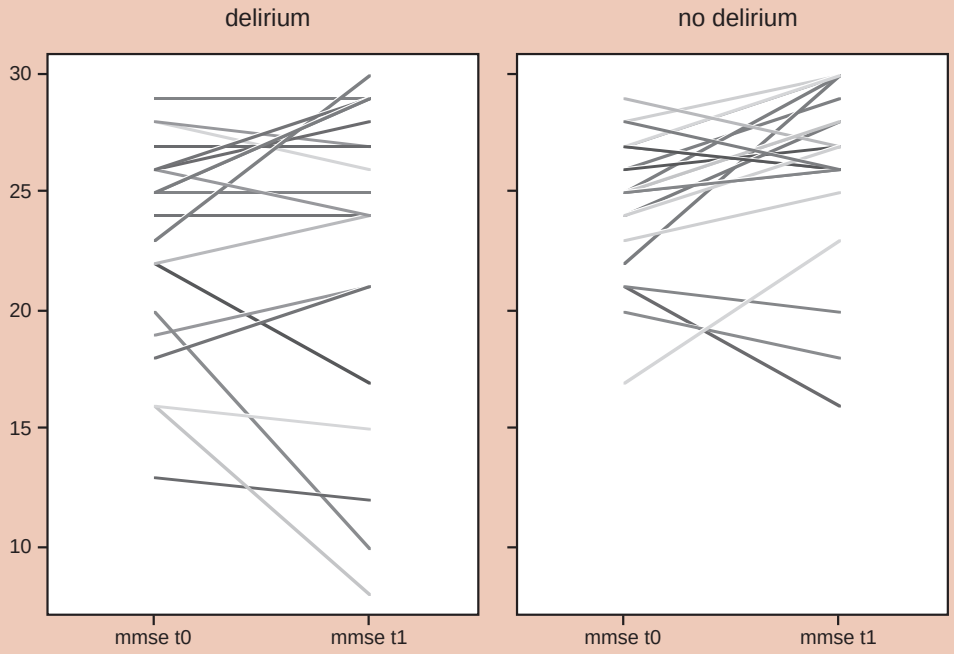
explanation for excess mortality at follow-up. Risk factor stratification for poor outcome was examined, based on presence of delirium and other risk factors. Base rate mortality in the reference group at low risk was 6.1%. Prognosis of incident delirium was not significantly different when only few risk factors were present; all but two of the delirium patients with few risk factors survived. However, 40.7% of the delirium patients with two or three risk factors died; 59.3% died in case of four or five risk factors. So, prognosis of post hip-surgery delirium is reasonably good when you are relatively young and healthy. It is worse for cognitively impaired older men, who are acutely admitted to hospital and who have poor vision.

We conclude from chapter 7 that vulnerability in delirium patients as expressed by presence of predisposing and precipitating factors explains excess mortality, at least to some extend. Results from the risk factor stratification analysis seem to support this hypothesis.

Developing postoperative delirium and earlier mortalities seem to share the same basis. In chapter 7, one of the conclusions was that the prognosis of post hip-surgery delirium is reasonably good when you are relatively young and healthy. It is worse for cognitively impaired older men who are acutely admitted to hospital and who have poor vision. This shows that there is a connection between suffering delirium and the presence of cognitive impairment with poor prognosis. It is likely that in patients developing delirium already incipient neurodegenerative processes associated with dementia were present before admission. One explanation was found in analyzing the MMSE's, which could be carried out in both follow up studies (**chapter 6 and 7**). In chapter 6 it is determined that delirium occurs mainly with low premorbid MMSE scores. Chapter 7 shows that patients in the deceased group had significantly lower average baseline values (pre-operatively) on the MMSE than the survivors (22.1 vs. 25.8). This group consisted for 32.2% in patients with postoperative delirium. In the survivors group, this was only 8.8%, approximately a 4:1 ratio. As far as cognitive functioning is concerned, it can be concluded from the results found in the chapters 6 and 7 that delirium (as a neuropsychiatric syndrome) is highly prevalent among elderly and that it may be a clinical manifestation of a premorbid cognitive disorder already present. In other words, there seems to be a pathogenetic relation between delirium and the premorbid presence of a cognitive disorder.

Box 1. MMSE and Cognitive outcome

In chapter 6 we conclude that dementia or MCI at follow-up is almost doubled in elderly hip surgery patients with postoperative delirium compared with at-risk patients without delirium and that delirium may indicate underlying dementia. The study shows that delirium occurs more frequently in patients with a low, pre-operative baseline value on the MMSE (<21) and that this value is also an important predictor of cognitive decline after 2.5 years. Further analysis of individual MMSE patterns between the moments t0 (on admission, pre-operatively) and t1 (2.5 yrs later) in both groups (delirium vs. no delirium), yielded the following findings (figure).



In both groups, therefore irrespective of the occurrence of delirium, at t0 MMSE values tended to be similar to or even somewhat lower than MMSE scores at t1 in most cases. Apparently, high baseline values were associated with similar scores on follow up, whereas patients showing deterioration also had relatively low scores at baseline.

One remarkable additional finding is that MMSE scores tend to increase on follow up. This raises critical questions on the use of this internationally recognized 'golden standard' with this type of research. Scores do not always appear to be consistent: they can improve even and sensitivity to stress seems to be of influence (see chapter 6). We have found no earlier comments on this matter in other follow up studies.

Future research

This thesis calls for attention to a broader dementia concept, in which the psychiatric phenomenology too is fully recognized. Based on several studies on neuropsychiatric aspects of dementia we come to the following recommendations.

First of all, it is important that the neuropsychiatric syndromes found are considered as an integral part of clinical symptoms of dementia. The question whether these are merely independent psychiatric syndromes or parts of the body of symptoms of dementia disorder remains relevant. Further research into this is required. Clinical pictures with cognitive decline and associated neuropsychiatric symptoms (e.g. the psychotic symptom described with DLB) might lead to different treatment than the one needed for a psychotic disorder resembling schizophrenia, not likely to be expected during the course of dementia. This avenue has also been recommended internationally.[89,90]

Another, important research field for the future relates to the question whether there are specific neuropsychiatric problems in the early stages of dementia or during the Mild Cognitive Impairment (MCI) phase.[30,32] As outlined in the introduction of this thesis it is not appropriate to reserve the notion of cognition exclusively to intellectual functions and to 'ban' perception and thinking. This also applies to the motivational aspects of dementia, like apathy. Next to attention paid to mild 'cognitive' symptoms, there should also be further research into profiles of early dementia, in which np-symptoms play a full, integrated role. Quoting Lishman:[91] 'Many disease processes affecting the brain will come to attention with psychological symptoms alone and well before the appearance of definite neurological signs, and it is often by the correct appreciation of these common forms of reaction that a mistaken diagnosis of non-organic (or so-called 'functional') psychiatric disorder will be avoided'. Analogous to the MCI concept, one could speak of Mild Affective Impairment (MAI), Mild Psychotic Impairment (MPI) and Mild Motivational Impairment (MMI).

For such a model to be applied consequently, matching neuropsychological test examinations are indispensable. 'Classic' routine neuropsychological examinations were developed based on the assumption that dementia is primarily a 'cognitive' disorder, highly focused on testing memory and (other) intellectual functions (derived from the traditional Alzheimer concept). Full research into neuropsychiatric symptoms of dementia calls for a new sort of neuropsychological examination that integrates these problems into the whole of the findings. Currently, these phenomena are too often only discussed after extensive 'cognitive' profiles have been made. As a result, this inventory made might be qualified as an appendix (read by-product) with the neuropsychiatric symptoms merely as the total score of a short screening instrument.

For further characterization and differential diagnostics of neuropsychiatric phenomenology of dementia, both neuropsychiatric and neuropsychological research need to systematically pay attention to:

1. The spectrum of *affective* derangement, with attention for slight differences in grief, depression, inhibition, apathy (like diminished emotional involvement), emotional instability, fear, anxiety, agitation;
2. The spectrum comprising phenomena that have *distorted reality testing* as a key issue. One should think of paranoia, misidentifications, delusional/false perceptions, illusionary falsifications, hallucinations, delusions;
3. The spectrum of np-symptoms with *motivational aspects* at the centre: active withdrawing, avoidance, apathy (as a disorder of drive and attention), impulsive and repetitive behaviour, disinhibition and aboulia;

The following recommendations concerning future research are directly derived from the studies included in this thesis.

The findings on the emotional stress with partners of patients with dementia gave us the idea to further examine their specific characteristics. Why does apathy bother one partner more than the other? Is there a relation with coping, personality characteristics or role patterns? Eventually, this could lead to more customized care. Such research could also be useful from a system theoretical point of view. Patient-caregiver interaction crises and psychological problems in caregivers might be prevented. A recent review of predictors of nursing home admission for persons with dementia found that caregiver indicating greater emotional stress, a desire to institutionalize the care recipient and feelings of being “trapped” in care responsibilities were more likely to result in admission of patients with dementia to nursing homes.[92] This finding underlines the importance of further research into specific caregiver characteristics in the interaction between patients and their environment.

Especially for nursing homes, the NPI could be a particularly useful instrument to initiate research into the np-symptoms of dementia that occur very frequently in this setting. One should think of agitation, apathy and repetitive behaviour. Very little is known yet about repetitive behaviour in particular. What is the relation with apathy and the dementia severity stage? How specific is this syndrome for dementia or should we conclude that it is an a-specific phenomenon, occurring in many more psycho-organic diseases or is it a sign of a (hypoactive) delirium based on (other) somatic disorders? Which interventions could be most efficient? Are not antipsychotics actually counterproductive with repetitive behaviour? The question whether this behaviour

results from growing deprivation (under stimulation) or a clinical expression of progressive brain disease, in which contact with the environment is lost more and more (disinhibition, autism, loss of contact with reality?) is also relevant too treatment. Streim et al.[93] submit that 'of all long term care settings, the nursing home has served as the most productive laboratory for the study of mental health problems of late life. Lessons from geriatric psychiatry research and practice in the nursing home have relevance to general psychiatry and to other health care settings'.

The Dutch association of nursing home physicians (NVVA) published a Guideline for Problem Behaviour. Using these guidelines may increase awareness of behavioural problems in the nursing home setting. However, the NVVA guideline approach is based on symptoms, while thorough assessment of underlying neuropsychiatric disorders seems not to be a big issue. As a consequence there is a risk for misdiagnosis and wrong treatment decisions. Neuropsychiatric assessment can help making better diagnoses, also in the nursing home setting.

In the two delirium follow up studies described in this thesis, delirium as a neuropsychiatric syndrome served as a model for research into a possible correlation between neuropsychiatric symptoms and dementia. This model lends itself well for further research into this relation. However, delirium has several clinical presentations and one might ask oneself whether there is a difference in outcome between hyper- and hypokinetic delirium and how do they relate to cognitive (and which subtype?) decline at follow up? Unlike we did in the follow up studies, measuring the course at several moments deserves recommendation, certainly when subtle differences in np-syndromes are to be distinguished. In that case several measurements during admission are also indicated, for instance to gain a better view on the course of attention disorders with the neuropsychiatric phenomenology. Beforehand, patients need to be screened more carefully for dementia. The MMSE proved a stress sensitive instrument as a screening measure in our study. It would be interesting to see how other tests would perform in this respect.

Concluding remarks

The aim of this thesis was to study the neuropsychiatric symptoms of dementia more closely and to contribute to the integration of these phenomena into the diagnostics and treatment of dementia.

Neuropsychiatric disorders are highly prevalent, also in very early types of dementia. They constitute major burdens on patients and on informal and professional caregivers. Neuropsychiatric symptoms need to be a full part of a modern clinical assessment in dementia. Neuropsychiatry can help to refine differential diagnosis in dementia.

Implementation of exactly these innovations will allow for the definition of new (pre-senile) dementia syndromes, development of adequate pathogenic models and possibly for more specific symptomatic treatments. Neuropsychiatric insights, carrying the concept of dementia beyond the limited cognitive paradigm, can contribute to a change of our thinking on dementia, by broadening the scope of clinical research for the benefit of patients with dementia that suffer from more than memory problems alone.

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CHAPTER 9

Summary

Dementia is a neuropsychiatric syndrome in which impaired memory is considered to play a key role. Ever since the discovery of dementia little attention has been paid to psychiatric problems that often co-occur. These problems are referred to as neuropsychiatric symptoms (**np-symptoms**) in this thesis.

Chapter 1 consists of a brief historical review of how dementia was conceptualized throughout the past 125 years. Secondly, the aims and outline of this thesis are given. Until 1880 the disorder was defined as a broad concept comprising both 'organic' as well as 'functional' psychiatric syndromes. In the second half of the 19th century, as the consequence of the rise of a biological, clinicopathological oriented psychiatry, dementia became an 'organic' disorder. Senile dementia was defined as a cognitive disorder and focus was on the irreversible nature and the association with age. As amnesia was thought to be the key symptom, dementia became primarily a memory disorder.
Neuropsychiatric symptoms were considered to be non-cognitive in nature, and secondary to or a result of cognitive symptoms and no longer included in the core criteria for dementia. Even Alois Alzheimer's findings in his case study of Auguste D. (reported in 1907), a presenile form of dementia starting with neuropsychiatric symptoms besides memory and other intellectual problems, didn't change the view on dementia in those days. On the contrary, Alzheimer's disease became the prototype of the 'organic' dementias, either presenile or senile. Research during the period 1950-1980 lent further evidence supporting this hypothesis. The period after 1980 is the age of clinical epidemiological studies and psycho- and clinimetrics. This is the time when it gradually becomes clear that behavioural problems and psychiatric disorders are highly prevalent in dementia (up to 90%) and they should hold a prominent position in the diagnostic research and treatment. It is also established that these problems draw heavily upon the mental constitution of caregivers and cause early admissions to institutions. It is this awareness of neuropsychiatric symptoms of dementia and its consequences that triggered our interest and gave rise to the questions formulated in this thesis.

Chapters 2 and 3 deal with the first question to be answered: what is the most valid and reliable method that can measure np-symptoms of dementia? In **chapter 2** the research is described into psychometric aspects (interrater reliability, convergent validity and construct validity) of the Dutch version of the Neuropsychiatric Inventory (NPI). We started our research in 1997. No validated Dutch version was available then. We made and validated a new translation, including (independent) back translation into English.

Interrater agreement was very high for the separate as well as the sum scores (kappa >.90). The instrument proved construct-valid. Besides, correlations with cognitive tests and assessments of 'cognitive' decline were very modest, an argument in favour of the scales' divergent validity. The NPI had the best universal (and value free) design: it allowed the most widely differentiated spectrum of neuropsychiatric symptoms to be registered, and it was designed for a broad inclusion of dementia syndromes. Most other behaviour scales were developed based on the 'classic' Alzheimer dementia concept. Moreover, per domain serious and systematic attention is paid to the emotional distress the phenomenon at hand causes for caregivers. The NPI therefore produces the most accurate caregiver distress picture, because, unlike the other scales, it has a 'frequency x severity'-score per item. This renders the instrument a better predictor of distress relatedness.
The conclusion of this study is that the Dutch version of the NPI is a valid and reliable instrument to assess and evaluate neuropsychiatric symptoms of dementia. It is easily applicable in practice and has a wide range setup.

Chapter 3 discusses validity aspects of the Dutch NPI-Q. This instrument is a short version of the NPI. It is a self rating questionnaire for caregivers, and no interview is required. Correlations found with other measures supported NPI-Q validity. Behavioural and psychiatric symptomatology showed relatively high correlations with equivalent (sub) scales of other instruments, while no correlation was found between neuropsychiatric symptoms, memory and other 'cognitive' domains. Caregiver distress was strongly associated with NPI-Q symptom assessment. The conclusion is that the Dutch version of the NPI-Q is valid, and supplementary to the Dutch NPI. It is particularly useful as a screening instrument for np-symptoms in dementia and associated caregiver distress. The NPI-Q is highly suitable for e.g. evaluating treatments in daily practice. Contrary to the NPI, the NPI-Q lacks a clinical interview which brings about a slight risk of under or over reporting neuropsychiatric symptoms.

Chapters 4 and 5 deal with the second research question of this thesis pertaining to the associations between neuropsychiatric symptoms of dementia and environment variables. **Chapter 4** reports on a study of neuropsychiatric symptoms in dementia outpatients and also included primary caregivers. Dementia outpatients often rely on spouses or other relatives for support. The patients are often in the mild to moderately severe stages of the disease. Potential associations were studied between the presence of np-symptoms and caregiver and environment factors. We were especially interested in the relation between np-symptoms and the emotional distress

experienced by caregivers and whether other factors influence emotional distress too. Our study showed that 52% of the emotional impact variance could be explained by the neuropsychiatric symptoms as such. Other factors playing a role were sense of competence of the caregiver, care level required and its costs. It was concluded that emotional distress experienced by caregivers is, to a major extent, due to np-symptoms present in dementia. Depression and apathy had the highest prevalence rates. Together with agitation and irritability, caregivers experienced these symptoms as distressing the most, confirming what has been found in other (population based) studies. The study showed that caregiver distress is determined by patient, caregiver and environmental factors. The results of more recent research too show that several factors determine caregiver distress. Furthermore, if dementia comes with apathy, agitation and mood disturbances, they are important factors of caregiver distress. Also in our study it was possible to distinguish between apathy and depression and to evaluate different emotional reactions to those. The conclusion we draw in reference to this and other researched studies is that the validated Dutch NPI is an adequate instrument for detailed assessment of caregiver distress related to np-symptoms of dementia. Moreover, it appears that caregivers overall burden is only partly determined by this. Other factors too should be considered as well. As far as we know, our study is the first to examine caregiver burden by np-symptoms with the validated Dutch version of the NPI distress scale.

Chapter 5 describes the consultation study carried out among dementia patients admitted to a nursing home (n=325). The patients are in the moderate to severe stages of dementia and are cared for by professional caregivers. We were interested in the reasons why consultation was sought (at symptom level) and how this relates to prevalence data of np-symptoms in nursing home patients with dementia. As we suspected that dementia patients referred to mental health care specialists are very likely to have np-symptoms, we also wanted to know to what extent referral reasons could be adequately classified according to np-domains of the NPI. Prevalence data from another Dutch study were available.
Using the NPI domains it was possible to classify more than 85% of the reasons for consultation. So, the NPI subdomains encompassed all referrals for consultation in this dementia population. The remaining 10-15 % mostly concerned (other) diagnostic questions or indication consultations. Large differences were found between referral reasons and normative data on symptom prevalence. Specialized mental health service was provided for agitated and disinhibited patients in particular. Chances are that this was at the expense of the apathetic, retarded and quietly ‘not causing any trouble’

patients. To our knowledge this is the first time reasons for psychiatric consultation were compared to independent prevalence estimates of np-symptoms in a large sample of nursing home patients with dementia. More research into the generalizability of our findings and the factors influencing the observed differences is needed. Especially the finding that 'hypo-behaviours' like apathy and retarded depressive behaviours seem a minor problem in nursing homes, while they can be experienced as a heavy burden in the outpatient population, needs to be analysed further.

Chapters 6 and 7 concern the last question of this thesis: the pathogenesis and outcome of np-symptomatology of dementia. Two prospective studies are presented. Cognitive function was monitored over a 2.5 years period in a cohort of delirious patients and matched control subjects (chapter 6). Secondly, the long term hazard risk associated with post-operative delirium was examined (chapter 7). **Chapter 6** focuses on predictors for cognitive decline. A total of 71 postoperatively delirious patients was followed up, and 41 of them were matched with patients who did not develop delirium, but did have the same number of risk factors (preoperative at T=0). At follow-up 2.5 years later, patients were independently assessed using the same tests as on T=0. Dementia or Mild Cognitive Impairment (MCI) was diagnosed in 77.8% of the surviving patients with postoperative delirium and in 40.9% of the control patients (relative risk = 1.9, 95% CI = 1.1 - 3.3). In our study, care was taken that, prior to surgery, no major cognitive differences existed between patients with delirium and controls. Nevertheless, no match was found for 30/71 delirium patients because of differences in risk factor profiles at baseline (T=0). Unmatched delirium patients did worse on the MMSE than those matched, indicating more cognitive impairment. Moreover, a wide score range was observed for the MMSE (10-29). So, it is clear that some patients already had dementia or MCI before inclusion in the study. Although no conclusions on causality can be drawn from this study, it further reinforces the finding that underlying dementia may be a contributor to inpatient delirium. In conclusion, this study was carefully controlled in order to evaluate the relationship between the occurrence of postoperative delirium and long-term cognitive impairment. Dementia or MCI at follow-up is almost doubled in elderly hip surgery patients with postoperative delirium compared with at-risk patients without delirium. Delirium may indicate underlying neurodegenerative disease. Under certain circumstances, e.g. following surgery, the neuropsychiatric syndrome of delirium can be a marker of underlying cognitive decline. The relation between dementia and delirium can best be seen along a continuum of cognitive disorders, rather than two entirely separate conditions.

The aim of the second delirium follow-up study, described in **chapter 7**, was to examine delirium and delirium risk factors predicting mortality at two-years follow-up in elderly hip-surgery patients (n=603). Primary outcome was death during a 2 years follow-up period. Incidence of delirium was higher in patients who died (32.2%) compared with those who survived (8.8%). The effect of delirium on mortality was significant after adjusting for predefined delirium risk factors and other potential co-variables. First of all we concluded that delirium independently predicts long term mortality in elderly hip-surgery patients. Outcome for delirium is particularly poor when other risk factors are present. Risk factor stratification showed that 10% of patients with delirium and 0-1 risk factors had died, 40.7% of those with 2-3 risk factors and 59.3% with 4-5 risk factors compared to 6.1%, 13.5% and 43.1% of patients without delirium at low, intermediate and high risk of poor outcome. Prognosis of post hip-surgery delirium is reasonably good when you are relatively young and healthy. It is worse for cognitively impaired older men, who are acutely admitted to hospital and who have poor vision. The second conclusion is that vulnerability in delirium patients as expressed by presence of predisposing and precipitating factors explains excess mortality, at least to some extend. Results from the risk factor stratification analysis seem to support this hypothesis.

Developing postoperative delirium and premature death seem to share the same basis. In chapter 7, one of the conclusions was that the prognosis of post hip-surgery delirium is worse if the patient is old and cognitively impaired. It is likely that in patients developing delirium already incipient neurodegenerative processes associated with dementia were present before admission. One explanation was found in analyzing the MMSE‘s, which could be carried out in both follow-up studies (**chapters 6 and 7**). In chapter 6 it is determined that delirium occurs mainly with low premorbid MMSE’s. Chapter 7 shows that patients in the deceased group had significantly lower average baseline scores (pre-operatively) on the MMSE than the survivors (22.1 vs. 25.8). This group consisted for 32.2% in patients with postoperative delirium. In the survivors group, this was only 8.8%, approximately a 4:1 ratio. As far as cognitive functioning is concerned, it can be concluded from the results of the two follow-up studies that delirium, as an np-syndrome highly prevalent among the elderly, can under special circumstances be the clinical manifestation of a premorbid cognitive disorder already present. In other words, there seems to be a pathogenetic relation between delirium and the premorbid presence of a cognitive disorder.

Finally, **chapter 8** summarizes the main findings of this thesis and contains a general discussion about the relevance of the results, some methodological considerations

and the implications for daily clinical practice and future research. This thesis calls for attention to a broader dementia concept, in which the psychiatric phenomenology too is fully recognized. Answers were given to the three questions concerning the measurements, implementation, outcome and possible pathogenesis of the np-symptoms in dementia.

CHAPTER 10

Dutch Summary (Samenvatting)

Dementie is een neuropsychiatrisch syndroom waarin geheugenstoornissen een centrale plaats hebben. Zolang de hersenaandoeningen die ten grondslag liggen aan dementie bekend zijn is er relatief weinig aandacht geweest voor de frequent voorkomende psychiatrische problematiek in het kader van dementie. In dit proefschrift wordt deze aangeduid met neuropsychiatrische symptomen (**np-symptomen**).

In **hoofdstuk 1** wordt een beknopt overzicht gegeven van de verschillende zienswijzen in de laatste 125 jaar op het dementieconcept. Vervolgens worden de doelen en de opzet van het proefschrift besproken. Tot 1880 bestond er een breed gedefinieerd dementieconcept waaronder zowel 'organisch' als 'functioneel' psychiatrische ziektebeelden waren verenigd. In de tweede helft van de 19e eeuw werd dementie als gevolg van de opkomst van een organisch georiënteerde, clinicopathologische psychiatrie, beschouwd als een 'organische' hersenziekte. Seniele dementie werd daarmee een cognitieve stoornis die geassocieerd werd met irreversibiliteit en het voorkomen op oudere leeftijd. Doordat men amnesie als het belangrijkste kernsymptoom ging beschouwen werd dementie vooral een geheugenstoornis. Neuropsychiatrische symptomen werden beschouwd als non-cognitieve, secundaire of reactieve fenomenen en van ondergeschikt belang voor het stellen van de diagnose. Ook de bevindingen van Alois Alzheimer bij zijn patiënte Auguste D. (gepubliceerd in 1907), een preseniele vorm van dementie met al vroeg in het ziekteproces neuropsychiatrische symptomen naast geheugen- en andere intellectuele stoornissen, kon de visie op dementie in die tijd niet veranderen. Sterker nog, de ziekte van Alzheimer werd het prototype van de 'organische' dementieën, zowel voor de pre- als seniele vormen. De resultaten van wetenschappelijk onderzoek in de periode 1950-1980 werden beschouwd als ondersteuning voor deze hypothese.
Vanaf 1980 is het onderzoek meer klinisch (epidemiologisch) en psychometrisch van aard. Dit is ook de periode waarin geleidelijk aan duidelijk wordt dat gedrags- en psychiatrische stoornissen veel voorkomen bij dementie (tot 90%) en dat deze een belangrijke plaats dienen te krijgen in het onderzoek en de behandeling. Bovendien wordt bekend hoe groot de mentale en fysieke belasting is ten gevolge van deze problematiek voor de direct betrokkenen en hoe deze kan leiden tot vervroegde opname in een verpleeghuis. Mede door deze ontwikkelingen zijn de eerste ideeën ontstaan voor dit proefschrift, wat uiteindelijk resulteerde in de hier gestelde onderzoeksvragen.

In de hoofdstukken 2 en 3 wordt de eerste vraag n.l. wat de meest valide en betrouwbare methode is om np-symptomen bij dementie te meten, beantwoord.
In **hoofdstuk 2** wordt het onderzoek beschreven naar psychometrische aspecten

(interbeoordelaarsbetrouwbaarheid, construct- en convergente validiteit) van de Nederlandse versie van de Neuropsychiatric Inventory (NPI). Wij startten ons onderzoek in 1997. Toen was er geen gevalideerde Nederlandstalige NPI beschikbaar. Wij ontwikkelden onze eigen vertaling. Als controle werd deze (onafhankelijk) terugvertaald in het Engels. De interbeoordelaarsbetrouwbaarheid bleek zowel voor de afzonderlijke als de somscores zeer hoog (kappa >.90). Het instrument bleek constructvalide. Daarnaast waren de correlaties met cognitieve testen en de metingen naar cognitief verval zeer bescheiden, een argument dat als voordeel voor de divergente validiteit van de meetschaal kan gelden. De oorspronkelijke NPI had o.i. het meest universele (en waardevrije) ontwerp: men kan een zeer breed spectrum van np-symptomen hiermee vastleggen en is ontworpen voor vele vormen van dementie. De meeste andere schalen op dit gebied zijn ontwikkeld gebaseerd op het 'klassieke' Alzheimer concept. Bovendien wordt systematisch per domein gevraagd naar de emotionele belasting die het symptoom geeft voor de verzorgende. De NPI brengt hiermee het meest nauwkeurig de emotionele belasting voor de verzorgende in kaart, omdat er i.t.t. de andere schalen een 'frequentie x ernst'-score aanwezig is per item. Hierdoor heeft het instrument een betere correlatie met de ervaren stress.
De conclusie van deze studie is dat de Nederlandse versie van de NPI een valide, betrouwbaar, breed opgezet en voor de praktijk goed bruikbaar instrument is om np-symptomen bij dementie in kaart te brengen en te evalueren.

In **hoofdstuk 3** worden de bevindingen besproken ten aanzien van de validiteit van de Nederlandstalige NPI-Q. De NPI-Q is een verkorte versie van de NPI, het is een zelfinvullijst voor de verzorgende i.p.v. een interview met deze. De gevonden samenhang met andere meetinstrumenten ondersteunde de validiteit van de NPI-Q. Gedrags- en psychiatrische symptomatologie vertoonden relatief hoge correlaties met overeenkomstige (sub)schalen van andere instrumenten, terwijl er geen samenhang bleek met de geheugen- en andere 'cognitieve' domeinen. De emotionele belasting voor de verzorgende was sterk gecorreleerd met de NPI-Q symptoomscores.
De conclusie van deze studie is dat de Nederlandse versie van de NPI-Q voldoende valide is en een goede aanvulling is op de Nederlandse NPI. Het instrument is vooral bruikbaar als screeningsinstrument voor np-symptomen bij dementie en de daaraan gerelateerde emotionele belasting voor de verzorgende. De NPI-Q is zeer goed bruikbaar voor de dagelijkse praktijk bijvoorbeeld bij het evalueren van de behandeling. In tegenstelling tot de NPI is de NPI-Q geen interview wat het risico op onder- of overrapportage kan vergroten.

In de hoofdstukken 4 en 5 wordt de tweede vraag over het verband tussen np-symptomen bij dementie en omgevingsvariabelen, beantwoord. In **hoofdstuk 4** wordt een onderzoek beschreven bij een groep thuiswonende dementiepatiënten en de belangrijkste personen die hen ondersteunen. De patiënten verkeerden in lichte tot matig ernstige stadia van dementie. Het verband tussen np-symptomen en een aantal omgevingsvariabelen werd bestudeerd. We waren vooral geïnteresseerd in de relatie met de ervaren emotionele belasting van de verzorgende en of hierbij ook andere factoren een rol spelen. Onze studie wees uit dat 52% van de ervaren emotionele belasting kon worden verklaard door de np-symptomen zelf. Andere factoren van belang bleken het gevoel van competentie van de verzorgende, de mate van zorg die nodig was en de kosten die dit meebracht. Er werd geconcludeerd dat de ervaren emotionele belasting bij de verzorgende voor het grootste deel werd bepaald door de np-symptomen van de patiënt. Depressie en apathie werden het meest gerapporteerd. Samen met agitatie en prikkelbaarheid werden deze als het meest belastend ervaren, overeenkomend met wat ook in andere (bevolking-) studies werd gevonden. Het onderzoek toonde aan dat de emotionele overbelasting van de verzorgende wordt bepaald door patiënt-, verzorgende en omgevingsvariabelen. Ook resultaten van recenter onderzoek liet een soortgelijk, multifactorieel verband zien. Bovendien bleek ook hier dat apathie, agitatie en stemmingsstoornissen, indien aanwezig bij dementie, belangrijke voorspellers zijn voor mentale overbelasting bij verzorgenden. Ook in onze studie was het mogelijk om onderscheid te maken tussen apathie en depressie en om hierbij verschillen in emotionele reacties vast te stellen.
De conclusie op grond van onze studie en de resultaten van andere onderzoeken luidt dat de gevalideerde Nederlandse versie van de NPI een adequaat instrument is om ervaren emotionele belasting van verzorgenden bij dementiepatiënten met np-symptomen, nauwkeurig vast te leggen. Bovendien blijkt dat deze belasting slechts voor een deel hierdoor wordt verklaard en dat ook andere factoren hierop van invloed zijn.
Zover wij weten is onze studie de eerste die emotionele belasting bij verzorgenden van dementiepatiënten met np-symptomen heeft onderzocht met de gevalideerde Nederlandse versie van de ‘NPI distress scale’.

In **hoofdstuk 5** wordt een consultstudie beschreven die werd uitgevoerd bij dementiepatiënten opgenomen in het verpleeghuis (n=325). Patiënten verkeerden in matig tot ernstige stadia van de ziekte en kregen professionele hulp. Wij waren geïnteresseerd in de reden (op symptoomniveau) waarom psychiatrische consultatie werd aangevraagd en hoe zich deze verhield tot de prevalentiegegevens van np-

symptomen bij dementiepatiënten in het verpleeghuis. Daar wij vermoedden dat de verwezen populatie hoogstwaarschijnlijk np-symptomen zou hebben, wilden wij ook weten in hoeverre de verwijsredenen te classificeren waren volgens de np-domeinen van de NPI. Prevalentiegegevens uit een andere Nederlandse studie waren beschikbaar. Door gebruik te maken van de NPI subdomeinen was het mogelijk meer dan 85% van de consultredenen te classificeren. De NPI voldeed dus om alle verwijsredenen onder te brengen in deze onderzoekspopulatie. De resterende 10-15% betroffen meestal (andere) diagnostische vragen of indicatieadviezen. Er werden grote verschillen gevonden tussen enerzijds verwijsredenen en anderzijds normatieve data uit de prevalentiestudie. Gespecialiseerde psychiatrische consultatie werd vooral ingeroepen voor geagiteerde en ontremde patiënten, terwijl dit mogelijk ten koste is gegaan van de apathische, geretardeerde en stille patiënten die (voor de omgeving) geen problemen geven. Voor zover onze kennis reikt is dit de eerste keer dat redenen voor psychiatrische consultatie worden vergeleken met onafhankelijke prevalentie schattingen van np-symptomen in een grote populatie dementiepatiënten verblijvend in het verpleeghuis. Er is meer onderzoek nodig naar de generaliseerbaarheid van deze bevindingen en de factoren die van invloed zijn op de gevonden verschillen. Vooral de bevinding dat 'hypogedrag' zoals apathie en geremde depressie nauwelijks als een probleem ervaren wordt in het verpleeghuis en juist tot grote mentale belasting kan leiden bij thuiswonende dementiepatiënten, verdient een nadere analyse.

In de hoofdstukken 6 en 7 wordt de laatste vraag betreffende de pathogenese en het beloop van np-symtomen bij dementie beantwoord. Er worden twee prospectieve studies beschreven. Het beloop van het cognitief functioneren werd gevolgd over een periode van 2.5 jaar in een cohort patiënten (en hun controles) die een postoperatief delier doormaakten (hoofdstuk 6). In de tweede studie worden het delier en de risicofactoren voor het delier als predictoren voor mortaliteit onderzocht tijdens een 2 jaar durende vervolgperiode (hoofdstuk7). In **hoofdstuk 6** wordt stilgestaan bij predictoren van cognitief verval. Er werd een cohort van 71 patiënten gevolgd die een postoperatief delier ontwikkelden en 41 van hen werden gematched met patiënten zonder delier, maar met hetzelfde aantal risicofactoren voor het ontwikkelen van een delier (op T=0, preoperatief). Na 2.5 jaar werden de patiënten onafhankelijk beoordeeld gebruikmakend van dezelfde testen als bij T=0. In 77.8% van de nog levende patiënten met een doorgemaakt delier werd dementie of Mild Cognitive Impairment (MCI) gevonden. Dit was 40.9% in de controlegroep (relatieve risico = 1.9, 95% CI = 1.1 - 3.3). In onze studie werd rekening gehouden met het feit dat er, voorafgaande aan de operatie, geen grote verschillen ten aanzien van cognitief functioneren bestonden tussen patiënten

met en zonder doorgemaakt delier. Niettemin konden er geen gematchde controles gevonden worden voor 30/71 delierpatiënten vanwege verschillen in risicoprofielen op T=0. Niet gematchde delierpatiënten scoorden lager op de MMSE dan de gematchden wat wees op meer cognitief verval. Bovendien bleek dat de MMSE-scores een brede spreiding lieten zien (10-29). Het is dan ook duidelijk dat sommige patiënten al dementie of MCI hadden voordat zijn werden geincludeerd in de studie. Hoewel er in deze studie geen conclusies getrokken kunnen worden over de causaliteit, ondersteunen onze bevindingen de hypothese dat een onderliggende degeneratieve aandoening kan bijdragen tot het ontwikkelen van een delier tijdens opname.
Concluderend, in deze studie werd zorgvuldig gecontroleerd om het verband tussen het optreden van een postoperatief delier en het ontwikkelen van cognitief verval op termijn, te kunnen evalueren. Het risico op het optreden van dementie en MCI op lange termijn is bijna verdubbeld bij ouderen die na een heupoperatie een postoperatief delier kregen, vergeleken met patiënten die wel 'at risk' waren maar geen delier ontwikkelden. Het delier kan een aanwijzing zijn voor het bestaan van een onderliggende (geleidelijk progressieve) degeneratieve hersenaandoening. Onder bepaalde omstandigheden, bijvoorbeeld na een chirurgische ingreep, kan het neuropsychiatrisch syndroom delier een uiting zijn van onderliggend cognitief verval. Het verband tussen dementie en het delier kan het best gezien worden als verlopend volgens een continuüm van cognitieve stoornissen, beter dan deze te beschouwen als aparte, van elkaar gescheiden ziektebeelden.

In **hoofdstuk 7** wordt het onderzoek beschreven naar het delier en risicofactoren voor het delier als predictoren voor mortaliteit op de langere termijn bij ouderen die werden opgenomen voor een heupoperatie (n=603). De primaire uitkomstmaat was het overlijden tijdens de 2 jaar durende vervolgperiode. De incidentie van het delier was hoger in de groep van overleden patiënten (32.2%) vergeleken met de patiënten die overleefden (8.8%). Het effect van het delier op overlijden was significant na correctie voor risicofactoren voor delier en andere potentiële co-variabelen. Wij concludeerden allereerst dat het delier onafhankelijk is geassocieerd met overlijden bij ouderen die een heupoperatie ondergaan. Dit geldt vooral als ook (andere) risicofactoren aanwezig zijn. Stratificatie van risicofactoren toonde aan dat 10% van de patiënten met een delier en 0-1 risicofactor waren overleden. Dit was 40.7% in de groep met een delier en 2-3 risicofactoren en 59.3% bij delierpatiënten met 4-5 risicofactoren, vergeleken met respectievelijk 6.1%, 13.5% en 43.1% overledenen bij de patiënten die geen postoperatief delier ontwikkelden. De prognose is gunstiger als de patiënt relatief jong en gezond is en slechter bij oudere mannen met cognitieve stoornissen, die bovendien acuut worden

opgenomen en een slechte visus hebben. De tweede conclusie is dat het kwetsbaar zijn van delirante patiënten, uitgedrukt in de aanwezigheid van predisponerende en uitlokkende factoren, de toename van sterfte voor een deel lijkt te verklaren. De resultaten van de risicostratificatie lijken deze hypothese te ondersteunen.

Het ontwikkelen van een postoperatief delier en het vroegtijdig overlijden lijken een gemeenschappelijke basis te hebben. In hoofdstuk 7 was één van de conclusies dat de prognose slechter is als de patiënt ook nog oud is en cognitieve stoornissen vertoont. Het is aannemelijk dat opgenomen patiënten die een delier krijgen reeds voor opname een beginnende neurodegeneratieve aandoening, die verband houdt met dementie, doormaken. Een verklaring hiervoor vonden we in een nadere analyse van de MMSE-scores die kon worden uitgevoerd bij beide beloopstudies (**hoofdstuk 6 en 7**). In hoofdstuk 6 werd vastgesteld dat het delier vooral ontstaat bij patiënten met een lage uitgangswaarde op de MMSE (T=0). In hoofdstuk 7 werd gezien dat patiënten die waren overleden significant lagere gemiddelde MMSE-scores hadden op T=0 (pre-operatief) dan de patiënten die overleefden (22.1 vs. 25.8). De eerste groep bestond voor 32.2% uit patiënten met een postoperatief delier. In de groep van patiënten die overleefden was dit slechts 8.8%, een verhouding van ongeveer 4:1. Concluderend, de twee delierbeloopstudies lieten zien dat het delier, als neuropschiatrisch syndroom frequent voorkomend bij ouderen, onder speciale omstandigheden de eerste klinische manifestatie kan zijn van een vroeg stadium van een neurodegeneratieve aandoening.

Tot slot worden in **hoofdstuk 8** de belangrijkste bevindingen van dit proefschrift besproken en worden de relevantie en implicaties van de resultaten voor de dagelijkse praktijk bediscussieerd. Er wordt gepleit voor een breder dementieconcept waarin ook psychiatrische fenomenologie een volwaardige plaats heeft. De studies die zijn verricht geven antwoord op de drie gestelde onderzoeksvragen gericht op het meten, implementeren, vervolgen en de mogelijke pathogenese van np-symptomen bij dementie. Het hoofdstuk sluit af met een aantal aanbevelingen voor toekomstig onderzoek.

Appendix

1. NPI Nederlandse versie
2. NPI-Q Nederlandse versie

1. NPI NEDERLANDSE VERSIE

Naam patiënt: _____
Datum afname: _____
Identificatienummer: _____
Bron/informant: _____

Item	*NVT*	*Afwezig*	*Frequentie*	*Ernst*	*FxE*	*Emoti.belasting*
Wanen	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Hallucinaties	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Agitatie/agressie	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Depressie/dysforie	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Angst	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Euforie/opgetogenheid	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Apathie/onverschilligheid	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Ontremd gedrag	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Prikkelbaarheid/labiliteit	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Doelloos repetitief gedrag	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Nachtelijke onrust/slaapst.	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*
Eetlust/eetgedragverandering	*x*	*0*	*1 2 3 4*	*1 2 3*		*1 2 3 4 5*

Diagnose: _____
MMSE: _____
Geboortedatum: _____
Leeftijd: _____
Geslacht: _____
Opleiding: _____
Duur van de ziekte: _____
Medicatie: _____

Instructies voor de afname van de NPI
Met de Neuropsychiatrische Inventarisatie (NPI) wordt een beeld verkregen van eventueel aanwezige psychopathologische verschijnselen bij patiënten met hersenletsel. De NPI werd ontwikkeld voor toepassing bij patiënten met de ziekte van Alzheimer en andere dementiesyndromen, maar kan ook gebruikt worden voor

onderzoek naar gedragsveranderingen bij andere ziektebeelden. De NPI omvat twaalf gedragsaspecten, te weten:

Wanen	Apathie/onverschilligheid
Hallucinaties	Ontremd gedrag
Agitatie/agressie	Prikkelbaarheid/labiliteit
Depressie/dysforie	Doelloos repetitief gedrag
Angst	Nachtelijke onrust/slaapstoornis
Euforie/opgetogenheid	Eetlust/eetgedragverandering

De NPI is gebaseerd op een interview met een verzorgende van de patiënt die goed op de hoogte dient te zijn van eventuele problemen; het liefst iemand die met hem of haar samenwoont. Indien een familielid of verzorgende niet beschikbaar is, dan kan deze vragenlijst niet zonder meer worden gebruikt. Het heeft de voorkeur om de verzorgende niet in aanwezigheid van de patiënt te interviewen. Zo kan openlijk worden gesproken over gedragsproblemen die wellicht moeilijker aan bod komen wanneer de patiënt hierbij wel aanwezig zou zijn. Bij de introductie van de NPI stelt u de verzorgende van de volgende punten op de hoogte:

1 Het doel van het vraaggesprek.
2 Beoordelingen – frequentie, ernst, belasting (zie onder).
3 De antwoorden dienen betrekking te hebben op gedrag dat is ontstaan sinds het begin van de ziekte en dat in de afgelopen vier weken voorkwam (of een andere van tevoren overeengekomen periode).
4 Vragen kunnen over het algemeen met ‘ja’ of ‘nee’ worden beantwoord. Antwoorden dienen beknopt te zijn, indien ‘ja’ of ‘nee’ niet afdoende is.

Zeg bij aanvang van het interview tegen de verzorgende: ‘Deze vragen zijn bedoeld om het gedrag van uw echtgenoot (vader, moeder, enzovoort) te beoordelen. U kunt de vragen over het algemeen beantwoorden met ‘ja’ of ‘nee’, dus probeer zo beknopt mogelijk antwoord te geven.’ Wanneer de geïnterviewde toch uitgebreide antwoorden geeft – die weinig of geen nuttige informatie bevatten – herinnert u hem dan eraan beknopt te antwoorden. Sommige onderwerpen die aan bod komen kunnen emotioneel belastend zijn voor familieleden. De interviewer dient de verzorgende ervan te verzekeren dat het onderwerp uitgebreider besproken zal worden nadat de vragenlijst in zijn geheel is afgenomen.

Stel de vragen letterlijk. Als de verzorgende een vraag niet begrijpt, verduidelijk de vraag dan. Uitleg is alleen toegestaan in termen die overeenkomen met de strekking van de vraag (synoniemen). De vragen hebben betrekking op de veranderingen in gedrag die zijn opgetreden sinds het begin van de ziekte. Gedragingen die daarvoor al aanwezig waren en die niet veranderd zijn gedurende de ziekte worden niet gescoord, ook al zijn deze afwijkend (bijvoorbeeld angst, depressie). Gedrag dat altijd al aanwezig is geweest en sinds de ziekte is veranderd, wordt wel gescoord (bijvoorbeeld de patiënt is altijd al apathisch geweest, maar er is een duidelijke toename van apathie in de periode die de vragenlijst bestrijkt).

De NPI is bij uitstek geschikt voor het beoordelen van verandering in het gedrag van de patiënt zoals dat zich voordeed in een bepaalde periode (bijvoorbeeld de afgelopen vier weken of een andere van tevoren vastgestelde periode). In sommige onderzoeken kan de NPI toegepast worden om veranderingen vast te stellen die optreden als gevolg van een behandeling, of veranderingen die opgetreden zijn sinds het laatste bezoek aan de (poli)kliniek. In dat geval zou de tijdsformulering van de vraag herzien moeten worden om aan te geven dat het gaat om recente veranderingen. Maak duidelijk aan de verzorgende dat de vragen betrekking hebben op nieuw gedrag of veranderingen in het gedrag sinds het begin van de ziekte. De vragen kunnen bijvoorbeeld zo geformuleerd worden: ‘Is hij veranderd sinds de behandeling met de nieuwe medicatie is gestart?’ of ‘Vanaf het moment dat de dosering van ... verhoogd is ...?’

Alle twaalf secties van de NPI bestaan uit een screeningsvraag (verplicht te stellen) en verdiepende vragen (optioneel). De screeningsvraag wordt gesteld om te bepalen of de gedragsverandering wel of niet aanwezig is. Indien ontkennend wordt geantwoord op de screeningsvraag, vul dan ‘nee’ in en ga verder naar de volgende screeningsvraag. Als bevestigend wordt geantwoord op de screeningsvraag, of als u hierover ook maar enigszins twijfelt, of als het antwoord van de verzorgende niet strookt met andere informatie waarover u beschikt (bijvoorbeeld de verzorgende antwoordt ontkennend op de euforiescreeningsvraag, maar de patiënt komt op de behandelaar euforisch over), dan wordt ‘ja’ ingevuld en de vraag meer uitgediept door middel van de subvragen. Indien de subvragen de screeningsvraag bevestigen, dan worden de ernst en de frequentie van het gedrag bepaald volgens de criteria die bij elke sectie vermeld staan. De bepaling van de frequentie en de ernst is gebaseerd op de meest afwijkende gedragingen die bij de subvragen naar voren zijn gekomen. Bijvoorbeeld: tijdens de vragen over afgifte heeft de verzorgende aangegeven dat

'zich verzetten bij hulp' de meeste problemen oplevert. Gebruik in dat geval 'zich verzetten bij hulp' om een uitspraak te verkrijgen over de frequentie en ernst van agitatie. Indien twee gedragingen als zeer problematisch worden ervaren, gebruik dan de frequentie en ernst van beide gedragingen om de sectie te scoren. Bijvoorbeeld, als de patiënt twee of meer typen waan koestert, gebruik dan bij het inschatten van de ernst en frequentie alle waanbelevingen.

Het kan voorkomen dat de naaste verzorgende de screeningsvraag bevestigend beantwoordt, maar alle subvragen met 'nee' beantwoordt. Als dit gebeurt vraag dan aan de verzorgende om uit te leggen waarom hij de screeningsvraag met 'ja' heeft beantwoord. Mocht blijken dat hij toch relevante informatie over het gedragsdomein naar voren brengt, maar hiervoor andere woorden gebruikt, scoor dan alsnog de ernst en de frequentie. Als blijkt dat het 'ja'-antwoord onjuist was, verander de screeningsvraag dan in 'nee'.

Sommige secties, zoals de vragen over eetlust, zijn zo geformuleerd dat gevraagd wordt naar een toe-of afname van gedrag (toe-of afgenomen eetlust of gewicht). Als de verzorgende bevestigend antwoordt op de eerste van twee paarsgewijze vragen, stel dan niet de tweede vraag. Bijvoorbeeld: de eerste vraag luidt 'Is zij/hij afgevallen?', hierop antwoordt de verzorgende 'Ja'. Vraag dan niet 'Is zij/hij aangekomen?'. Het antwoord op de tweede vraag zit al in het antwoord op de eerste vraag. Als de verzorgende 'nee' antwoordt op een eerste, paarsgewijze vraag, dan moet de tweede uiteraard wel gesteld worden.

Voor het bepalen van de frequentie zegt men tegen de verzorgende: 'Ik wil nu graag weten hoe vaak ... (noem de meest problematisch ervaren gedragingen van de subvragen) ... is voorgekomen. Kwam het minder dan één keer per week voor, of ongeveer één keer per week, verschillende keren per week maar niet iedere dag, of iedere dag?' Bepaald gedrag zoals apathie kan op gegeven moment blijvend aanwezig zijn. In plaats van de woorden 'iedere dag' kunt u dan 'continu aanwezig' gebruiken. Om de ernst te bepalen zegt u tegen de verzorgende: 'Nu zou ik graag willen weten hoe ernstig dit gedrag is. Met ernstig bedoel ik, in welke mate verstoort of beperkt het hem/haar? Vindt u de ernst van (... het gedrag ...) licht, matig of ernstig?' Iedere sectie wordt voorzien van extra beschrijvingen over de ernstbepaling. Deze dienen om aan de verzorgende duidelijk te maken wat er precies bedoeld wordt. Zorg ervoor dat de verzorgende bij iedere vraag eenduidig de frequentie en ernst beoordeelt. Het is belangrijk om niet te raden naar de antwoorden van de

verzorgende (‘hij zal wel dit of dat bedoelen ...’). De ervaring leert dat het handig is om de geïnterviewde een kaart te geven waarop de frequentie-en ernstbeschrijvingen vermeld staan (minder dan één keer per week, ongeveer één keer per week, verschillende keren per week maar niet dagelijks en dagelijks of continu aanwezig, en voor ernst: licht, matig en ernstig). Zo heeft hij de antwoordalternatieven zichtbaar voor zich. Dit is ook handig voor de onderzoeker, deze hoeft dan niet bij iedere vraag alle alternatieven te herhalen.

Bij ernstig gestoorde patiënten of bij patiënten met ernstig somatische complicaties zijn sommige vragen niet van toepassing: Bijvoorbeeld: bedlegerige patiënten kunnen hallucinaties vertonen of agitatie, maar geen doelloos repetitief gedrag. Als de onderzoeker of de verzorgende vindt dat de vragen niet van toepassing zijn, noteer dan voor de betreffende sectie NVT (in de rechterbovenhoek van de pagina) en ga verder met de volgende screeningsvraag. Hetzelfde geldt als de interviewer het idee heeft dat de antwoorden onbetrouwbaar zijn (bijvoorbeeld de verzorgende lijkt bepaalde vragen uit de sectie niet te begrijpen). Kruis ook dan NVT aan.

Nadat een sectie is afgerond en de verzorgende de frequentie en de ernst heeft beoordeeld, kunt u vragen naar de emotionele belasting voor de verzorgende (afhankelijk van het onderzoeksprotocol). Vraag aan de verzorgende hoe emotioneel of psychisch belastend of stresserend het net besproken gedrag voor hem/ haar is (de verzorgende). De verzorgende moet deze emotionele belasting zelf scoren op een zespunts schaal:
0 = geen, 1 = minimaal, 2 = licht, 3 = matig, 4 = ernstig, 5 = zeer ernstig of extreem.
(De emotionele-belastingschaal voor dit meetinstrument werd ontwikkeld door Daniel Kaufer M.D.)

Het scoren van de NPI

Frequentie wordt gescoord als:
1 Soms – minder dan een keer per week
2 Regelmatig – ongeveer een keer per week
3 Vaak – meerdere keren per week, maar minder dan iedere dag
4 Heel vaak – dagelijks of vrijwel continu aanwezig

Ernst wordt gescoord als:
1 Licht – weinig belastend voor patiënt
2 Matig – belastend voor de patiënt, maar de verzorgende kan het gedrag corrigeren

3 Ernstig – zeer storend voor de patiënt, en moeilijk te corrigeren gedrag

De score voor iedere sectie is: frequentie x ernst
Emotionele belasting, van de verzorgende wordt gescoord als: 0 geen 1 minimaal 2 licht 3 matig 4 ernstig 5 zeer ernstig, extreem

Dus, voor elk sectie (gedragsdomein) zijn vier scores te verkrijgen
- Frequentie
- Ernst
- Totaal (frequentie x ernst)
- Emotionele belasting van de verzorgende

A. Wanen

Is hij/zij overtuigd van bepaalde gedachten waarvan u weet dat ze niet waar zijn? Beweert hij/zij bijvoorbeeld dat andere mensen hem/haar kwaad willen doen of van hem/haar stelen? Heeft hij/zij gezegd dat familieleden anderen zijn dan ze zeggen te zijn of denkt hij/zij dat 't huis niet het huis is waar ze in wonen? Ik vraag u niet naar een beetje achterdochtig zijn, maar ik wil weten of hij/zij ervan overtuigd is dat deze zaken hem overkomen. Dus, of hij/zij denkt dat het echt zo is.
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Gelooft hij/zij dat er gevaar dreigt, dat anderen van plan zijn om hem/haar te kwetsen of pijn te doen?
2 Denkt hij/zij dat anderen hem/haar bestelen?
3 Denkt hij/zij dat zijn/haar partner vreemdgaat of ontrouw is?
4 Denkt hij/zij dat er ongenode gasten in zijn/haar huis verblijven?
5 Gelooft hij/zij dat zijn/haar partner of anderen niet zijn wie ze zeggen dat ze zijn?
6 Gelooft hij/zij dat hij/zij niet in zijn/haar huis woont?
7 Denkt hij/zij dat familieleden hem/haar in de steek willen laten?
8 Gelooft hij/zij dat personen van televisie of uit tijdschriften ook daadwerkelijk aanwezig zijn in huis? (Praat hij/zij met hen, of zoekt hij op een andere manier contact?)
9 Gelooft hij/zij andere ongewone of vreemde zaken die ik hier nog niet genoemd heb?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de frequentie en de ernst van de wanen.

Frequentie:
1 Soms – minder dan een keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – meerdere malen per week, maar niet iedere dag
4 Heel vaak – één of meerdere keren per dag

Ernst:
1 Licht – wanen zijn aanwezig maar lijken onschuldig en benauwen, beangstigen patiënt niet of nauwelijks
2 Matig – patiënt raakt overstuur en ontregeld door de wanen
3 Ernstig – de wanen zijn zeer verstorend en vormen de belangrijkste bron van gedragsproblemen (indien neuroleptica zijn voorgeschreven, betekent dit dat de wanen ernstig tot zeer ernstig zijn)

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

B. Hallucinaties

Hallucineert hij/zij? Ziet of voelt hij/zij iets dat er niet is of hoort hij/zij stemmen die een ander niet kan horen? Ik bedoel met deze vraag niet vergissingen, zoals het idee hebben dat iemand nog leeft terwijl deze al overleden is. Ik vraag echter of hij/zij abnormale ervaringen heeft wat betreft iets horen, zien of voelen.
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Zegt hij/zij dat hij/zij stemmen hoort of gedraagt hij/zij zich alsof hij/zij stemmen hoort?

2 Spreekt hij/zij tegen mensen die er niet zijn?
3 Zegt hij/zij iets te zien dat een ander niet ziet of gedraagt hij/zij zich alsof hij/zij iets ziet wat een ander niet kan zien (zoals mensen, dieren, lichten enzovoort)?
4 Zegt hij/zij iets te ruiken wat een ander niet ruikt?
5 Zegt hij/zij iets te voelen op zijn/haar huid? Of lijkt het alsof hij/zij iets voelt kruipen of kriebelen of dat iets hem/haar aanraakt?
6 Zegt hij/zij iets te proeven zonder dat daar een duidelijke reden voor is?
7 Heeft hij/zij u over andere ongewone gewaarwordingen verteld?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de frequentie en ernst van de hallucinaties.

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – één of meerdere keren per dag

Ernst:
1 Licht – hallucinaties zijn aanwezig maar onschuldig en beangstigen of benauwen patiënt niet of nauwelijks
2 Matig – patiënt raakt overstuur en ontregeld door de hallucinaties
3 Ernstig – de hallucinaties zijn zeer verstorend en vormen de belangrijkste bron van gedragsproblemen (neuroleptica kunnen geïndiceerd zijn om de hallucinaties te behandelen)

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

C. Agitatie/agressie

Komt het voor dat hij/zij weigert mee te werken, of zich niet laat helpen door een

ander? Is hij/zij lastig om mee om te gaan?
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Raakt hij/zij overstuur of wordt hij/zij kwaad op anderen die hem/haar willen verzorgen? Of verzet hij/zij zich bij het aankleden of wassen?
2 Is hij/zij koppig of eigenwijs? Wil hij/zij dat alles moet gaan zoals hij/zij het wenst?
3 Werkt hij/zij niet goed mee? Verzet hij/zij zich als anderen helpen? Als de subvragen de screeningsvraag bevestigen, bepaal dan de frequentie en de ernst van de agitatie.
4 Zijn er andere gedragingen die het moeilijk maken om hem/haar te begeleiden?
5 Vloekt of schreeuwt hij/zij kwaad?
6 Slaat hij/zij met deuren, schopt hij/zij tegen meubilair of smijt hij/zij met voorwerpen?
7 Probeert hij/zij anderen pijn te doen of anderen te slaan?
8 Is hij/zij nog op een andere manier agressief of geagiteerd?

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – één of meerdere keren per dag

Ernst:
1 Licht – het gedrag is verstorend maar is positief te beïnvloeden door afleiding of geruststelling
2 Matig – het gedrag is verstorend en moeilijk bij te sturen of te corrigeren
3 Ernstig – de agitatie is zeer verstorend en de belangrijkste bron van problemen; het kan zijn dat de patiënt fysiek bedreigend is naar zijn omgeving. Vaak is medicatie geïndiceerd.

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig

4 ernstig
5 zeer ernstig of extreem

D. Depressie/dysforie

Lijkt het alsof hij/zij verdrietig of depressief is? Zegt hij/zij dat hij/zij zich verdrietig of depressief voelt?
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Heeft hij/zij perioden dat hij/zij snel 'volschiet' of veel huilt, wat erop wijst dat hij/zij verdrietig is?
2 Doet of zegt hij/zij iets waaruit op te maken valt dat hij/zij verdrietig of 'down' is?
3 Haalt hij/zij zichzelf naar beneden of zegt hij/zij zichzelf niets waard, een mislukkeling te vinden?
4 Zegt hij/zij dat hij/zij een slecht persoon is of straf verdient?
5 Lijkt hij/zij erg ontmoedigd of zegt hij/zij dat de toekomst hem/haar niets te bieden heeft?
6 Zegt hij/zij dat hij/zij anderen tot last is of dat familieleden beter af zouden zijn zonder hem/haar?
7 Zegt hij/zij liever dood te willen zijn of zegt hij/zij zichzelf wat aan te willen doen, er een einde aan te willen maken?
8 Zijn er andere signalen waaruit blijkt dat hij/zij verdrietig of depressief is?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de frequentie en de ernst van de depressie.

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – in essentie continu aanwezig

Ernst:
1 Licht – de depressie veroorzaakt leed, maar klaart meestal op bij afleiding of geruststelling
2 Matig – de depressie veroorzaakt leed, depressieve symptomen worden spontaan

geuit door patiënt en deze zijn moeilijk te verlichten
3 Ernstig – de depressie veroorzaakt veel leed en vormt de belangrijkste bron van lijden voor de patiënt

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

E. Angst

Is hij/zij erg nerveus, bezorgd, of schrikachtig zonder duidelijke reden? Lijkt hij/zij erg gespannen, rusteloos of zenuwachtig? Is hij/zij bang om alleen te zijn, zonder u?
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Zegt hij/zij dat hij/zij zich zorgen maakt over uitjes of activiteiten die gepland zijn?
2 Voelt hij/zij zich wel eens trillerig, niet in staat zich te ontspannen of erg gespannen?
3 Komt het voor dat hij/zij last heeft van kortademigheid, het moeten happen naar lucht, of zuchten (of klaagt hij/zij hierover), zonder duidelijke reden anders dan nervositeit?
4 Klaagt hij/zij over kriebels in zijn/haar buik of over hartkloppingen die samengaan met nervositeit? (niet i.h.k.v. bijkomende ziekte)
5 Vermijdt hij/zij bepaalde plaatsen of situaties die hem/haar nerveus maken, zoals autorijden, het ontmoeten van vrienden, of naar een plek gaan waar veel mensen zijn?
6 Wordt hij/zij zenuwachtig of overstuur wanneer u (of verzorgende) weggaat? Houdt hij/zij zich dan krampachtig aan u vast om dat te voorkomen?
7 Is er nog iets anders dat erop wijst dat hij/zij angstig is?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de ernst en frequentie van de angst.

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – één of meerdere keren per dag

Ernst:
1 Licht – de angst veroorzaakt leed, maar reageert meestal gunstig op afleiding of geruststelling
2 Matig – de angst veroorzaakt leed, angstsymptomen worden spontaan geuit door patiënt en deze zijn moeilijk te verlichten
3 Ernstig – de angst veroorzaakt veel leed en vormt de belangrijkste bron van lijden voor de patiënt

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

F. Euforie/opgetogenheid

Lijkt hij/zij te vrolijk, opgewekt of blij zonder duidelijke aanleiding? Ik bedoel niet de normale opgewektheid wanneer men vrienden ontmoet, een cadeau krijgt of tijd doorbrengt met familie. Ik vraag of hij/zij voortdurend een abnormaal goed humeur heeft of ergens om lacht waar een ander de humor niet van inziet.
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Lijkt hij/zij zich te goed of te opgewekt te voelen, vergeleken met hoe hij/zij normaal gesproken is?
2 Vindt hij/zij iets grappig of lacht hij/zij ergens om waar een ander de humor niet van inziet?
3 Lijkt het net alsof hij/zij een kinderachtig gevoel voor humor heeft en giechelt of

ongepast lacht? (bijvoorbeeld als iemand iets vervelends overkomt)
4 Vertelt hij/zij moppen of plaatst hij/zij opmerkingen die hij/zij zelf wel grappig vindt, maar waar anderen niet om kunnen lachten?
5 Haalt hij/zij kinderachtige streken uit, zoals verstoppertje spelen of iemand knijpen, gewoon voor de grap?
6 Schept hij/zij op, bijvoorbeeld door te zeggen dat hij/zij rijk is of iets bijzonders kan, terwijl dat niet zo is?
7 Is er nog iets anders waaruit blijkt dat hij/zij zich te goed of te opgewekt voelt?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de frequentie en de ernst van de euforie.

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – in essentie constant aanwezig

Ernst:
1 Licht – uitgelatenheid valt op bij vrienden en familie maar is niet storend
2 Matig – de uitgelatenheid is duidelijk abnormaal
3 Ernstig – de uitgelatenheid is zeer opvallend; patiënt is eufoor en hij/zij vindt alles amusant en grappig

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

G. Apathie/onverschilligheid

Is hij/zij niet langer geïnteresseerd in de wereld om hem/haar heen? Heeft hij/zij geen belangstelling meer om iets te doen of ontbreekt de motivatie om aan iets nieuws te beginnen? Is hij/zij moeilijker te betrekken in een gesprek of het doen van

huishoudelijke klusjes? Is hij/zij apathisch of onverschillig?
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Lijkt hij/zij minder spontaan en minder actief dan gewoonlijk?
2 Begint hij/zij minder vaak een gesprek?
3 Toont hij/zij minder affectie of misschien wel helemaal geen emoties, vergeleken met hoe hij/zij normaal gesproken was?
4 Helpt hij/zij minder bij huishoudelijke klussen?
5 Lijkt hij/zij minder geïnteresseerd in de activiteiten en plannen van een ander?
6 Heeft hij/zij geen belangstelling meer voor vrienden of familie?
7 Is hij/zij minder enthousiast over zaken die hem/haar gewoonlijk interesseren?
8 Is er nog iets anders waaruit blijkt dat hij/zij geen interesse heeft om iets nieuws te gaan doen?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de ernst en de frequentie van de apathie.

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – bijna continu aanwezig

Ernst:
1 Licht – apathie valt op maar interfereert niet met de dagelijkse bezigheden; is slechts een beetje anders dan het gewone gedrag van patiënt; hij/zij reageert op uitnodigingen om deel te nemen aan activiteiten
2 Matig – apathie is evident; verzorgende kan ermee omgaan door op patiënt in te praten of aan te moedigen; slechts indringende gebeurtenissen leiden tot een spontane reactie, zoals het bezoek van naaste familieleden
3 Ernstig – de apathie is evident en reageert niet langer op aanmoediging of gebeurtenissen in de omgeving

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?

0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

H. Ontremd gedrag

Lijkt hij/zij impulsief te handelen, zonder er bij na te denken? Doet of zegt hij/zij iets wat men normaal gesproken niet in het openbaar zegt of doet? Brengt hij/zij u of iemand anders in verlegenheid met wat hij/zij doet?
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Handelt hij/zij impulsief zonder over de gevolgen na te denken?
2 Praat hij/zij tegen volstrekt onbekenden alsof hij/zij ze goed kent?
3 Maakt hij/zij kwetsende of tactloze opmerkingen tegen anderen?
4 Maakt hij/zij botte of seksueel getinte opmerkingen, die hij/zij normaal gesproken nooit gezegd zou hebben?
5 Praat hij/zij openlijk over zeer persoonlijke of privé-zaken, waarover men gewoonlijk niet spreekt in het openbaar?
6 Gaat hij/zij te ver of is hij/zij handtastelijk of knuffelt hij/zij anderen, op zo'n manier dat het niet past bij zijn/haar karakter?
7 Is er nog iets anders dat erop wijst dat hij/zij zijn/haar impulsen minder onder controle heeft?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de frequentie en de ernst van het ontremde gedrag

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – in essentie continu aanwezig

Ernst:
1 Licht – ontremd gedrag is aanwezig, maar reageert op afleiding en begeleiding
2 Matig – ontremd gedrag is duidelijk aanwezig en moeilijk voor de verzorgende om mee om te gaan
3 Ernstig – ontremd gedrag neemt niet af, wat de verzorgende ook probeert, het brengt anderen in verlegenheid of is een bron van ergernis

Emotionele belasting
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

I. Prikkelbaarheid/labiliteit

Is hij/zij snel geïrriteerd of uit evenwicht? Is zijn/haar stemming nogal veranderlijk? Is hij/zij erg ongeduldig? Ik bedoel niet dat hij/zij zich gefrustreerd voelt over de vergeetachtigheid of alledaagse taken die niet meer lukken. Ik wil graag weten of hij/zij erg prikkelbaar en ongeduldig is of dat hij/zij snel van humeur verandert, anders dan u van hem/haar gewend bent?
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Is hij/zij opvliegend, schiet hij/zij gemakkelijk uit zijn/haar slof om iets kleins?
2 Verandert hij/zij snel van stemming, het ene moment is alles nog goed en het andere moment is hij/zij kwaad?
3 Heeft hij/zij plotselinge woede-uitbarstingen?
4 Is hij/zij ongeduldig? Kan hij/zij moeilijk omgaan met een vertraging of het moeten wachten op een activiteit die gepland is?
5 Is hij/zij humeurig of snel geïrriteerd?
6 Gaat hij/zij snel in discussie en is het moeilijk met hem/haar op te schieten?
7 Is er nog iets anders wat erop wijst dat hij/zij prikkelbaar is?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de frequentie en de

ernst van de prikkelbaarheid/labiliteit.

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – in essentie continu aanwezig

Ernst:
1 Licht – prikkelbaarheid wordt opgemerkt, maar is d.m.v. geruststelling of afleiding te corrigeren
2 Matig – prikkelbaarheid is evident aanwezig en moeilijk mee om te gaan voor de verzorgende
3 Ernstig – prikkelbaarheid is evident aanwezig, is niet bij te sturen door de verzorgende en is zeer belastend

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

J. Doelloos repetitief gedrag

Loopt hij/zij doelloos rond, te ijsberen? Doet hij/zij een handeling telkens weer, zoals keer op keer een la opentrekken, aan iets zitten te plukken of touwtjes of draadjes opwinden?
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Loopt hij/zij doelloos rond in huis?
2 Loopt hij/zij rond te zoeken en te rommelen met spullen, zoals het openen van laden en het leeghalen van kasten?
3 Kleedt hij/zij zich herhaaldelijk aan en dan weer uit?

4 Zijn er gewoonten of activiteiten die hij/zij constant herhaalt?
5 Doet hij/zij telkens dezelfde handeling zoals peuteren aan knopen, ergens aan plukken, draadjes opwinden, enzovoort?
6 Beweegt hij/zij zenuwachtig, alsof hij/zij niet stil kan blijven zitten, of schuift hij/zij met de voeten heen en weer of trommelt hij/zij vaak met de vingers?
7 Zijn er andere activiteiten die hij/zij telkens weer herhaalt?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de frequentie en de ernst van het doelloos repetitieve gedrag.

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – in essentie continu aanwezig

Ernst:
1 Licht – doelloos repetitief gedrag wordt opgemerkt, maar interfereert nauwelijks met de dagelijkse bezigheden
2 Matig – doelloos repetitief gedrag is duidelijk aanwezig, maar de verzorgende weet er mee om te gaan
3 Ernstig – doelloos repetitief gedrag is duidelijk aanwezig, is nauwelijks te corrigeren door de verzorgende en vormt een grote belasting

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

K. Nachtelijke onrust/slaapstoornis

Heeft hij/zij moeite met slapen? (scoor als ‘niet aanwezig’ indien patiënt slechts een of twee keer per nacht opstaat om naar het toilet te gaan en daarna weer meteen in slaap valt). Is hij/zij ’s nachts op? Loopt hij/zij ’s nachts rond, kleedt hij/zij zich aan of

verstoort hij/zij uw nachtrust?
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Heeft hij/zij moeite met in slaap vallen?
2 Staat hij/zij 's nachts op? (scoor als afwezig indien patiënt een of twee keer opstaat om naar het toilet te gaan en snel weer inslaapt)
3 Loopt hij/zij 's nachts doelloos rond, te ijsberen of is hij/zij dan bezig met ongebruikelijke activiteiten?
4 Maakt hij/zij u 's nachts wakker?
5 Wordt hij/zij 's nachts wakker en kleedt hij/zij zich dan aan in de veronderstelling dat het al morgen is en tijd om aan een nieuwe dag te beginnen?
6 Wordt hij/zij 's ochtends te vroeg wakker (vroeger dan hij/zij gewend was)?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de ernst en de frequentie van de slaapproblemen en nachtelijke onrust
7 Slaapt hij/zij buitensporig veel overdag?
8 Is hij/zij 's nachts nog met iets anders bezig dat u hindert, waar we het nog niet over gehad hebben?

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – in essentie continu aanwezig

Ernst:
1 Licht – nachtelijke onrust komt voor maar is niet echt hinderlijk
2 Matig – nachtelijke onrust komt voor, is storend voor de patiënt en voor de nachtrust van de verzorgende. Meerdere gedragingen kunnen zich per nacht voordoen
3 Ernstig – nachtelijke onrust komt voor; er kunnen meerdere gedragingen voorkomen; patiënt is zeer ontdaan en verstoort in ernstige mate de nachtrust van de verzorgende

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?

0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

L. Eetlust/eetgedragverandering

Is hij/zij veranderd qua eetlust, gewicht of eetgewoonten (beoordeel nvt als de patiënt niet in staat is om zelf te eten en gevoed moet worden)? Is er verandering gekomen in het soort eten dat hij/zij lekker vindt?
NEE (indien nee, stel dan de volgende screeningsvraag)
JA (indien ja, stel dan de subvragen)

Subvragen:
1 Is zijn/haar eetlust verminderd?
2 Is zijn/haar eetlust toegenomen?
3 Is hij/zij afgevallen?
4 Is hij/zij aangekomen in gewicht?
5 Is zijn/haar eetgedrag veranderd, zoals te veel eten tegelijkertijd in de mond stoppen?
6 Is zijn/haar voorkeur voor bepaald eten veranderd? Bijvoorbeeld, heeft hij/zij veel meer trek gekregen in zoetigheid of iets anders?
7 Heeft hij/zij bepaald eetgedrag ontwikkeld, zoals elke dag precies hetzelfde willen eten of alles in dezelfde volgorde opeten?
8 Zijn er andere veranderingen in de eetlust en het eetgedrag die ik hier nog niet genoemd heb?

Als de subvragen de screeningsvraag bevestigen, bepaal dan de ernst en de frequentie in eetgedrag en eetlust.

Frequentie:
1 Soms – minder dan één keer per week
2 Regelmatig – ongeveer één keer per week
3 Vaak – verscheidene keren per week maar niet iedere dag
4 Heel vaak – in essentie continu aanwezig

Ernst:

1 Licht – veranderingen in eetlust en eetgewoonten zijn aanwezig, maar hebben niet geleid tot een verandering in het gewicht en zijn niet storend
2 Matig – veranderingen in eetlust en eetgewoonten zijn aanwezig en leiden tot kleine toe- of afname in lichaamsgewicht
3 Ernstig – er zijn duidelijke veranderingen in eetlust en eetgewoonten aanwezig die leiden tot toe- of afname in lichaamsgewicht, genant zijn, of anderszins storend zijn voor patiënt

Emotionele belasting:
Hoe emotioneel belastend is dit gedrag voor u?
0 geen
1 minimaal
2 licht
3 matig
4 ernstig
5 zeer ernstig of extreem

Een totale NPI-score kan berekend worden door alle scores van de secties op te tellen. De emotionele-belastingscore wordt niet opgenomen in de totale NPI-score.

Instructievideoband
Een instructievideoband waarin het gebruik van de Nederlandse versie van de NPI wordt gedemonstreerd, is verkrijgbaar bij M.G. Kat (psykat@hetnet.nl).

2. NPI-Q NEDERLANDSE VERSIE

Achtergrond en Afname

De Neuropsychiatrische Vragenlijst-Questionnaire is ontwikkeld om in het alledaags klinische werk neuropsychiatrische symptomen beknopt in kaart te brengen. De NPI-Q is een bewerking van de NPI (Cummings et al, Neurology 1994; 44:2308-2314) en is ten opzicht van deze lijst gevalideerd (Kaufer et al, J Neuropsychiatry Clin Neurosci 2000, 12:233-239). De reguliere NPI is een gevalideerd interview met een familielid van de patiënt, gericht op het inventariseren van neuropsychiatrische symptomen die zich in de afgelopen maand hebben voorgedaan. De NPI omvatte aanvankelijk tien neuropsychiatrische domeinen; twee andere, Nachtelijke onrust/slaapstoornissen en veranderingen in Eetlust/eetgedrag, zijn nadien toegevoegd. Een andere recente wijziging van de NPI betreft de toevoeging van een schaal voor de Emotionele belasting voor de verzorger, waarmee wordt nagegaan in welke mate de aanwezige symptomen het psychisch functioneren van de verzorger beinvloeden (Kaufer et al, JAGS, 1998; 46:210-215). De NPI-Q bevat beide aanvullingen.

Een naast familielid, of een ander die voor de patiënt zorgt, vult zelf de NPI-Q in. Elk van de 12 NPI-Q domeinen bevat een onderzoeksvraag die de belangrijkste symptomen op dat gebied weergeeft. Voor elk domein wordt eerst geantwoord met “Ja” (is aanwezig) of met “Nee” (is afwezig). Als het antwoord “Nee” is dan gaat de informant verder naar de volgende vraag. Als het antwoord “Ja” is dan beoordeelt hij of zij zowel de ernst van de symptomen die zich voordeden in de afgelopen maand (drie-puntschaal), als de psychische belasting die het voor hem of haar betekende (6-puntschaal). De NPI-Q levert voor elk gerapporteerd symptoom een bepaling van de ernst op en een beoordeling van de emotionele belasting, alsmede gesommeerde totaalscores voor Ernst en Emotionele belasting.

De meeste mensen zijn in staat de NPI-Q in ongeveer vijf minuten in te vullen. Het verdient aanbeveling dat de clinicus bij iedere afname controleert of de lijst volledig is ingevuld, of dat onduidelijkheden verheldering behoeven. Wanneer iemand voor het eerst de lijst invult kan het nuttig zijn de instructies mondeling door te nemen. In sommige gevallen is het nodig de NPI-Q gedeeltelijk of in het geheel als interview af te nemen.

Wilt u bij het beantwoorden van deze vragen steeds uitgaan van veranderingen die

zich hebben voorgedaan vanaf het moment dat hij/zij geheugenproblemen kreeg.

Omcirkel alleen “Ja” indien het symptoom in de afgelopen maand aanwezig was. In andere gevallen omcirkelt u “Nee”. Voor elke vraag die u met “Ja” beantwoordt:

a) Beoordeel de ERNST van het symptoom (hoe beïnvloedt het haar):
1 = Licht (merkbaar, maar geen belangrijke verandering)
2 = Matig (belangrijk, maar geen ingrijpende verandering)
3 = Ernstig (erg duidelijk of opvallend, een ingrijpende verandering)

b) Beoordeel de mate waarin het symptoom voor u EMOTIONEEL BELASTEND is (hoe het u beïnvloedt):
0 = In het geheel niet belastend
1 = Minimaal (enigszins belastend, geen probleem om mee om te gaan)
2 = Licht (niet erg belastend, meestal makkelijk om mee om te gaan)
3 = Matig (nogal belastend, niet altijd makkelijk om mee om te gaan)
4 = Ernstig (erg belastend, moeilijk om mee om te gaan)
5 = Zeer ernstig/extreem (uiterst belastend, niet in staat er mee om te gaan)

Beantwoord de vragen zorgvuldig. Vraag gerust om uitleg indien nodig.

	ja nee	Ernst	Emotionele belasting
Wanen Is hij/zij overtuigd van bepaalde gedachten, waarvan u weet dat ze niet waar zijn; denkt hij/zij bijvoorbeeld dat andere mensen hem/haar kwaad willen doen of van hem/haar stelen?	ja nee	1 2 3	0 1 2 3 4 5
Hallucinaties Hallucineert hij/zij; ziet hij/zij iets, dat er niet is, of hoort hij/zij geluiden of stemmen die een ander niet kan horen?	ja nee	1 2 3	0 1 2 3 4 5
Agitatie/Agressie Komt het voor dat hij/zij weigert mee te werken of zich niet laat helpen door een ander? Is hij/zij lastig om mee om te gaan?	ja nee	1 2 3	0 1 2 3 4 5
Depressie/Dysforie Lijkt het alsof hij/zij verdrietig of depressief is, of zegt hij/zij dat hij/zij zich somber voelt?	ja nee	1 2 3	0 1 2 3 4 5
Angst Raakt hij/zij overstuur of wordt hij/zij zenuwachtig wanneer u (of verzorgende) weggaat? Is er nog iets anders dat erop wijst dat hij/zij angstig is; zoals naar adem happen, zuchten, zich niet kunnen ontspannen of erg gespannen voelen?	ja nee	1 2 3	0 1 2 3 4 5
Euforie/Opgetogenheid Lijkt hij/zij zich te goed of te opgewekt te voelen?	ja nee	1 2 3	0 1 2 3 4 5
Apathie/Onverschilligheid Lijkt hij/zij minder geïnteresseerd te zijn in zijn/haar gewone activiteiten of in de activiteiten en plannen van een ander?	ja nee	1 2 3	0 1 2 3 4 5
Ontremd gedrag Handelt hij/zij impulsief zonder over de gevolgen na te denken? Praat hij/zij bijvoorbeeld tegen onbekenden alsof hij/zij ze goed kent, of maakt hij/zij kwetsende of tactloze opmerkingen tegen anderen?	ja nee	1 2 3	0 1 2 3 4 5
Prikkelbaarheid/Labiliteit Is hij/zij ongeduldig of snel geïrriteerd? Kan hij/zij er niet goed tegen als iets vertraagd is of als hij/zij moet wachten op een geplande activiteit?	ja nee	1 2 3	0 1 2 3 4 5
Doelloos repetitief gedrag Doet hij/zij telkens dezelfde handelingen, zoals doelloos rondlopen in huis, peuteren aan knopen, ergens aan plukken, draadjes opwinden en dergelijke?	ja nee	1 2 3	0 1 2 3 4 5
Gedrag 's nachts Maakt hij/zij u 's nachts wakker; staat hij/zij te vroeg op of doet hij/zij te vaak een dutje overdag?	ja nee	1 2 3	0 1 2 3 4 5
Eetlust/eetgedrag Is hij/zij afgevallen of in gewicht aangekomen, of is zijn/haar voorkeur voor bepaald eten veranderd?	ja nee	1 2 3	0 1 2 3 4 5
Totaal			

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(submitted)

Abstracts

From 1994 on several national and international abstracts on old age psychiatry subjects: late onset psychosis, neuropsychiatric disorders (dementia, delirium) and consultation- and liaisonpsychiatry.

Dankwoord

Promoveren op gevorderde leeftijd kan een aanleiding zijn om velen te bedanken. In mijn geval zijn dat al die mensen die mij tijdens mijn ontwikkeling en werk in de psychiatrie hebben gestimuleerd, gemotiveerd en geleerd mijn weg te vinden. Allen hier persoonlijk te bedanken is onmogelijk, ik moet mij beperken tot de belangrijksten.

Ik denk in de eerste plaats aan mijn patiënten, zonder wie dit proefschrift niet tot stand gekomen zou zijn en die mij, ieder met zijn eigen levensgeschiedenis, in staat stelden een grote schat aan klinische ervaring op te doen. Later bleek dat ik met die kennis ook onderzoek kon doen, een mooi cadeau.

Piet Eikelenboom, promotor: Jij superviseerde mij tijdens de stage op de afdeling Neuropsychiatrie (1983). Samen met Chris Hooijer en Cees Jonker maakte jij ons, arts-assistenten in opleiding tot psychiater, al vroeg wegwijs in de differentiaaldiagnostiek en behandeling van ouderen met (neuro)psychiatrische stoornissen. Hier ligt de kern voor mijn affiniteit met deze doelgroep, terwijl dit helemaal niet zo voor de hand lag. De meesten van ons beschouwden ouderen immers, zeker in die tijd, als afgeschreven en waarom zou je je daar dan nog in verdiepen. Het wetenschappelijk dementieonderzoek van jullie voorganger Frans Stam, de gewaardeerde en tegelijkertijd - het was de periode van de 'antipsychiatrie' - 'verketterde' hoogleraar psychiatrie werd door jullie respectvol voortgezet en daar plukte ik de vruchten van. Het is dan ook geen toeval dat dit proefschrift gaat over een neuropsychiatrisch onderwerp en dat ik weer contact met je zocht, inmiddels zo'n 23 jaar later. Het was een genoegen om na zoveel jaren uitvliegen weer even terug te zijn op het VK-nest. Ik dank je voor je kennis en creativiteit en de sobere, haast monnikachtige wijze waarop je wetenschap bedrijft, je beperkt tot de essentialia, ontdaan van alle franje. Ik herinner me jouw gedrevenheid op de momenten dat je mij begeleidde naar de uitgang van de VK en zelfs meeliep tot aan mijn geparkeerde fiets, om me snel nog even een aantal tips aan de hand te doen: 'Kijk ook hier nog even naar', was dan vaak de laatste zin tijdens ons afscheid.

Pim van Gool, promotor: Ik kende jou voordat ik concrete plannen had om te promoveren alleen van papier, via jouw artikelen en de vaak kritische ondertoon in casuïstische mededelingen, ingezonden brieven of interviews. Vaak bekroop mij dan het gevoel: 'Wat doen we nu weer niet goed daar op die werkvloer?' Je bent enorm meegevallen! Ik heb als psychiater zelden zo'n aardige, serieuze en tegelijkertijd humorvolle neuroloog meegemaakt die bovendien ook erg geïnteresseerd bleek in de neuropsychiatrie (of moet ik zeggen gedragsneurologie?). Ik dank je voor jouw warme ontvangst in het AMC en de prettige en intelligente wijze (wie ben ik?) waarop jij m'n artikelen hebt gelezen en becommentarieerd.

Bovendien bleek je een grote steun bij de vertalingen en prees ik je snelle reacties op mijn e-mails. ‘Less is more’ was hierbij vaak het devies, niet altijd goed te verdragen voor iemand die de neiging heeft nogal eens zijpaden te willen bewandelen. Komend van de VU is het voor mij een voorrecht om nu, mede dankzij jou, te mogen promoveren aan de UvA. Amsterdamser kan het niet!

Een bijzonder woord van dank wil ik richten tot Willem van Tilburg, mijn hoofdopleider: Willem, dankzij jou was ik in de gelegenheid om me te scholen op een breed terrein van de psychiatrie met ruime aandacht voor organisch psychiatrische, systeemgeoriënteerde, psychoanalytische en cognitief-gedragstherapeutische gezichtspunten en theorieën. Deze ruime oriëntatie vormde de basis voor de wijze waarop ik mijn vak ging uitoefenen en nog altijd beoefen: de clinicus die zich niet gevangen hoeft te voelen in dogma’s van één bepaalde leer. Ik heb goede herinneringen aan de wijze waarop jij de supervisie over mijn psychotherapieën gaf. Het bleek altijd veilig genoeg en haast kameraadschappelijk om mijn ‘beginnersworstelingen’ inclusief overdrachts- en tegenoverdrachtsfenomenen, met je te delen. Regelmatig moest ik hierbij denken aan de tekst van jouw inaugurele rede (1982) met de titel ‘Van diagnostiek naar dialoog’. Hierin hield je een pleidooi voor het diagnostisch werken ‘vanuit de postulaten van de dialoog’. Die dialoog was altijd mogelijk. Zeer bedankt voor dit alles.

Jos de Jonghe, co-promotor: Jij was degene die met jouw grote voorliefde voor klinisch wetenschappelijk onderzoek op prachtige wijze aansloot bij mijn werk als clinicus. Wij leerden elkaar kennen in het Psychiatrisch Centrum Vogelenzang, op de afdeling Ouderenpsychiatrie (Duinoord). Ik herinner me het enthousiasme dat wij deelden om op de afdeling wetenschappelijk onderzoek van de grond te krijgen. Ook jij bleek geïnteresseerd in het zoeken naar verbanden tussen gedrag en ‘substraat’ en de interactie met de omgeving, met name bij ouderen met ‘cognitieve’ stoornissen. Je stond ook altijd open voor nieuwe plannen. Zo werkte je destijds mee aan de totstandkoming van het GERON, de Geheugen- en Ouderenpolikliniek Amsterdam Noord, de eerste geheugenpoli waarin de neuropsychologische onderzoeken aan huis werden verricht (1990). Het was voor mij een genoegen om een bijdrage te kunnen leveren aan de artikelenreeks die heeft geleid tot jouw promotie in 2001. Man, wat heb jij mij bijgestaan bij mijn promoveren. Zonder jou was er niets (of misschien pas veel later) van terechtgekomen: ‘Gaat het niet rechtsom, dan linksom, maar komen zal je er’. Heel erg bedankt hiervoor. Ik prijs je affiniteit met de ‘cijfers’: ‘Even een Chi-kwadraatje doen?’. Bedankt ook voor de vele momenten waarop wij na gedane arbeid (Peppie en Kokkie!) als ware ‘broertjes’ onze afleiding zochten in een spelletje golf in het buitenland of het musiceren in een ‘ziekenhuisband’. Ik hoop nog lange

tijd met je samen te werken.

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De promotiecommissie dank ik voor het zorgvuldig en kritisch lezen van het manuscript.

Ralph Vreeswijk: Wat heb je mij fantastisch geholpen bij de beloopstudies! Ik herinner me de momenten dat we 's morgens vroeg (kort na zevenen) de polikliniek openden. Mijn eerste kop koffie stond dan al klaar voordat ik het wist. Samen hebben wij menig huisbezoek gedaan om de patiënten uit de studie na twee jaar opnieuw in kaart te brengen. Dank voor je hulp, trouw en gezelligheid. Ik wens je heel veel succes met jouw promotieactiviteiten en met je nieuwe baan.

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trekken en samen onderzoek te doen aan de NPI en een artikel te schrijven. Jullie waren de eersten via wie ik het contact met de Valeriuskliniek weer oppakte: het was een beetje thuiskomen! Ook Anne Kat dank ik zeer voor haar bijdrage aan deze studie. Het was een voorrecht om de huisbezoeken en het testwerk met je te kunnen doen An!

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Curriculum vitae

Martin Kat werd in Nieuwer-Amstel geboren op 6 oktober 1951 en woont sinds 1961 in Amsterdam. Hij studeerde geneeskunde aan de Vrije Universiteit in Amsterdam (1974-1982). Aan deze universiteit specialiseerde hij zich in de psychiatrie (1983-1987). Van 1986 tot 1995 werkte hij als parttime psychiater in de RIAGG Amsterdam Noord, team Ouderen. Daarnaast was hij verbonden aan de afdeling Verblijfspsychiatrie van het Psychiatrisch Centrum Amsterdam van 1987-1990. In 1991 trad hij in dienst bij het Psychiatrisch Centrum Vogelenzang (afdeling Ouderenpsychiatrie), tot 1999. Van 1999 tot heden werkt hij in het Medisch Centrum Alkmaar, afdeling Klinische Geriatrie.
Hij is sinds 1991 parttime vrijgevestigd psychiater-psychotherapeut in Amsterdam. Hij ontwikkelde in deze praktijk de psychiatrische consultatie aan verzorgings-, verpleeg- en gezinsvervangende (te)huizen in Amsterdam en omstreken. Kat is docent ouderen- en neuropsychiatrie aan verschillende opleidingen. Hij schrijft over ouderenpsychiatrische en neuropsychiatrische onderwerpen en ontving twee prijzen op dit gebied. Zijn wetenschappelijk onderzoek is gaandeweg verricht.
Martin is getrouwd met Paulien Koch. Zij hebben drie dochters Anne, Pam en Sophie.