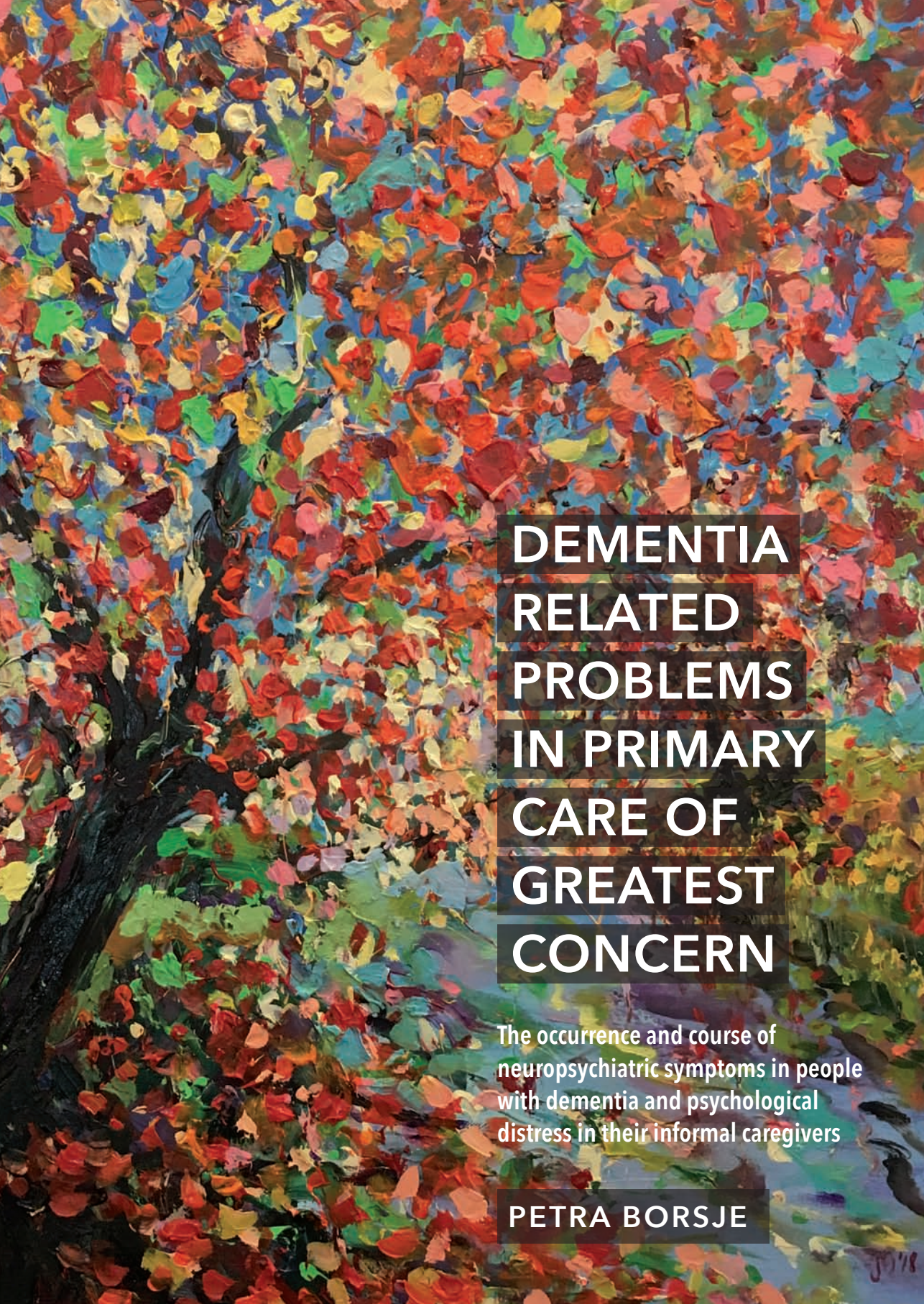

DEMENTIA RELATED PROBLEMS IN PRIMARY CARE OF GREATEST CONCERN

The occurrence and course of neuropsychiatric symptoms in people with dementia and psychological distress in their informal caregivers

PETRA BORSJE

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The research presented in this thesis was performed within the Department of Primary and Community Care and the Radboudumc Alzheimer center, Radboud university medical center, Nijmegen, the Netherlands.

An electronic version of this thesis can be found on http://www.ukonnetwerk.nl/PetraBorsje

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Als professional ontmoet ik mensen met dementie in de laatste, soms moeilijke fase van hun leven. Zij hebben daarvoor een veelkleurig bestaan geleid, zoals deze boom uitdrukt. (Petra Borsje)
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“Alles kan als jij het laat gebeuren”
(Mary Poppins)

Voor Sebastiaan, Anne en Thijs

CONTENTS

CHAPTER 1

General introduction

BACKGROUND

Dementia is a syndrome characterized by deterioration in memory, thinking and the ability to perform everyday activities. Worldwide, around 50 million people have dementia, and there are nearly 10 million new cases every year.[1] Dementia has a physical, psychological and social impact on people with dementia, their family members, their caregivers and on society as a whole.[1] Many people with dementia live in the community and are cared for by their general practitioner (GP). During the course of dementia most people develop some type of behavioural symptoms, also called neuropsychiatric symptoms (NPS). These NPS affect their quality of life and their relation with their (informal) caregivers negatively.[2,3] Psychotropic drugs are often prescribed in this process. GPs have an important role in diagnosing and managing NPS. In the following, each of these elements are introduced in more detail.

OCCURRENCE OF DEMENTIA AND TRANSITION OF DEMENTIA CARE

In the Netherlands, it is estimated that there are 254.000 to 270.000 people with dementia of whom approximately 70% are community-dwelling, that is not institutionalized in long-term care facilities (LTCF).[4,5] Sixty percent of the community-dwelling people with dementia live with their informal caregiver and 40% alone.[6] The prevalence rate of dementia in an average general practice of 2095 patients is 36 (2%).[7] In the last few years, due to the preference of older people to remain in their own home, the high healthcare costs associated with living in LTCF and the government policy, the number of people with dementia living in their own homes increases. The governments' motto is "At home as long as possible". In 2015, a new Long-term Care Act (Wet langdurige zorg) was introduced in the Netherlands, that replaced the Exceptional Medical Expenses Act (Algemene Wet Bijzondere Ziektekosten). The objective of this new act was to safeguard the financial sustainability of long-term care and to improve the quality of it by making it more client-tailored.[8] People with dementia living at home and their informal caregivers, on the other hand, now have to deal with 3 different legal frameworks for the organization and financing of their dementia care during the trajectory of the disease i.e.: Social Support Act (Wet maatschappelijke ondersteuning) run by municipalities, Health Insurance Act (Zorgverzekeringswet) and the Long-term Care Act.[5,8] This has a considerable impact on the structure and level of health care for both the person with dementia and their informal caregivers as well as on professional caregivers and the medical care provided by the GP.[5] For dementia care in primary care, a joint venture between GP, dementia case manager and elderly care physicians is recommended.[7,9,10]

ROLE OF THE GENERAL PRACTITIONER

GPs play a pivotal role in the care of people with dementia and their family members. The GP is most often the first physician consulted for dementia-related problems. Many GPs are aware of the additional workload attached to caring for dementia patients in their daily practice. On the other hand, dementia is still under-detected in primary care. Approximately 40 to 45 % people with dementia are not registered with a diagnosis of dementia in the electronic medical records of the GP.[11,12] Moreover, GPs find making the diagnosis, disclosing the diagnosis and the management of dementia and particularly NPS difficult.[13-15] This is a consequence of limited confidence in their diagnostic skills, reluctance in disclosing the diagnosis and lack of knowledge in the management of NPS and other problems in dementia.[14,15] Moreover, the care provided to people with dementia and NPS is often reactive. Repeated phone calls as signs of a deteriorating situation or mismatch of expectations of the family and the capabilities of the GP concerning people with dementia have a high impact on GPs.[13-15]

According to the Dutch GP guideline for Dementia, problem behaviour is defined as all behaviour of the patient that is perceived as difficult to manage by the patient themselves or his/her environment.[7] The guideline mentions as examples: agitation or aggression, apathy, diminished empathy, rejecting any assistance, reversion of day en night rythm, incompassionate excessive crying or laughing, disinhibition with food or sexual disinhibition, physical hyperactivity, wandering, compulsive hoarding, hiding things and loss of appropriateness.[7] The guideline provides management strategies for non-pharmacological and pharmacological interventions in case NPS occur in people with dementia. In the guideline there is no recommendation for actively identifying problem behaviour in patients with dementia and for psychological distress by their informal caregivers by the GP.[7]

DEVELOPMENT OF NEUROPSYCHIATRIC SYMPTOMS

Human behaviour is the result of a complex interaction of biological, psychological and social factors in the context of the environment (biopsychosocial model).[16] This complex model also applies to the behaviour of people with dementia. The behaviour of people with dementia is not only dependent on changes in brain function, but also on how that impacts their perception, coping and ability for response control.[17] The determining factor for considering (changes in) behaviour of people with dementia as problem behaviour is not the behaviour itself, but how behaviour is perceived by others.[18] In this thesis we used the term NPS instead of problem behaviour, since our research was carried out from a doctor-patient relationship, focusing on generating information for GPs.

During the course of dementia most people develop some type of NPS.[19-25] NPS include psychiatric and behavioural symptoms. The Neuropsychiatric Inventory (NPI), for example,

is a widely-used rating scale assessing 12 different NPS: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, nighttime behaviour disturbances and eating changes. [26-28] Based on the NPI, NPS can be categorized in subsyndromes: mood/apathy, hyperactivity and psychosis.[29,30] The prevalence and incidence rates of NPS measured with the NPI in community-dwelling people with dementia are high and moreover NPS are persistent although frequency parameters vary considerably across studies.[19,21,25,31,32] Apathy, depression, aberrant motor behaviour, agitation, irritability and sleep disturbance are the most common individual NPS among people with dementia.[19,21] For hallucinations, delusions, agitation, aberrant motor behaviour, disinhibition, apathy, and sleep disturbance increasing trends in point prevalence rates during the course of the disease have been found.[19,21,25,31] The mood/apathy and the hyperactivity subsyndrome are the most common NPI subsyndromes .[19,21]

IMPACT OF NEUROPSYCHIATRIC SYMPTOMS

NPS in general and depression in particular, are predictors of institutionalization.[33,34] They are also associated with psychological distress among informal caregivers.[35-37] NPS result in a lower quality of life for both people with dementia and their caregivers and negatively affect the quality of the patient-caregiver relationship.[2,3] Greater cognitive impairment, higher baseline severity of NPS and increased functional impairment lead to more NPS.[30,38-42] The use of support services, like day and respite care and training courses for caregivers, are associated with less NPS over time.[38]

Informal caregivers of people with dementia experience psychological distress including feelings of burden and depressive and anxiety symptoms and disorders. Therefore, they are at risk for a deteriorating mental health.[43,44] In cross-sectional studies, caregiver characteristics associated with more psychological distress are: (younger) age, (female) gender, (lower) educational level/socioeconomic status, longer duration of caregiving and caregiver-patient relationship.[45,46] Patient characteristics that are associated with increasing psychological distress in informal caregivers over time are: higher frequency of NPS, deterioration of dementia and decline in activities of daily living (ADL) of the patient. High baseline burden, living with the patient, and poor mental health of the caregiver are caregiver characteristics that are associated with increasing psychological distress over time. NPS are the most significant contributors to the course of psychological distress in the informal caregivers.[32,37,47-52] Although depression, aggression, and sleep disturbances are the most frequently identified NPS to impact negatively on caregivers, a wide range of NPS is associated with psychological distress. However, the evidence is not conclusive as to whether some NPS are more important than others.[53]

USE OF PSYCHOTROPIC DRUGS

The GP has an important role in prescribing psychotropic drugs.[13,54] Practice guidelines for NPS recommend non-pharmacological management as first-line treatment and these predominantly psychosocial interventions may lead to a substantial reduction of antipsychotic drug prescription.[55,56] However, psychotropic drugs, such as antipsychotics and antidepressants, are frequently prescribed to patients with dementia with agitation, psychosis and anxiety. The prevalence of psychotropic drug use is related to the presence of NPS.[11,54] There is only limited evidence for the effectiveness of psychotropic drugs in the treatment of NPS in people with dementia. Moreover, they cause serious adverse effects, such as extrapyramidal, anticholinergic and cardiovascular symptoms and increase of NPS.[57-59]

WHAT IS KNOWN ABOUT NEUROPSYCHIATRIC SYMPTOMS IN PRIMARY CARE?

Almost all studies on the course of NPS in community-dwelling people with dementia were conducted in ambulatory patients with dementia visiting outpatients' memory, (old-age) psychiatry, neurological or geriatric clinical centres or dementia services. In these studies, most participants were living at home, but still part of them were living in LTCF or it was not clear what part of the study population was institutionalized.[19-23,25,31,32,39-41,60,61] In the Netherlands, GPs provide basic medical care for people who live at home. For LTCF there are specifically trained medical doctors called elderly care physicians.[62] Only a limited proportion of people in general practice in the Netherlands are referred to secondary care. Therefore, it is likely that a study population visiting outpatient clinical centres has more severe and frequent symptoms than the total group of people with dementia in general practice.

AIM OF THIS THESIS

So far, prospective studies on the course of NPS have not been conducted in patients exclusively from general practices. For GPs, it is important that accurate data of NPS and psychotropic drug use of patients with dementia in general practices are available. Therefore, the general aim of this thesis is to investigate the prevalence of NPS and psychotropic drug use, as well as the course and determinants of NPS in people with dementia and the psychological distress in their informal caregivers in primary care.

The following research questions are addressed:

1. What is known from previous research about the prevalence and course of NPS in community-dwelling people with dementia? (chapter 3)
2. What is the prevalence of NPS and psychotropic drug use in people with dementia in general practice? (chapter 4)
3. What is the course of NPS and which are the determinants for the course of NPS in people with dementia in primary care? (chapter 5)
4. What is the course of and which are the determinants of psychological distress in informal caregivers of people with dementia in primary care? (chapter 6)

OUTLINE OF THIS THESIS

The study protocol of this study is described in **chapter 2**.

In **chapter 3** the existing literature is systematically reviewed to know the prevalence and course of NPS in community-dwelling people with dementia.

In **chapter 4** the prevalence of NPS and the prevalence of psychotropic drug use are assessed in patients with dementia in general practice

In **chapter 5** the course of NPS in patients with dementia in primary care is investigated and determinants for the course of NPS in people with dementia in primary care were detected.

In **chapter 6** the course and determinants of psychological distress in informal caregivers of people with dementia in primary care are investigated.

In **chapter 7** the main findings of this study are summarized and discussed together with methodological considerations. In addition, the impact for dementia care and management in general practices and implications and recommendations for future education and research are addressed.

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CHAPTER 2

Neuropsychiatric symptoms in patients with dementia in primary care: a study protocol

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BMC Geriatr 2014;14:32.

ABSTRACT

Background

Neuropsychiatric symptoms (NPS) frequently occur in patients with dementia. To date, prospective studies on the course of NPS have been conducted in patients with dementia in clinical centres or psychiatric services. The primary goal of this study is to investigate the course of NPS in patients with dementia and caregiver distress in primary care. We also aim to detect determinants of both the course of NPS in patients with dementia and informal caregiver distress in primary care.

Methods/design

This is a prospective observational study on the course of NPS in patients with dementia in primary care. Thirty-seven general practitioners (GPs) in 18 general practices were selected based on their interest in participating in this study. We will retrieve electronic medical files of patients with dementia from these general practices. Patients and caregivers will be followed for 18 months during the period January 2012 to December 2013. Patient characteristics will be collected at baseline. Time to death or institutionalization will be measured. Co-morbidity will be assessed using the Charlson index. Psychotropic drug use and primary and secondary outcome measures will be measured at 3 assessments, baseline, 9 and 18 months. The primary outcome measures are the Neuropsychiatric Inventory score for patients with dementia and the Sense of Competence score for informal caregivers. In addition to descriptive analyses frequency parameters will be computed. Univariate analysis will be performed to identify determinants of the course of NPS and informal caregiver distress. All determinants will then be tested in a multivariate regression analysis to determine their unique contribution to the course of NPS and caregiver distress.

Discussion

The results of this study will provide data on the course of NPS, which is clinically important for prognosis. The data will help GPs and other professionals in planning follow-up visits and in the timing for offering psycho-education, psychosocial interventions and the provision of care. In addition, these data will enlarge health professionals' awareness of NPS in their patients with dementia.

BACKGROUND

Dementia is a chronic and mostly progressive disease with great impact on patients and their family members. Current estimates indicate that 35.6 million people worldwide are living with dementia. This number is expected to double by 2030 and more than triple by 2050.[1] The estimated standardized prevalence of dementia among persons aged 60 and over in Western Europe, Central Europe and Eastern Europe is 7.3 %, 5.8 % and 5.7 %, respectively.[1] In the Netherlands 250,000 people have dementia, and most of these patients reside in the community.

Neuropsychiatric symptoms (NPS), such as psychosis (delusions and hallucinations), depressive mood, anxiety, irritability/lability, apathy, euphoria, disinhibition, agitation/aggression, aberrant motor activity, sleep disturbance and eating disorder, often occur in patients with dementia. NPS result in lower quality of life for both the patient and caregiver and affect the quality of the patient-caregiver relationship.[2,3] NPS, severity of cognitive impairment, Alzheimer's dementia, high rates of functional dependence and depressive symptoms are predictors of nursing home admission.[4] Major depression is a predictor of early institutionalization in the first year following the dementia diagnosis.[5] The baseline severity of NPS, stage of dementia and use of support services predict the future severity of NPS.[6] However, there is a lack of knowledge about the determinants of neuropsychiatric symptoms in community-dwelling patients with dementia.

Studies in various countries reported NPS prevalence rates that ranged from 66 to 94 %.[7-13] Incidence rates of NPS were reported in only a few studies. In a United States of America (USA) Cache County study, Steinberg et al. found an incidence rate of 69 % after an 18-month follow-up.[14] Only one Dutch study has been conducted on the course of NPS in community-dwelling people with dementia. In the MAASBED (MAAstricht Study of BEhaviour in Dementia) study it was found that 81 % of the patients with dementia from a memory clinic and an ambulatory mental health institute showed any type of NPS, such as agitation (19 %), irritability (24 %), aberrant motor behaviour (26 %), depression (35 %), apathy (40 %), anxiety (21 %) and delusions (22 %).[15] After a 6 - 12-month follow-up, the cumulative incidence of NPS was 74 %.[15] Several prospective studies of NPS in community-dwelling patients with dementia have been conducted in other countries. In most of these studies, the Neuropsychiatric Inventory (NPI) was used to evaluate NPS. Eighty-one percent of those without any NPS at baseline had at least one symptom after 18 months in the USA Cache County study.[16] In the same study, 67 % of the participants with at least 1 clinically significant NPS (total NPI score ≥ 4) at baseline continued to display clinically significant NPS after 18 months. Among the 10 neuropsychiatric symptoms assessed at baseline, delusions persisted in 66 %, depression in 58 % and aberrant motor behaviour in 56 % of the individuals. Hallucinations and disinhibition persisted in 25 % and 11 % of the participants, respectively.[16] In a study in the United Kingdom, 94 % of the participants had at least one NPS and 75 % of the participants

had an NPI score ≥ 4 for at least one symptom. Of the latter group, 80 % had a persistent NPI score ≥ 4 in at least one domain after 6 months.[12] Furthermore, a 2-year follow-up study in England and Wales showed that NPS co-occur.[17] Anxiety and depression as well as misidentification, persecution and hallucinations were strongly associated.[17] The REAL-FR (Réseau sur la Maladie d' Alzheimer Français) cohort study found that the percentage of patients presenting one or more clinically relevant NPS as measured by the NPI increased from 66 % at baseline to 88 % after 4-year follow-up.[13] Prevalence of agitation increased from 17.9 % to 29.1 %, apathy from 43.0 % to 62.9 %, disinhibition from 2.6 % to 14.6 %, hallucinations from 2 % to 4.6 % and aberrant motor behaviour from 13.9 % to 29.1 %. Prevalence of hyperactivity and apathy increased significantly during the follow-up, whereas the prevalence of affective and psychotic symptoms did not increase.[13]

To date, prospective studies on the course of NPS have been conducted on ambulatory patients with dementia in memory clinics or clinical centres[13,15], using ambulatory services[15] or who were approached through local psychiatric services, the volunteer sector and nursing and residential care homes.[12] High (cumulative) prevalence and (cumulative) incidence rates of NPS were found in these studies. In the REAL-FR cohort, a prevalence of 66 % at baseline increased to 88 % after 4 years.[13] In the MAASBED study, a prevalence of 80.9 % at baseline increased to a cumulative prevalence of 88.9 % after 2 years, and the cumulative incidence after 6 - 12 months was 74 % in ambulatory patients of memory clinics or psychiatric services.[15] In the LASER-AD (London And the South East Region - Alzheimer's Disease) study, 33 % of the participants were recruited from 24-hour care settings and 67 % were living at home. The prevalence rates of NPS at baseline were 93.8 % for at least one NPS, and 88.4 % of the participants had a NPI score ≥ 4 in at least one domain. At 6-month follow-up, 96.2 % had at least one NPS in any domain. Of these participants 80.3 % had a persistent NPI score ≥ 4 in at least one domain.[12]

Steinberg and Savva have studied a community-dwelling population.[16,17] In Cache County, 62 % of the participants with dementia had at least one NPS at baseline and 23 % had a NPI score ≥ 4 in at least one domain. After 18 months, 95 % of the participants had at least one NPS at baseline and 49 % had a NPI score ≥ 4 in at least one domain. However, of the 5092 individuals who were enrolled in this study, 265 resided in nursing homes. Information was not provided on the percentage of the 329 participants with dementia who resided in nursing homes.[16] In the Medical Research Council Cognitive Function and Aging Study, prevalence rates of 5.8 % for confabulation to 50.3 % for apathy were found in dementia patients. Incidence rates of 2 % for anxiety to 61 % for apathy were found after 2 years. Furthermore, persistence rates were 13 % for confabulation and 66 % for apathy. The percentage of participants who lived in institutions was 38 % at baseline and 66 % after 2-year follow-up.

It appears as though the prevalence and incidence rates of NPS in community-dwelling patients with dementia are lower (23 % to 50 % and 49 % to 60 % respectively) than those of ambulatory patients of memory clinics or clinical centres and ambulatory patients of

psychiatric services (66% to 96.2% and 74% respectively). Finally, the relationship between caregiver characteristics and caregiver distress and NPS was unclear in these studies.

Aims of the study

The first aim of this study is to investigate the course of NPS in patients with dementia and informal caregiver distress in primary care. We also aim to detect determinants of both the course of NPS in patients with dementia and informal caregiver distress in primary care.

METHODS/DESIGN

Study design

This is a prospective observational cohort study in primary care. For this study, all 192 known general practitioners (GPs) in 114 general practices in the region West- and Middle-Brabant in the southern part of the Netherlands were invited to participate. All GPs of the 114 practices individually received a letter with information on the study and were invited to attend a meeting about NPS and the study. Announcements of this study were also posted on the websites of the regional GP corporations. Thirty-seven GPs in 18 general practices were selected based on their interest in participating in the study. The presence of specialized care for elderly people in the general practices will be determined by asking whether the participating GPs followed a specialized management training course in elderly care medicine in primary care and whether specialized staff members are available in these general practices to support the GP in managing the care for elderly patients. We will retrieve electronic medical files of patients with dementia from these general practices. Patients and informal caregivers will be approached by letter. Informal caregivers are persons who are listed in the electronic medical files of the GP as the main informal caregiver and contact person. There will be no restriction in the amount of time that the informal caregiver spends with the patient. After the letter is mailed to the patient and informal caregiver, the GP will contact the patient or informal caregiver by telephone to stimulate participation in the study. The assessment interviews will take place at the patients' home by a trained interviewer.

Patients and informal caregivers will be followed for 18 months. In case that a patient dies or will be institutionalized, length of time to death or institutionalization, respectively, will be measured. The study began in January 2012 and will end in December 2013.

In the Netherlands, many psychosocial interventions and care services are available for community-dwelling people with dementia, including cognitive training and stimulation, physical exercise, reminiscence, education and support for both patient and informal caregiver and respite care. Dementia case management is stimulated by the Dutch government and is available in all parts of the country. Dementia case management involves assessment, planning and advocacy for patients with dementia and their informal caregivers. It also aims

to empower informal caregivers and facilitate timely access to essential care services to support their caregiver needs. In the southern region of the Netherlands, a dementia case manager (CM) is provided by many care organizations and care services. We consider this single component dementia case management.

In 14 of the participating general practices, a multicomponent collaborative care program named CONCERN (Care Optimization for Non-professional Caregivers of Elderly with dementia and Reduction of Neuropsychiatric symptoms) will be provided. In CONCERN, a dementia CM together with an elderly care physician and the GP focus on optimization of care and improvement of quality of life for patients with dementia suffering from NPS and their informal caregivers. Following assessment and diagnosis of the NPS, a care plan is designed for the treatment and support of both the patient and informal caregiver. This care plan is periodically evaluated in a multidisciplinary meeting with the GP, elderly care physician, dementia CM and other involved care services.

We will measure whether the patients with dementia and their informal caregivers are treated by single component dementia case management, CONCERN or care as usual (no CM).

Patients and their informal caregivers

All patients in the participating general practices with a diagnosis of dementia as registered in the electronic medical files of the general practice, and living at home are eligible to participate in this study together with their informal caregiver (spouse, child or neighbour). We will select patients with the International Classification of Primary Care (ICPC) code for dementia (P70) from the electronic medical systems. This code includes Alzheimer's disease and senile dementia. We will also select patients with memory disturbance (ICPC code P20) who are diagnosed with dementia. Patients with an estimated life expectancy of less than 3 months will be excluded from the current study. All patients and caregivers will receive a complete written description of the study and be asked to sign an informed consent document. If the patient is unable to provide informed consent, his or her legal representative will be asked to provide informed consent on the patient's behalf.

Ethical approval

This research project was presented for medical ethics review at the Committee on Research Involving Human Subjects (CMO) of the district Arnhem - Nijmegen, the Netherlands. The CMO judged that the current project is not subject to the Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek) and can be conducted without review by the CMO.

Assessment instruments

Data are collected by a trained research assistant during an interview with the patient and the caregiver at home at baseline (T0), after 9 months (T1) and at 18 months (T2). The same

set of questionnaires will be used in all 3 assessments (Table 1). The outcome measures have good psychometric properties. The primary outcome for the patient is the NPI and that for the informal caregiver is the Sense of Competence Questionnaire (SCQ).

Table 1. Assessment instruments

	Instrument	T0	T1	T2
	Baseline variables	X		
Patient	Mini Mental State Examination	X	X	X
	Neuropsychiatric Inventory	X	X	X
	Cohen-Mansfield Agitation Inventory	X	X	X
	Cornell Scale for Depression in Dementia	X	X	X
	Quality of life in Alzheimer's disease	X	X	X
	Charlson Index	X		
	Psychotropic drug use	X	X	X
Informal Caregiver	Center for Epidemiological Studies Depression Scale	X	X	X
	General Health Questionnaire	X	X	X
	EuroQol	X	X	X
	Sense of Competence	X	X	X

Patient characteristics

The following patient characteristics will be collected at baseline (T0): age, gender, marital state, socio-economic status/educational level and profession, use of health care services (psychiatric services; home care: nursing, domestic; day care services; on waiting list for residential care facility or nursing home). Co-morbidity will be assessed using the Charlson index. The Charlson Index comprises 19 categories of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) diagnose codes and is based on a set of risk factors for 1-year mortality risk.[18] The Charlson Index contains a weighted index for each disease, with a score that is a significant predictor of 1-year survival. Psychotropic drug use (antipsychotics, anticonvulsants, antidepressants, anxiolytics, hypnotics and medication for dementia) will be collected in all 3 assessments.

Neuropsychiatric symptoms

The Neuropsychiatric Inventory (NPI), developed by Cummings[19,20], will be the primary outcome. This inventory assesses 12 neuropsychiatric symptoms in dementia outpatients. The validity and reliability of the NPI[21] and of its Dutch version[22] were previously established. Since then, the NPI has been the most widely used rating scale for the assessment of NPS. The NPI comprises 12 categories of problem behaviour, as follows: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, sleeping disorder and eating disorder. For each positive symptom,

the severity and frequency are scored on the basis of structured questions administered to the patients' caregiver. The continuous score for each symptom is obtained by multiplying severity (1 - 3) by frequency (1 - 4). In line with previous studies[8,13-16], a score of 4 or more on one symptom will be taken to indicate the presence of specific 'clinically relevant' symptoms. Caregiver distress is also assessed (0 - 5), but is not calculated in the NPI total score. Frequency and severity scores of individual symptoms can be multiplied (FxS score) and summed over 12 items, yielding a total NPI score that ranges from 0 to 144. The following five NPI factor scores (based on the findings of previous studies) will be used[23,24]: (1) agitation, consisting of agitation/aggression, euphoria, disinhibition and irritability; (2) depression, consisting of depression and anxiety; (3) psychosis, consisting of hallucinations and delusions; (4) psychomotor agitation, consisting of aberrant motor behaviour and nighttime behaviour, and (5) apathy, consisting of apathy and eating disorder.[23] The NPI will be assessed by a trained interviewer during an interview with the informal caregiver.

The Cohen-Mansfield Agitation Inventory (CMAI), originally developed by Cohen-Mansfield[25], is the most widely used assessment scale for measuring the frequency of agitation and aggression. This inventory defines agitation as inappropriate verbal, vocal or motor activities not explained by apparent needs or confusion. The informant is the patient's caregiver. Symptoms are assessed for the preceding 2 weeks. The original and translated Dutch version was found to be valid and reliable.[26-28] It consists of 29 individual items and can be categorized in 3 subscales, which assess physically aggressive (directed against a person or object), physically non-aggressive (not directed against a person or object, such as pacing and wandering) and verbally agitated behaviour. Items are scored on a 7-point frequency scale, as follows: 1 = never; 2 = < once a week; 3 = 1 - 2 times per week; 4 = several times per week; 5 = 1 - 2 times per day; 6 = several times per day; 7 = several times per hour.[26] In community-dwelling persons with Alzheimer's disease, the CMAI appears useful as an overall measure of behavioural disturbances, but scoring by subscale does not seem applicable.[29]

The Cornell scale for depression in dementia (CSDD) is widely used for the screening of depressive symptoms in dementia. The CSDD consists of 19 items, each rated as 0 = absent, 1 = mild or intermittent or 2 = severe. The scores of the individual items are summed, and a cut-off of 8 or more indicates depression.[30] With a cut-off value of > or = 6 the CSDD has a sensitivity and specificity of 93 % and 97 %, respectively. It seems equally valid in demented and non-demented populations.[31] The CSDD will be administered by interviewing the informal caregivers about their observations of the patients' behaviour.

Cognition

Cognition will be assessed by the Mini-Mental State Examination (MMSE), which is the most widely used screening instrument to detect cognitive impairment.[32] It has a fair reliability and construct validity, with a high sensitivity for moderately to severe cognitive impairment and a lower sensitivity for mild cognitive impairment.[33] It comprises items that test

orientation, attention, memory, language and constructive abilities. An important bias in using the MMSE is the extensive use of language, which leads to unreliable results in aphasic patients and patients who are incapable of speaking the local language.[33]

Quality of life

The Quality of life in Alzheimer's disease **(**Qol-AD) is used to measure quality of life. It is an easy-to-use 13-item instrument that covers physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores around the house, ability to do things for fun, money and life as a whole. Each of the 13 items is rated on a 4-point Likert scale, as follows: 1 - 'poor'; 2 - 'fair'; 3 - 'good' and 4 - 'excellent'.[34,35] Logsdon found satisfactory validity and reliability, but a limited use for patients with an MMSE score of less than 10.[36] In other studies, the Qol-AD showed very good psychometric properties, with satisfactory reliability and validity. Furthermore, it can be completed with people with a wide range of severity of dementia.[37-40]

Informal caregiver characteristics

The following general characteristics of the informal caregivers will be collected at baseline (T0): age, gender, marital state, socio-economic status/ educational level and profession.

Impact on informal caregiver

The psychological burden of caring for a patient with dementia, measured using the Sense of Competence Questionnaire (SCQ), will be the primary outcome for the informal caregivers. The SCQ is based on the family-crisis model[41] and derived from Zarit's Burden Interview.[42] This interview was developed for informal caregivers of patients diagnosed with dementia and consists of 27-items that are rated on a 5-point scale, as follows: 1 'yes, completely agrees', 2 'yes, agrees', 3 'on the one hand agrees but on the other hand disagrees', 4 'no, disagrees' and 5 'no, completely disagrees'.[43,44] The SCQ consists of the following three subscales: 1. satisfaction with the elderly person as the recipient of care (7 items; range 7 - 35; Cronbach's alpha = 0.55); 2. satisfaction with one's own performance as a caregiver (12 items; range 12 - 60; Cronbach's alpha = 0.63); and 3. consequences of involvement in care for the personal life of the caregiver (8 items; range 8 - 40; Cronbach's alpha = 0.50). For each dimension, higher scores indicate a better sense of competence. Overall sum-scores range from 27 to 135.[43,45,46] The validity and usefulness of the SCQ when applied to informal caregivers of older adults with dementia symptoms (i.e., cognitive impairment, pre-diagnostic dementia or dementia in its early stages) has also been studied. The 3 subscales of the SCQ showed good homogeneity and feasibility, but their construct validity was insufficient. Only the subscale 'consequences of involvement in care for the personal life of the caregiver' was found to be partly valid.[44]

Depression

The Center for Epidemiological Studies Depression Scale (CES-D) is a 20-item instrument that assesses the frequency of experienced depressive symptoms within the past week. The items are rated on a 4-point Likert scale from 0 'rarely or none of the time to 3 'most or all of the time'. Scores range from 0 to 60. A score of 16 or over has been clinically associated with a greater risk of depression.[47,48] Test-retest reliability at 3-month intervals over a 12-month period for the CES-D was reported to be 0.49 - 0.54.[47] This instrument has been widely used in dementia research and most of these studies have used the CES-D total score.[49-54] The original 4-factor model of item responses is informative for identifying meaningful clusters of depressive symptoms in dementia caregivers.[55,56]

General health

The General Health Questionnaire (GHQ-12) is a 12-item questionnaire, with sum scores ranging from 0 to 36 (lower scores indicate better health status).[57] It is a widely used self-report instrument, that is assumed to cover a wide range of common psychiatric morbidity, in particular, anxiety and depressive disorders. The GHQ was originally developed as a screening instrument for use in general practice. Several short-form versions (30, 28, 20 and 12 items) of the original 60-item version have been developed. Good psychometric properties have been reported, in particular for the GHQ-12.[58,59]

EuroQol (EQ-5D) is a self-administered questionnaire in which respondents evaluate their health state "today" on the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. A 1-to-3 scale is used for each dimension, representing no problem, some problem, or extreme problem for the subject to engage in the activity alone; for the pain and anxiety items, the three ratings relate to the severity of symptoms. The instrument also has a visual analog scale "thermometer" (VAS), a 20-cm scale anchored at 0 "worse imaginable health state" and 100 "best imaginable health state".[60] The EuroQol has been translated into several languages and has been validated and employed in many studies on general populations and subjects with mild dementia.[61,62]

Data analysis

All data will be analyzed using the Statistical Package for Social Science 20.0 (SPSS 20.0). Descriptive analysis will be used for general patient and caregiver characteristics, disease characteristics and time to death or time to institutionalization. Only data of patients and caregivers with complete follow-up of 18 months will be used for data analysis. Patient and caregiver characteristics of withdrawals (subjects included, but no data received) and losses to follow-up/drop-outs will be described and compared with the patients and caregivers who will complete follow-up. If patients become institutionalized during follow-up, data collection will be continued with the same informant/informal caregiver. Patient and caregiver characteristics, baseline MMSE and baseline NPI total scores will be compared to the

non-institutionalized subjects. If these data are comparable, then they will be used for data analysis.

The frequency (point and cumulative prevalence), cumulative incidence, and persistence of symptoms are expressed as the percentage of patients with scores greater than 3 on any item of the NPI, at study onset and/or at any follow-up evaluations. Point prevalence will be defined as the proportion of patients with specific symptoms at each assessment. The accumulative prevalence will be defined as the proportion of patients developing a specific symptom on at least one assessment over the 18-month study period. The cumulative incidence will be rated as the proportion of patients who are symptom-free at baseline but develop the specific symptom at subsequent assessments. A symptom will be considered as persistent if it was present on at least two subsequent assessments, regardless of time of first manifestation of the symptom. In addition, the proportion of patients with persistence of symptoms during all 3 assessments will be calculated.

Univariate analysis will be performed to identify determinants of NPS in patients with dementia in primary care as dependent variable for each assessment. Univariate analysis will also be performed to identify determinants of caregiver distress as dependent variable. Independent determinants will be multicomponent collaborative care (CONCERN), single component dementia case management, NPS at baseline, cognition and use of health care services (home care: nursing and domestic; use of day care services).

All determinants will then be tested in a multivariate regression analysis to determine their unique contribution to the course of NPS and informal caregiver distress. To take into account the clustering of patients with dementia/informal caregivers in general practices and the repeated measurements within patients' random coefficient analyses will be used.

According to the National Public Health Compass, developed and coordinated at the Dutch National Institute of Public Health and the Environment, absolute prevalence of patients with dementia in registrations of general practices is 20 per general practice per year. Based on their interest in participating 18 practices were selected. With an assumed response rate of 50% and loss to follow-up rate of 30% after 18 months, the expected study population will be 126 patients with dementia. In analysis of causal influences in observational data, as a rule of thumb 1 candidate predictor can be studied for every 10 patients. For logistic regression, this rule can be relaxed to 5 - 9 events per candidate predictor.[63] The assumed prevalence rate of NPS in primary care is 60%.[16,17] The number of independent variables in this study will be 7. Therefore 126 patients with dementia will suffice for the regression analyses.

Proportions (prevalence, incidence, persistence) can be estimated with absolute precision of 10% and a confidence level of 95% taking into account design effect of 1.25 based on an intraclass correlation coefficient (ICC) of 0.05 and a mean cluster size of 6, assuming a conservative estimate of anticipated proportion of 50%.

DISCUSSION

To our knowledge, this study is the first to focus on the course of NPS in patients with dementia and informal caregiver distress in primary care. All selected outcome measures have been proven and validated. The data will be collected by one research assistant. Therefore, measurement inaccuracies will be minimal.

This study has some limitations. Only 19 % of the GPs we invited are willing to participate. This might limit the generalizability of the findings. Data will be collected at baseline, after 9 months and after 18 months. Variations in course between two successive assessments will be unknown. Because this is a naturalistic study, the course of NPS can be influenced by psychosocial and pharmaceutical interventions that we will not specifically assess in this study. Furthermore, we will select patients coded with dementia as classified in the ICPC code P70 and P20. Dementia in these patients is not necessarily defined with international criteria and Dutch consensus guidelines, causing a risk of bias. In the different general practices variability exists in the usage of the classification according to ICPC in the electronic medical files. However, because GPs often wait before diagnosing dementia, we expect that this bias will be small. On the other hand, this may bias the sample towards a more severe spectrum of illness.

The current study will provide more detailed information about consequences of NPS for the quality of life of both patients and informal caregivers as well as the influence of NPS on depressive symptoms and experienced health state of the caregiver, which is clinically important. The data will help GPs and other professionals in planning follow-up visits and in the timing of offering psycho-education, psychosocial interventions and the provision of care. It will enlarge their awareness of NPS in their patients with dementia. An individually tailored approach for patients with dementia and their informal caregivers may offer more and better treatment opportunities.

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CHAPTER 3

The course of neuropsychiatric symptoms in community-dwelling patients with dementia: a systematic review

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ABSTRACT

Background

Neuropsychiatric symptoms (NPS) often occur in patients with dementia. Understanding the course of NPS in dementia is important for health care professionals for psycho-educational purposes and adequate and timely interventions to prevent or diminish NPS as much as possible.

Methods

We conducted a systematic literature search in several electronic databases. We combined search strings for the terms dementia, community-dwelling, cohort studies and NPS. Screening titles and abstracts, assessing the methodological quality and data-extraction were independently conducted by at least two authors.

Results

This literature search revealed 6605 unique records of which 23 studies were included in data synthesis. In total 7184 patients participated in the included studies with a mean number of 312. Sixty percent of the subjects were female and the mean age of all subjects was 74.8 years. Follow-up varied between 1 and 6 years; in 17 studies loss to follow-up was less than 20 % per year. NPS are highly prevalent, incident and persistent although frequency parameters vary considerably across studies. Delusions/delusional misidentification, wandering/agitation, aberrant motor behaviour/motor hyperactivity and apathy are the most common NPS. For hallucinations, delusions/delusional misidentification, paranoia, aggression, wandering/agitation, aberrant motor behaviour/motor hyperactivity, disinhibition, apathy and sleep disturbance increasing trends in point prevalence rates have been found.

Conclusions

NPS in community-dwelling patients are frequent and persistent. The increasing trends of several NPS in the course of dementia require a preventive approach of professional caretakers. For such an approach, a timely diagnosis and adequate professional support to prevent or diminish these problems is necessary.

INTRODUCTION

Dementia is a chronic and progressive disorder with great impact on people with dementia and their family members.[1] Neuropsychiatric symptoms (NPS), also termed behavioural and psychological symptoms of dementia (BPSD), frequently complicate the course of dementia. Examples of NPS are psychosis (delusions and hallucinations), depressive mood, anxiety, irritability/lability, apathy, euphoria, disinhibition, agitation/aggression, aberrant motor activity, sleep disturbance and eating disorder. Studies from various countries reported NPS prevalence rates in community-dwelling people that ranged from 61 to 96 %.[2-5] NPS result in lower quality of life for both the people with dementia and their caregivers and affect the quality of the relationship with the caregivers.[6,7]

Nursing home admission is predicted by NPS, severity of cognitive impairment, Alzheimer's dementia, high rates of functional dependence and depressive symptoms.[8] Major depression is a predictor of early institutionalization in the first year following the dementia diagnosis.[9] The future severity of NPS is predicted by the baseline severity of NPS, stage of dementia and use of support services.[10]

For people with dementia and their informal caregivers, as well as general practitioners and the other professionals involved in long-term care, it is important to understand the course of NPS. If we are able to recognize patients at risk of persistent NPS we can develop individual approaches in the different stages of dementia for both patients with dementia and their professional and informal caregivers. Knowledge on NPS in dementia is important for psycho-educational purposes and timely interventions to prevent or diminish NPS as much as possible. The aim of this systematic review is to study the prevalence and course of NPS in community-dwelling patients with dementia.

METHODS

We performed a systematic review of prospective cohort studies according to the guidelines of the Cochrane Collaboration and the PRISMA-Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).[11,12] Conform the PROGnosis RESearch Strategy (PROGRESS) we aimed for studies that can be classified as fundamental prognosis research.[13] The following steps were described in a predefined research protocol: (1) inclusion criteria; (2) exclusion criteria; (3) search methods for identification of studies; (4) data extraction; (5) assessment of methodological quality; (6) data synthesis.

Inclusion criteria

Types of studies.	This review included prospective cohort studies.
Types of participants.	Patients with dementia.
Setting.	Primary care or community dwelling patients.
Study size.	At least 25 or more patients at baseline.
Follow-up.	Three months or more.
Types of outcome measures.	Neuropsychiatric symptoms.

Exclusion criteria

Types of studies.	Case-studies, case-control studies, clinical trials, cross-sectional studies and trend studies (repeated cross-sectional studies).
Types of participants.	Caregivers, patients with mild cognitive impairment (MCI).
Setting.	Assisted living facilities, chronic care institutions, home of the aged, housing for the elderly, intermediate care facilities, nursing home and residential care.

Search method for identification of studies

On November 27th, 2012, we conducted an electronic search in the databases PubMed, EMBASE, CINAHL, PsycINFO and the Cochrane Library for all studies that were published until that date. We modified a previously used search strategy for residents with dementia in long-term care institutions for this review on patients with dementia in primary care.[14,15] We combined search strings for dementia, primary care, cohort studies and NPS with the Boolean operator AND. An overview of the terms used in the computerized search strategy as performed in PubMed is presented in supplementary table 1. The search strategy was adapted for the other four databases to fit database-specific features. The reference lists of selected articles and previous reviews on the course of NPS in primary care were searched for articles not identified by the initial search. The results of the 5 databases were aggregated and duplicates were deleted. No books or dissertations were included in this review. There were no limitations regarding the language of the publication.

Selection method

Two authors (PB and RBW) independently screened titles and abstracts to identify eligible papers. When there was insufficient information to evaluate the inclusion and exclusion criteria, we retrieved the full text article. We excluded all studies that clearly did not meet all inclusion criteria or that met at least one of the exclusion criteria. Inter-rater agreement about in and exclusion based on titles and abstracts was measured and reported as Cohen's kappa (κ).[16] Subsequently, two authors (PB and RBW) independently reviewed the full publications of the remaining papers. We discussed disagreements in consensus meetings.

All discussions led to consensus about inclusion. When needed we corresponded with co-authors of this paper for further information to clarify study eligibility.

Data extraction and assessment of methodological quality

At least 2 reviewers (PB, RBW and/or PLL) independently extracted the information from the selected publications by using standardized and pre-tested data-extraction forms. The extracted information involved data on study population, diagnostic criteria, inclusion and exclusion criteria, setting, type of prognostic factors, duration of follow-up, outcomes, and data on methodological quality. In a case of disagreement, we reached consensus after discussion with all 3 reviewers.

For assessing the methodological quality of the included studies we used a standardized checklist of predefined criteria (see Table 1), which has been used in previous prognostic reviews [17] and is based on theoretical considerations and methodological aspects described earlier.[18-20] Two authors (PB and RBW) tested the quality assessment checklist in a pilot assessment. Each criterion was scored positive (+, design or conduct adequate), negative (-, design or conduct inadequate), or unclear (?, insufficient information). The total quality score is expressed as the sum of all criteria that are scored positive. The maximum quality score is 21 and we calculated the quality of a study as the percentage of the maximum score. We discussed disagreements in the scoring of quality items in consensus meetings and categorized the quality criteria into four major forms of bias: selection bias, completeness of follow-up, information bias, and confounding. For judging selection bias, quality criteria description of inception cohort, study population, relevant inclusion and exclusion criteria, definition of dementia and NPS, response rate ≥ 75 % and information about non-responders versus responders were used. The quality criteria loss to follow-up < 20 % per year and information about completers versus those lost to follow-up/dropouts were used to judge completeness of follow-up. Furthermore, the quality criteria standardized assessment of symptoms and functional outcome, as well as potential prognostic factors were used to judge information bias; the quality criteria description of possible treatment in cohort and appropriate univariate crude estimates and multivariate analysis techniques were used to judge confounding. Finally, the quality criteria number of subjects in study population ≥ 100 at baseline, follow-up of at least 12 months, prospective data collection, clinically relevant outcome measures, frequencies of most important outcome measures and prognostic factors presented and influence of prognostic factors presented were used to judge descriptive items. We defined studies with a quality score of 60 % or higher as studies with high quality.[17,21]

Table 1. Explanation of the criteria for assessing the methodological quality.

A.	*Description of inception cohort.* Positive if it is described in what setting the participants were recruited (i.e. general population, patients attending the general practitioner, inpatient or outpatient setting).
B.	*Description of study population.* Positive if it is described which participants from the inception cohort are recruited and if age and sex are described.
C.	*Description of relevant inclusion and exclusion criteria.* Positive if it is described how participants were identified with dementia. + = Dementia diagnosed by standardized diagnostic interview and or assessment scales − = Dementia not diagnosed by standardized diagnostic interview (including DSM) or assessment scale ? = Not clear
D.	*Definition of dementia and neuropsychiatric symptoms.* Positive if the definition of dementia and neuropsychiatric symptoms is described.
E.	*Number of subjects in study population ≥ 100.* Positive if the number of subjects with dementia in the study population was at least 100 at baseline.
F.	*Response rate ≥ 75 %.* Positive if response rate is at least 75 %. Response rate: the number of patients in the study population at baseline, divided by the number of subjects in the inception cohort.
G.	*Information about non-responders versus responders.* Positive if demographic or clinical information (such as age and sex) was presented for responders and non-responders, or if there was no selective response, or no nonresponse.
H.	*Follow-up of at least 12 months.* Positive if the follow-up period was at least 12 months.
I.	*Loss to follow-up < 20 % per year.* Positive if mean number of patients with dementia is less than 20 % per year. Loss to follow-up: the number of patients in the study population at baseline minus the number of patients at the main NPS outcome measure for each year, divided by the number of patients in the study population at baseline.
J.	*Information about completers vs. those lost to follow-up/dropouts.* Positive if demographic or clinical information (such as age and gender, disease characteristics, and other potential prognostic predictors) was presented for completers with dementia and those lost to follow-up at the main moment of outcome measurement, or if there was no selective loss to follow-up, or no loss to follow-up.
K.	*Prospective data collection.* Positive if main outcome measures on potential prognostic predictors were collected prospectively.
L.	*Description of possible treatment in cohort.* Positive if treatment subsequent to inclusion in cohort is fully described or standardized. Also positive if no treatment is given. + = treatment/multivariate correction for treatment in analysis, or no treatment given − = different treatment regimens, not clear how outcome is influenced by it ? = not clear if any treatment is given
M.	*Clinically relevant outcome measures.* Positive if at least one clinically relevant outcome measures is presented.

Table 1. Explanation of the criteria for assessing the methodological quality. (continued)

N.	*Standardized assessment of symptom outcome.* Positive if standardized questionnaires or objective outcome measurements of NPS were used for each follow-up measurement.
O.	*Standardized assessment of functional outcome.* Positive if standardized questionnaires or objective outcome measurements were used for each follow-up measurement.
P.	*Standardized assessment of potential prognostic factors.* Positive if standardized questionnaires or objective measurements of potential prognostic factors were used at baseline.
Q.	*Appropriate univariate crude estimates.* Positive if separate univariate (repeated measures) analysis of variance was calculated for each dependent measure.
R.	*Appropriate multivariate analysis techniques.* Positive if multivariate (repeated measures) analysis of variance was calculated for changes among the dependent measures occurring during the follow-up interval.
S.	*Frequencies of most important outcome measures presented.* Positive if frequency, percentage or mean, median (interquartile range), and standard deviation/ confidence intervals are reported of the most important outcome measures
T.	*Frequencies of most important prognostic factors presented.* Positive if: a. frequency of percentage is reported, or b. mean and standard deviation or standard error are reported, or c. median and interquartile range are reported, or d. if the influence of each separate factor is reported
U.	*Influence of prognostic factors presented.* Positive if the influence of each separate prognostic factor on the natural course of NPS is presented.

Data synthesis

The following main study characteristics were extracted from the papers: setting/country, number enrolled in cohort, criteria for diagnosis (dementia and NPS), duration of follow-up (years and range), loss to follow-up (number and %), gender and age (years ± S.D. and range) at baseline, living situation of participants at baseline, number of assessments and presentation of results for number of patients per assessment (PPA) or completers.

Information on the course of NPS is presented in three subgroups according to the factor analysis of Aalten.[22] The three subgroups we present are a psychotic subgroup including hallucinations, delusions, delusional misidentification and paranoia, a hyperactivity subgroup including agitation, aggression, euphoria, disinhibition, irritability and aberrant motor behaviour and finally an affective subgroup including depression, anxiety, apathy, night-time behaviour disturbances and eating abnormalities. Data are presented as point and cumulative prevalence, (cumulative) incidence, persistence and resolution per assessment. Point prevalence is defined as the proportion of patients with specific NPS at each assessment. The

cumulative prevalence is defined as the proportion of patients developing a specific NPS on at least one assessment over the follow-up period including baseline assessment. Incidence is defined as the proportion of patients who develop a specific NPS at one assessment but did not show the symptom on the preceding assessment. The cumulative incidence is defined as the proportion of patients who are symptom free at baseline, but develop a specific NPS at next assessments. A symptom is persistent if it is present on at least two subsequent assessments, regardless of time of first manifestation of the symptom. Resolution is defined as the proportion of patients who showed a specific NPS at one assessment but not at the next assessment and is displayed for each successive assessment.[22] Not statistically tested increasing or decreasing changes are presented as trends. In case of significant changes *p*-values are presented.

RESULTS

Search results and study selection

The process of selecting publications for the review is illustrated in Figure 1. We retrieved a total of 9167 publications from searches of the various electronic databases (PubMed 2370, EMBASE 2428, CINAHL 2899, PsychINFO 1123 and the Cochrane Library 347) and 15 through hand-search of reference lists of other studies. After screening the titles and abstracts, 53 publications seemed eligible according to the inclusion and exclusion criteria. The inter-observer agreement (unweighted κ) for inclusion between the two reviewers (PB, RBW) for screening titles and abstracts was κ = 0.60 (95% CI: 0.43 - 0.76), which is considered 'moderate' agreement.[16] Proportion of agreement was 0.9965 (95% CI: 0.9947 - 0.9977). After assessing the full publications, 23 papers were definitively included in our review.[23-45] Major reasons for excluding publications were retrospective data analysis, studies on samples of informal caregivers and major or unclear part of participants living in institutions.

Study characteristics

The quality score of the 23 studies ranged from 52% to 86% (see Table 2). Twenty of these have a score of 60% or higher. Selection bias was present in all studies. Response rate was given in only two studies and information about responders versus non-responders was given in only one other study. Confounding was present in 19 studies and in 17 studies information bias was present. Follow-up in all studies was at least 12 months. In 17 studies loss to follow-up was less than 20% per year. After close inspection, no direct association was found between setting/country, number enrolled in cohort, criteria for diagnosis, duration of follow-up, loss to follow-up, gender, age, living situation, year of publication and the total quality score.

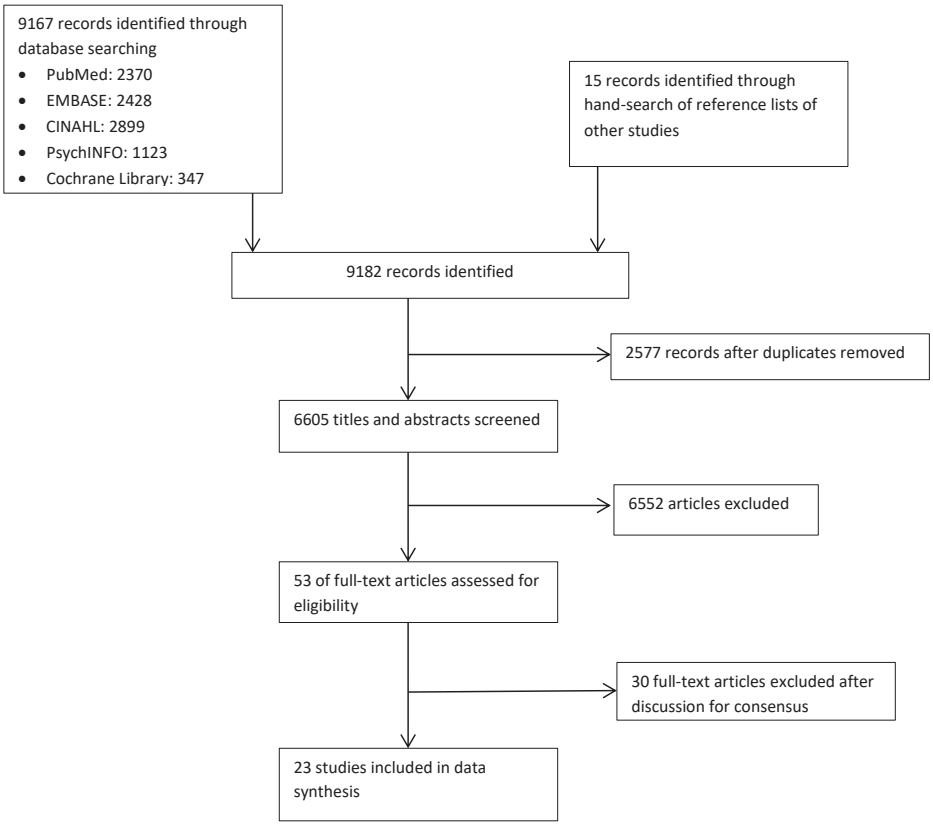

Figure 1. Results of database searches and selection of studies.

Eight studies are performed in the United States of America (USA), five in the United Kingdom, two in Germany and two in France, one study in Japan, one study in Finland and one study in the Netherlands (see Table 3). Two studies are performed in 3 sites (USA, France, Greece) and 1 study is performed in 12 European countries. In total 7184 patients participated in the included studies. The mean number of study participants was 312 and the median number 170 (range 30 - 2288).

Dementia was diagnosed according to several diagnostic criteria and in one of them according to histopathological criteria.[34] NPS were assessed by using 15 different instruments. Five studies used the Columbia Scale for Psychopathology in Alzheimer's disease (CUSPAD) of which three papers described the results of the Predictors study, four used the Neuropsychiatric Inventory (NPI) of which two papers described the results of the Reseau sur la Maladie d'Alzheimer Francais (REAL.FR) study, three studies used the Present Behavioural Examinations (PBE) of which two papers described the results of the same study and two studies used the Diagnostic and Statistical Manual of Mental Disorders

Table 2. Results of the methodological quality assessment of prospective cohort studies on the course of NPS.

	SELECTION BIAS						COMPLETENESS OF FOLLOW-UP		INFORMATION BIAS			CONFOUNDING			DESCRIPTIVE ITEMS							QUALITY SCORE*	SCORE (%)
QUALITY CRITERIA	**A**	**B**	**C**	**D**	**F**	**G**	**I**	**J**	**N**	**O**	**P**	**L**	**Q**	**R**	**E**	**H**	**K**	**M**	**S**	**T**	**U**		
Holtzer, *et al* (2005)[a]	+	+	+	+	?	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	18	86
Devanand, *et al* (1997)[a]	+	+	+	+	?	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	18	86
Kunik, *et al* (2010)	+	+	+	+	-	+	+	-	+	-	+	+	+	-	+	+	+	+	+	+	+	17	81
Holtzer, *et al* (2003)[a]	+	+	+	+	?	-	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	17	81
Ballard, *et al* (2001)	+	+	+	+	?	-	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	17	81
Paulsen, *et al* (2000)	+	+	+	+	?	-	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	17	81
Wilson, *et al* (2000)	+	+	+	+	+	-	+	-	+	-	+	+	+	-	+	+	+	+	+	+	+	17	81
Ballard, *et al* (1997)	+	+	+	+	+	-	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	17	81
Swearer, *et al* (1996)	+	+	+	+	?	-	-	-	+	+	+	+	+	+	-	+	+	+	+	+	+	16	76
Haupt, *et al* (2000)	-	+	+	+	?	-	+	-	+	-	+	+	+	+	-	+	+	+	+	+	+	15	71
Förstl, *et al* (1993)	+	+	+	+	?	-	+	-	+	-	+	-	+	+	-	+	+	+	+	+	+	15	71
Rosen and Zubenko (1991)	+	+	+	+	?	-	+	-	+	-	+	+	+	-	-	+	+	+	+	+	+	15	71
Asada, *et al* (1999)	+	+	+	+	?	-	+	-	+	+	-	-	+	-	+	+	+	+	+	+	-	14	67
Keene and Hope (1998)[c]	+	-	+	+	?	-	+	-	+	-	+	-	+	-	+	+	+	+	+	+	+	14	67
McShane, *et al* (1998)[c]	+	+	+	+	?	-	+	-	+	-	+	-	+	-	+	+	+	+	-	+	+	14	67
Juva, *et al* (1997)	+	+	+	+	-	-	-	+	-	+	+	-	+	-	+	+	+	+	+	+	-	14	67
Gonfrier, *et al* (2012)[d]	+	+	+	+	?	-	+	+	+	+	-	-	-	-	+	+	+	+	+	-	-	13	62
Froehlich, *et al* (2009)	+	+	+	-	?	-	+	+	+	+	-	+	-	-	+	+	+	+	+	-	-	13	62
Zhu, et al (2006[b]	+	+	+	+	?	-	-	+	+	+	-	+	-	-	+	+	+	+	+	-	-	13	62
McShane, *et al* (1995)	-	+	+	+	-	-	+	-	+	-	+	+	+	-	-	+	+	+	+	-	+	13	62
Li, *et al* (2001)	+	+	+	+	?	-	+	+	+	-	-	-	-	-	+	+	+	+	+	-	-	12	57
Aalten, *et al* (2005)	+	+	+	+	?	-	-	+	+	-	-	-	-	-	+	+	+	+	+	-	-	11	52
Cortes, *et al* (2005) [d]	+	-	+	+	?	-	-	+	+	+	-	-	-	-	+	+	+	+	+	-	-	11	52

+: positive (design or conduct adequate); -: negative (design or conduct inadequate); ?: unclear (insufficient information).

* Total '+', [a] Predictors, [b] Predictors 2, [c] Keene/McShane, [d] REAL.FR.

(DSM) criteria for delusions and hallucinations. The Cohen Mansfield Agitation Inventory (CMAI), Cornell Scale for Depression in Dementia (CSDD), DSM criteria for depression, DSM criteria for psychosis, Burns' Symptom checklist, Caretaker Obstreperous - Behavior Rating Assessment (COBRA) scale, Behavioural Abnormalities in Alzheimer's Disease (BEHAVE-AD), Troublesome Behavior Scale (TBS) and Hamilton Depression Rating Scale (HADRS) were each used in one study. One study used a semi-standardized carers' interview and one study used a structured clinical interview.

Follow-up varied between 1 and 6 years with a mean of 3 years and median of 3.5 years. Twenty-two studies reported data on loss to follow-up: a total of 3024 patients (44%) were lost to follow-up with a mean of 38% (range 0 - 85,3%)

Nineteen studies reported data on gender. In these 19 studies 2256 of the participants were male (40%) with a mean of 119 per study and median 75 (range 13 - 857) and 3376 of the participants were female (60%) with a mean of 178 per study and median 102 (range 10 - 1431). In the 20 studies reporting data on age the mean age was 74.8 years (range 68.8 - 79.9). Two of these studies reported data on age per diagnosis. In one study for dementia with Lewy bodies (LBD) 76.5 ± 7.9 years and for Alzheimer's disease (AD) 81.1 ± 6.6 years. In the other study for AD 76.5 ± 7.1 years and for vascular dementia (VaD) 71.4 ± 8.1 years.

Three studies reported an outpatient setting, but did not give specific information on the living situation of the subjects at baseline.[23,32,43] Two studies reported that a small part of the subjects were not living at home. One study reported that 91.1% of the subjects lived at home, 6.8% in nursing home, 1.3% in retirement home, 0.9% other living situations.[24] The other study reported that 5.9% of the subjects were recruited from a long-term care facility.[26]

After close inspection, no direct association was found between total quality score and the frequency parameters of the studies.

Course of NPS in patient with dementia in primary care

In 22 studies 2 - 12 assessments were conducted (see Table 4). In one study the number of assessments was not given.[25] Twelve studies presented data of PPA, ten studies presented data of completers and for one study this was not clear. In one study the results were presented in figures per stage of dementia using the Clinical Dementia Rating scale (CDR) and not in numbers.[35] This study concluded that the patterns of NPS change depended on the baseline severity of AD. The NPS frequencies peaked in the middle stage (CDR 2) and followed a downward trend thereafter. Two studies reported on the psychotic, hyperactivity and affective subgroup as a whole, as well as on individual symptoms.[39,44] The study of Aalten *et al.* reported point and cumulative prevalence rates, (cumulative) incidence and persistence rates on all individual NPI symptoms as well as on the subgroups (see Table 4).

Table 3. Summary of main study characteristics.

FIRST AUTHOR	STUDY QUALITY (%)	SETTING/ COUNTRY	NUMBER ENROLLED IN COHORT	CRITERIA FOR DIAGNOSIS		DURATION OF FOLLOW-UP [YEARS (RANGE)]	LOSS TO FOLLOW-UP [*N*, (%)]	GENDER (M/F) AND AGE (YEARS ± S.D.; RANGE) AT BASELINE	LIVING SITUATION OF PARTICIPANTS AT BASELINE
				DEMENTIA	NPS				
Holtzer, *et al* (2005)[a]	86	Outpatient/USA (3 sites), France, Greece	536	DSM-III-R, NINCDS-ADRDA	CUSPAD	5.0	406 (75.7)	220/316; 74.0 ± 8.7	Not given
Devanand, *et al* (1997)[a]	86	Outpatient/USA (3 sites)	235	DSM-III-R, NINCDS-ADRDA	CUSPAD	3.0 ± 2.5	98 (41.7)	96/139; 73.1 ± 8.9	91.1% lived at home, 6.8% in nursing home, 1.3% in retirement home, 0.9% other living situations
Kunik, *et al* (2010)	81	Outpatient/USA	215	ICD-9-CM	CMAI	2.0	16 (7.4)	205/10; 76 ± 6.2	Community-dwelling, no nursing home
Holtzer, *et al* (2003)[a]	81	Outpatient/USA (3 sites)	236	DSM-III-R, NINCDS-ADRDA	CUSPAD	5.0	134 (56.8)	97/139; 72.7 ± 9.2	14 (5.9%) were recruited from a long-term care facility
Ballard, *et al* (2001)	81	Outpatient/UK	244	CAMCOG	CUSPAD, CSDD, DSM-II-R depression	1.0	20 (8.2)	LBD: 36/46; AD: 39/93 LBD: 76.5 ± 7.9; AD 81.1 ± 6.6	Consecutive referrals of psychiatric services
Paulsen, *et al* (2000)	81	Outpatient/USA	329	DSM-III, NINCDS-ADRDA	DSM-III Psychosis	5.0	Not given	Never psychotic (n = 194) 26/168; 72.4 ± 6.9; Psychotic at baseline (n = 75) 41/34; 73.4 ± 7.7; Psychotic at follow-up visit (n = 60) 31/29; 72.1 ± 6.4	Ambulatory patients

Table 3. Summary of main study characteristics. (continued)

FIRST AUTHOR	STUDY QUALITY (%)	SETTING/ COUNTRY	NUMBER ENROLLED IN COHORT	CRITERIA FOR DIAGNOSIS		DURATION OF FOLLOW-UP [YEARS (RANGE)]	LOSS TO FOLLOW-UP [*N*, (%)]	GENDER (M/F) AND AGE (YEARS ± S.D.; RANGE) AT BASELINE	LIVING SITUATION OF PARTICIPANTS AT BASELINE
				DEMENTIA	NPS				
Wilson, *et al* (2000)	81	Outpatient/USA	410	NINCDS-ADRDA	DSM-III-R subtypes of delusions	4.0	141 (34.4)	136/274; 75.5 ± 7.3 (45 - 95)	Community residence
Ballard, *et al* (1997)	81	Outpatient/UK	124	DSM-III-R, NINCDS-ADRDA	Burns's Symptom Checklist	1.0	37 (29.8)	38/102; 79.9	Consecutive referrals to old-age psychiatry services
Swearer, *et al* (1996)	76	Outpatient/USA	30	NINCDS-ADRDA	COBRA Scale	17.83 ± 9.9 months (range 0.5 - 3)	16 (53.3)	13/17; 72.7 ± 6.5	Community-dwelling
Haupt, *et al* (2000)	71	Outpatient/ Germany	90	NINCDS-ADRDA	BEHAVE-AD	2.0	30 (33.3)	Not given	Not given
Förstl, *et al* (1993)	71	Psychiatric University hospital/ Germany	50	NINCDS-ADRDA	semi-standardized carers' interview	2.0	7 (14.0)	20/30; 68.8 (49 - 92)	Living in the community independently or with their families
Rosen and Zubenko (1991)	71	Outpatient/USA	32	Histopathological criteria for Alzheimer's disease	DSM-III Delusions and hallucinations	6.0	0 (0)	17/15; 70.3 ± 7.9	Ambulatory patients, living in the community
Asada, *et al* (1999)	67	Outpatient/ voluntary/service providers/Japan	103	NINCDS-ADRDA	TBS	5.0	76 (73.8)	36/67; 79.4 ± 8.7	Living in a private residence with responsible caregivers
Keene and Hope (1998)[c]	67	Outpatient/UK	104	CAMDEX, NINCDS-ADRDA	PBE	1.0	5 (4.8)	Not given	Patients living at home

Table 3. Summary of main study characteristics. (continued)

FIRST AUTHOR	STUDY QUALITY (%)	SETTING/ COUNTRY	NUMBER ENROLLED IN COHORT	CRITERIA FOR DIAGNOSIS		DURATION OF FOLLOW-UP [YEARS (RANGE)]	LOSS TO FOLLOW-UP [*N*, (%)]	GENDER (M/F) AND AGE (YEARS ± S.D.; RANGE) AT BASELINE	LIVING SITUATION OF PARTICIPANTS AT BASELINE
				DEMENTIA	NPS				
McShane, *et al* (1998)[c]	67	Outpatient/UK	104	DSM-III-R, CERAD	PBE	4.0	18 (17.3)	43/43; 77 (IQR 8)	Patients living at home
Juva, *et al* (1997)	67	Outpatient/ Finland	100	DSM-III	structured clinical interview	1.0	9 (9.0)	48/52; 69.7 (48.3 - 89.0)	Living at home at first interview
Gonfrier, *et al* (2012)[d]	62	Outpatient/ France (multicentre; 16 sites)	686	DSM-IV, NINCDS-ADRDA	NPI	4.0	535 (78.0)	4-year follow-up (n = 151) 40/111; 76.1 ± 6.4 Others (n = 479) 150/329; 78.4 ± 6.8	Home with spouse 403 (58.7%), home alone 183 (26.7%), home with family 80 (11.7%), group home/other 20 (2.9%)
Froehlich, *et al* (2009)	62	Outpatient/ 12 European countries	2288	DSM-IV	NPI	2.0	906 (39.6)	857/1431; 77.0 (30 - 100)	Living in an ordinary household at baseline, non-institutionalised
Zhu, *et al* (2006)[b]	62	Outpatient/USA (3 sites)	170	DSM-III-R, NINCDS-ADRDA	CUSPAD	4.0 (median 2.5; maximum 6.0]	145 (85.3)	76/94; 75.0 ± 7.6	Patients living at home, not in institutions
McShane, *et al* (1995)	62	Not given/UK	98	DSM-III-R, CERAD	PBE	5.0	57 (58.2)	Not given	All patients were initially living at home with carers
Li, *et al* (2001)	57	Outpatient/USA	108	DSM-III-R	HDRS	3.5 (range 0.8 - 7.8)	74 (68.5)	AD 34/37; 76.5 ± 7.1 VaD 24/13; 71.4 ± 8.1	Not given

Table 3. Summary of main study characteristics. (continued)

FIRST AUTHOR	STUDY QUALITY (%)	SETTING/ COUNTRY	NUMBER ENROLLED IN COHORT	CRITERIA FOR DIAGNOSIS		DURATION OF FOLLOW-UP [YEARS (RANGE)]	LOSS TO FOLLOW-UP [*N*, (%)]	GENDER (M/F) AND AGE (YEARS ± S.D.; RANGE) AT BASELINE	LIVING SITUATION OF PARTICIPANTS AT BASELINE
				DEMENTIA	NPS				
Aalten, *et al* (2005)	52	Outpatient/the Netherlands (2 sites)	199	DSM-IV, NINCDS-ADRDA, NINCDS-AIREN	NPI	2.0	99 (49.7)	83/116; 76.4 ± 8.0 (53 - 96)	Ambulatory patients of psychiatric-based clinics
Cortes, *et al* (2005)[d]	52	Outpatient/ France (multicentre; 16 sites)	693	DSM-IV, NINCDS-ADRDA	NPI	4.0	195 (28.1) After 1 year	Gender not given No discontinuation (n = 544): 77.2 ± 6.9 Discontinuation (n = 121): 79.4 ± 6.9	28% alone at home, 69.4% with a caregiver at home. At 1 year 5% (n = 25) had entered an institution

AD: Alzheimer's disease; BEHAVE-AD: Behavioural Abnormalities in Alzheimer's Disease Rating Scale; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CMAI: Cohen-Mansfield Agitation Inventory; COBRA: Caretaker Obstreperous Behavior Rating Assessment Scale; CSDD: Cornell Scale for Depression in Dementia; CUSPAD: Columbia Scale for Psychopathology in Alzheimer's Disease; DSM: Diagnostic and Statistical Manual of Mental Disorders; HDRS: Hamilton Depression Rating Scale; IQR: Interquartile range; LBD: Dementia with Lewy bodies; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association; NPI: Neuropsychiatric Inventory; PBE: Present Behavioural Examination; TBS: Troublesome Behavior Scale; VaD: Vascular dementia.

[a] Predictors.

[b] Predictors 2.

[c] Keene/McShane.

[d] REAL.FR.

Table 4. Course of NPS

FIRST AUTHOR	STUDY QUALITY (%)	OUTCOME MEASURES (N, Y, N ASM)) COMPLETERS VERSUS PATIENTS PER ASM	PSYCHOTIC SUBGROUP (HALLUCINATIONS, DELUSIONS, DELUSIONAL MISIDENTIFICATION, PARANOIA)	HYPERACTIVITY SUBGROUP (AGITATION, AGGRESSION, EUPHORIA, DISINHIBITION, IRRITABILITY, ABERRANT MOTOR BEHAVIOUR)	AFFECTIVE SUBGROUP (DEPRESSION, ANXIETY, APATHY, NIGHT-TIME BEHAVIOUR DISTURBANCES, EATING ABNORMALITIES)	ANY SYMPTOM
Holtzer, *et al.* (2005)[a]	86	CUSPAD (5y fu, 6 asm) Patients per asm			Depression PP: 40 - 42 - 41 - 39 - 28 - 24% ↓ Completers PP: 39 - 43 - 42 - 40 - 30 - 29% ↓	
Devanand, *et al.* (1997)[a]	86	CUSPAD (3y fu, 7 asm) Patients per asm	Hallucinations PP: 8 - 8 - 12 - 17 - 11 - 20 - 12% Delusions (any type) (<.05) PP: 24 - 28 - 32 - 33 - 33 - 35 - 31% ↑	Behaviour disturbance (<0.001) PP: 52 - 52 - 62 - 61 - 67 - 71 - 66% ↑ Wandering or agitation (<0.001) PP: 39 - 40 - 47 - 51 - 52 - 62 - 57% ↑ Physical aggression (<0.001) PP: 6 - 9 - 10 - 11 - 20 - 21 - 19% ↑	Depressed mood PP: 25 - 20 - 27 - 23 - 22 - 20 - 23%	PP: 64% at baseline 8.5% remained free of all NPS CP: 91.5% CI: 27%
Kunik, *et al.* (2010)	81	CMAI (2y fu) Patients per asm		Aggression CP: 41%		
Holtzer, *et al.* (2003)[a]	81	CUSPAD (5y fu, 6 asm) Patients per asm	Hallucinations PP: 8 - 16 - 16 - 17 - 11 - 13% Delusions PP: 40 - 48 - 49 - 45 - 37 - 34% Similar prevalences and changes over time in completers	Wandering or agitation: PP: 39 - 49 - 52 - 57 - 54 - 46% ↑ Physical aggression PP: 6 - 11 - 17 - 18 - 22 - 21% ↑ Similar prevalences and changes over time in completers		
Ballard, *et al.* (2001)	81	CUSPAD, CSDD, DSM-II-R depression (1y fu, 2 asm) Completers	Visual hallucinations IN: 16%; 30% (LBD), 13% (AD) PE: 64%; 77% (LBD), 26% (AD) Auditory hallucinations IN: 13%; 28% (LBD), 7% (AD) PE: 42%; 41% (LBD), 45% (AD) Delusions IN: 25%; 30% (LBD), 24% (AD) PE: 42%; 40% (LBD), 44% (AD) Delusional misidentification IN: 16%; 30% (LBD), 12% (AD) PE: 25%; 30% (LBD), 18% (AD)		Depression IN: 8%; 12% (LBD), 6% (AD) PE: 35%; 38% (LBD), 31% (AD)	

Table 4. Course of NPS (continued)

FIRST AUTHOR	STUDY QUALITY (%)	OUTCOME MEASURES (N, Y, N ASM)) COMPLETERS VERSUS PATIENTS PER ASM	PSYCHOTIC SUBGROUP (HALLUCINATIONS, DELUSIONS, DELUSIONAL MISIDENTIFICATION, PARANOIA)	HYPERACTIVITY SUBGROUP (AGITATION, AGGRESSION, EUPHORIA, DISINHIBITION, IRRITABILITY, ABERRANT MOTOR BEHAVIOUR)	AFFECTIVE SUBGROUP (DEPRESSION, ANXIETY, APATHY, NIGHT-TIME BEHAVIOUR DISTURBANCES, EATING ABNORMALITIES)	ANY SYMPTOM
Paulsen, *et al.* (2000)	81	DSM-III Psychosis (5y fu, 6 asm) Patients per asm	Hallucinations or delusions CI: 20 - 36 - 50 - 51% (1 - 4y) ↑			
Wilson, *et al.* (2000)	81	DSM-III-R subtypes of delusions (4y fu, 5 asm) Patients per asm	Hallucinations PP: 41 - 40 - 43 - 34 - 31% CP: 70% Delusions PP: 55 - 48 - 46 - 34 - 30% ↓ CP: 80%			
Ballard, *et al.* (1997)	81	Burns's Symptom Checklist (1y fu, 2 asm) Completers	Hallucinations IN: 20% RE: 61% Delusions IN: 30% RE: 73% Delusional misidentification: IN: 17% RE: 65%			IN: 47% PE: 28% RE: 53%

Table 4. Course of NPS (continued)

FIRST AUTHOR	STUDY QUALITY (%)	OUTCOME MEASURES (N, Y, N ASM)) COMPLETERS VERSUS PATIENTS PER ASM	PSYCHOTIC SUBGROUP (HALLUCINATIONS, DELUSIONS, DELUSIONAL MISIDENTIFICATION, PARANOIA)	HYPERACTIVITY SUBGROUP (AGITATION, AGGRESSION, EUPHORIA, DISINHIBITION, IRRITABILITY, ABERRANT MOTOR BEHAVIOUR)	AFFECTIVE SUBGROUP (DEPRESSION, ANXIETY, APATHY, NIGHT-TIME BEHAVIOUR DISTURBANCES, EATING ABNORMALITIES)	ANY SYMPTOM
Swearer, *et al.* (1996)	81	COBRA Scale (mean 1.5y fu, 4 asm) Patients per asm	Hallucinations PP: 13 - 10 - 21 - 31% PP: 0 - 7 - 0 - 0% (severe) Delusions PP: 23 - 33 - 42 - 61%↑ PP: 7 - 10 - 5 - 15% (severe) Paranoia PP: 20 - 27 - 37 - 46%↑ PP: 13 - 3 - 9 - 8% (severe) Disordered ideation CP: 70%	Aggressive/assaultive PP: 17 - 7 - 26 - 23% PP: 13 - 7 - 9 - 8% (severe) CP: 40% Mechanical and motor abnormalities PP: 10 - 10 - 47 - 61%↑ PP: 7 - 3 - 16 - 0% (severe) CP: 50%		CP: 83%
Haupt, *et al.* (2000)	76	BEHAVE-AD (2y fu, 3 asm) Completers	Hallucinations CP: 35% PE: 0% RE: 27% Delusions CP: 53% PE: 0% RE: 57%	Agitation CP: 100% PE: 67% RE: 2% Aggressiveness CP: 74% PE: 22% RE: 25%	Depressiveness CP: 78% PE: 33% RE: 15% Anxiety CP: 66% PE: 12% RE: 38%	
Förstl, *et al.* (1993)	76	semi-standardized carers' interview (2y fu, 2 asm) Patients per asm	Hallucinations CP: 34% Delusions CP: 46% Tended to be persistent and nonelaborate Delusional misidentification CP: 34%			CP: 62%

Table 4. Course of NPS (continued)

FIRST AUTHOR	STUDY QUALITY (%)	OUTCOME MEASURES (N, Y, N ASM)) COMPLETERS VERSUS PATIENTS PER ASM	PSYCHOTIC SUBGROUP (HALLUCINATIONS, DELUSIONS, DELUSIONAL MISIDENTIFICATION, PARANOIA)	HYPERACTIVITY SUBGROUP (AGITATION, AGGRESSION, EUPHORIA, DISINHIBITION, IRRITABILITY, ABERRANT MOTOR BEHAVIOUR)	AFFECTIVE SUBGROUP (DEPRESSION, ANXIETY, APATHY, NIGHT-TIME BEHAVIOUR DISTURBANCES, EATING ABNORMALITIES)	ANY SYMPTOM
Rosen and Zubenko (1991)	76	DSM-III Delusions and hallucinations (6y fu, 7 asm) Completers	Hallucinations and delusions CP: 47% PE: 87% RE: 13%		Depression CP: 22%	
Asada, *et al.* (1999)	67	TBS per CDR stage (5y fu, 6 asm) Completers	Overall, the patterns of change in each of the three factors for each CDR stage group were similar; data given in graphics not in numbers			
Keene and Hope (1998)[c]	67	PBE (>1y fu, 4 monthly asm) Patients per asm			Hyperphagia: CP: 26% Eating change: Hyperphagia CP: 23% Hypophagia CP: 66% Duration: Hyperphagia 16 months Hypophagia: 16 months	
McShane, *et al.* (1998)[c]	67	PBE (4y fu, 4 monthly asm) Completers		Physical aggression: IN: 36% Motor hyperactivity: IN: 20%		
Juva, *et al.* (1997)	67	Not specified (1y fu, 2 asm) Completers				PP: 22 - 11%

Table 4. Course of NPS (continued)

FIRST AUTHOR	STUDY QUALITY (%)	OUTCOME MEASURES (N, Y, N ASM)) COMPLETERS VERSUS PATIENTS PER ASM	PSYCHOTIC SUBGROUP (HALLUCINATIONS, DELUSIONS, DELUSIONAL MISIDENTIFICATION, PARANOIA)	HYPERACTIVITY SUBGROUP (AGITATION, AGGRESSION, EUPHORIA, DISINHIBITION, IRRITABILITY, ABERRANT MOTOR BEHAVIOUR)		AFFECTIVE SUBGROUP (DEPRESSION, ANXIETY, APATHY, NIGHT-TIME BEHAVIOUR DISTURBANCES, EATING ABNORMALITIES)	ANY SYMPTOM
Gonfrier, *et al.* (2012)[d]	62	NPI (4y fu, 5 asm) Completers	Psychotic subgroup PP: 20 - 13 - 16 - 15 - 21% Hallucinations PP: 2 - 4.6%↑	Hyperactivity subgroup PP: 34 - 45 - 48 - 48 - 54% Agitation PP: 18 - 29%↑ Disinhibition PP: 3 - 15%↑ Aberrant motor behaviour PP: 14 - 29%↑		Affective subgroup PP: 23 - 24 - 25 - 23 - 26% Apathy subgroup:↑ PP: 49 - 56 - 51 - 60 - 65% Apathy PP: 43 - 63%↑	CP: 66 - 88% (<.0012)
Froehlich, *et al.* (2009)	62	NPI (2y fu, 5 asm) Patients per asm					NPI scores 9 - 10 - 10 - 10 - 12%
Zhu, *et al.* (2006)[b]	62	CUSPAD (mean 2.5y fu, semiannually asm) Patients per asm	Psychotic symptoms PP: 31 - 34 - 37 - 49 - 36%↑			Depressive symptoms PP: 19 - 26 - 17 - 10 - 20% CP: 20%	Behavioural problems PP: 42 - 49 - 62 - 54 - 56% CP: 49%
McShane, *et al.* (1995)	62	PBE (5y fu, median 8 times over mean of 2.7y) Completers	Hallucinations CP: 32%				
Li, *et al.* (2001)	57	HDRS (mean 3.5y fu, > 3 asm) Not given		AD MS: 6.2 - 4.9 CI: 15% PE: 27% RE: 67% FL: 7%	VaD MS: 6.1 - 7.1 CI: 27% PE: 67% RE: 22% FL: 11%		

Table 4. Course of NPS (continued)

FIRST AUTHOR	STUDY QUALITY (%)	OUTCOME MEASURES (N, Y, N ASM)) COMPLETERS VERSUS PATIENTS PER ASM	PSYCHOTIC SUBGROUP (HALLUCINATIONS, DELUSIONS, DELUSIONAL MISIDENTIFICATION, PARANOIA)	HYPERACTIVITY SUBGROUP (AGITATION, AGGRESSION, EUPHORIA, DISINHIBITION, IRRITABILITY, ABERRANT MOTOR BEHAVIOUR)	AFFECTIVE SUBGROUP (DEPRESSION, ANXIETY, APATHY, NIGHT-TIME BEHAVIOUR DISTURBANCES, EATING ABNORMALITIES)	ANY SYMPTOM
Aalten, *et al.* (2005)	52	NPI (2y fu, 5 asm) Patients per asm	Psychotic subgroup PP: 25 - 24 - 32 - 34 - 23% CP: 53% CI: 37% PE: 12 - 6 - 3 - 6% (2,3,4 times)	Hyperactivity subgroup PP: 46 - 59 - 65 - 64 - 64%↑ CP: 80% CI: 64% PE: 16 - 16 - 20 - 16% (2,3,4 times)	Affective subgroup PP: 67 - 68 - 80 - 71 - 75% CP: 86% CI: 57% PE: 8 - 24 - 10 - 37% (2,3,4 times) Anxiety: PP: 21 - 18 - 24 - 18 - 18% CP: 43% CI: 28% PE: 17 - 3 - 2 - 1%↓ (2,3,4 times)	NPI total PP: 81 - 86 - 90 - 87 - 89% CP: 95% CI: 74% PE: 8 - 11 - 9 - 65% (2,3,4 times)
Cortes, *et al.* (2005)[d]	52	NPI (1y fu, 2 asm) Completers		Aberrant motor activity↑	Depression: ↓ Anxiety: ↓ Apathy: Sleep disturbances:↑	NPI score: 14.45 - 16.30 Stable: 10% Worsening: 51% Improvement: 38% NPI problems: 2.96 - 3.08

asm: Assessments; AD: Alzheimer's disease; BEHAVE-AD: Behavioural Abnormalities in Alzheimer's Disease Rating Scale; CERAD: Consortium to Establish a Registry for Alzheimer's Disease;

CI: Cumulative incidence; CMAI: Cohen-Mansfield Agitation Inventory; COBRA: Caretaker Obstreperous Behavior Rating Assessment Scale; CP: Cumulative prevalence; CSDD: Cornell Scale for Depression in Dementia; CUSPAD: Columbia Scale for Psychopathology in Alzheimer's Disease; FL: Fluctuating; fu: follow-up; HDRS: Hamilton Depression Rating Scale; IN: Incidence; LBD: Dementia with Lewy bodies; MS: Mean scores; NPI: Neuropsychiatric Inventory; NPS: Neuropsychiatric symptoms; PBE: Present Behavioural Examination; PE: Persistence; PP: Point prevalence; RE: Resolution;

TBS: Troublesome Behavior Scale; VaD: Vascular dementia; y: year(s).

[a] Predictors, [b] Predictors 2, [c] Keene/McShane, [d] REAL.FR

Any symptom

Ten studies reported on NPI total scores or on NPS in general without symptom specification of which seven studies reported on PPA and three studies on completers.[24,30,31,33,38-41,44,45] The point prevalence rates ranged between 11% and 90% (PPA 11% - 88% and completers 42% - 90%) and cumulative prevalence rates ranged between 49% and 95% (PPA 49% - 95% and completers 66% - 88%). Incidence rate was 47% (PPA), cumulative incidence rates ranged between 27% to 74% (PPA), persistence rates ranged between 8% to 65% (PPA) and resolution rate was 53% (PPA). Two studies presented NPI scores per assessment and not frequency parameters and these increased during follow-up (one PPA and one completers).[40,45] One of these 2 studies (on completers) reported that NPI scores were stable in 10%, worsened in 51% and improved in 38% of the subjects.[45]

Psychotic subgroup

In the two studies (one on PPA and one on completers) that reported on the psychotic subgroup as a whole the point prevalence rates ranged between 13% and 34% (PPA 23% - 34% and completers 13% - 21%). Cumulative prevalence rate and cumulative incidence rate were 53% and 37%, respectively (PPA) and persistence rates ranged between 3% and 12% (PPA). Point prevalence rates on psychotic symptoms (not specified) presented in one study ranged between 31% and 49% (PPA).[41]

Hallucination point prevalence rates ranged between 0% (severe symptoms) to 43% (PPA) and cumulative prevalence rates ranged between 32% and 70% (PPA 34% - 70% and completers 32% - 47%). In one study there was a trend of an increasing rate of hallucinations during follow-up (completers).[39] One study reported an incidence rate of 20% (completers)[30] and another study (completers) reported incidence rates separately for visual hallucinations 16% (LBD 30% and AD 13%) and for auditory hallucinations 13% (LBD 28% and AD 7%). Persistence rate ranged between 0% and 64% (completers). One study (completers) reported persistence rates separately for visual hallucinations 64% (LBD 77% and AD 26%) and for auditory hallucinations 42% (LBD 41% and AD 45%).[27] Resolution rates ranged between 27% and 61% (completers).

Delusion/delusional misidentification point prevalence rates ranged between 5% (severe symptoms) and 61% (PPA). In two studies (PPA) there was a trend that delusions/delusional misidentification increased during follow-up[25,31], but in 1 study (PPA) there was a trend that these symptoms decreased.[29] Cumulative prevalence rates ranged between 34% to 80% (one study completers 53%). One study (completers) reported an incidence rate of 30% for delusions and 17% for delusional misidentification[30] and another study (completers) reported incidence rates for delusions 25% (LBD 30% and AD 24%) and for delusional misidentification 16% (LBD 30% and AD 12%).[27] Cumulative incidence rate was 34% (PPA). Persistence rate was 0% for delusions in one study[32] and in another study 42% (LBD 40% and AD 44%) for delusions and 25% (LBD 30% and AD 18%) for delusional misidentifica-

tion.[27] One study reported a resolution rate of 57%[32] and another study 73% for delusions and 65% for delusional misidentification (all completers).[30]

For hallucinations and/or delusions together (PPA) cumulative prevalence rate was 47%, persistence rate was 87% and resolution rate was 13%.[28,34] Increasing cumulative incidence rates ranged between 20% and 51% (PPA).[28]

On paranoia (PPA) increasing point prevalence rates were reported and ranged between 20% and 46%.[31] For severe symptoms there was no trend and point prevalence rates ranged between 3% to 13%.[31]

Hyperactivity subgroup

In the two studies that reported on the hyperactivity subgroup as a whole the point prevalence rates ranged between 34% and 65% (PPA 46% - 65%, completers 34% - 54%) and in both studies, there was a trend that hyperactivity increased during follow-up.

(Physical) aggression point prevalence rates ranged between 6% and 26% (all three studies PPA).[25,26,31] In two studies there was a trend that (physical) aggression increased during follow-up.[25,26] Cumulative prevalence rates ranged between 40% and 74% (PPA 40% and 41% and completers 74%) and incidence rate was 36% (completers), persistence rate was 22% (completers) and resolution rate was 25% (completers).

Wandering or agitation point prevalence rates ranged between 18% and 62%. In all three studies (PPA) there was a trend that wandering or agitation increased during follow-up.[25,26,39] Cumulative prevalence rates ranged between 40 and 100%, persistence rate was 0% - 67% and resolution rate 2%.

On mechanical and motor abnormalities/motor hyperactivity two studies reported increasing point prevalence rates that ranged between 10% and 61% (PPA 10% - 61% and completers 14% - 29%).[31,39] For severe symptoms (PPA) there was no trend and these point prevalence rates ranged between 0% and 16%. Cumulative prevalence rate was 50% (PPA) and incidence rate was 20% (completers). One study (completers) reported an increase in aberrant motor activity during follow-up.[45]

Affective subgroup

In the two studies that reported on the affective subgroup as a whole the point prevalence rates ranged between 23% and 80% (PPA 67% - 80% and completers 23% - 26%). Cumulative prevalence rate was 86%, incidence rate was 57% and persistence rates ranged between 5% to 37% (all for PPA).

Depression point prevalence ranged between 10% and 42% (PPA 10% - 42% and completers 29% - 43%) and two studies (one PPA and one completers) reported a decrease in prevalence of depression during follow-up.[23,45] Cumulative prevalence rates ranged between 20% and 78% (PPA 20% and completers 22% - 78%) and incidence was 8% (12% LBD and 6% AD) (completers). Persistence rates ranged between 33% and 35% (38% LBD and 31%

AD) (completers) and resolution rate was reported in one study (completers) and was 15%.[32] One study (PPA or completers not given) reported cumulative incidence, persistence, resolution and fluctuating rates separately for AD and VaD.[43] For AD these rates were 15%, 27%, 67% and 7%, respectively. For VaD these rates were 27%, 67%, 22% and 11%, respectively.

Anxiety point prevalence rate ranged between 18% and 24% (PPA) and one study (completers) reported a decreasing number of affected patients with anxiety during follow-up.[45] Cumulative prevalence rates ranged between 43% (PPA) to 66% (completers) and cumulative incidence rate was 28% (PPA). One study (completers) reported a persistence rate of 12%[32] and another study presented a decreasing trend in persistence rates that ranged from 22% to 1% (PPA).[44] Resolution rate was reported in only one study (completers) and was 38%.[32]

Apathy point prevalence rates with increasing trend were reported in one study (PPA) and ranged from 43% to 63%.[39] In another study (completers) also an increasing number of affected patients with apathy during follow-up was reported.[45]

Hyperphagia, eating change in hyperphagia and eating change in hypophagia cumulative prevalence rates were reported in one study (PPA).[36] These rates were 26% for hyperphagia, 23% for eating change in hyperphagia and 66% for eating change in hypophagia.

One study (PPA) reported point prevalence rates on sleeping disturbance 9% - 18%, cumulative prevalence 34%, cumulative incidence 31% and persistence 1% - 20%.[44] One study (completers) reported on sleep disturbances and an increasing number of affected patients with sleep disturbances during follow-up was reported.[45]

DISCUSSION

We found 23 prospective cohort studies with 7184 community-dwelling patients with dementia. NPS in general are highly prevalent, incident and persistent although frequency parameters vary considerably across studies. Results presented for PPA compared to completers are diverse but not conclusive. Virtually all patients with dementia show any NPS during a period of 1 - 6 years. The overall quality of the studies was rather good (20 of 23 studies have a score of 60% or higher) although selection bias was present in all studies and confounding and information bias in the majority (19 of 23) of the studies.

Delusions/delusional misidentification, wandering/agitation, aberrant motor behaviour/motor hyperactivity, and apathy are the most common NPS. For hallucinations, delusions/delusional misidentification, paranoia, aggression, wandering/agitation, aberrant motor behaviour/motor hyperactivity, disinhibition, apathy and sleep disturbance increasing trends in point prevalence rates have been found. Decreasing trends in depression and anxiety have been found in some studies. For VaD compared to AD there were higher cumulative incidence and persistence rates. Resolution rate is higher for AD compared to VaD.

NPS in the hyperactivity subgroup have higher point prevalence rates than in the psychotic subgroup and NPS in the affective subgroup have higher point prevalence rates than in the hyperactivity subgroup.

The variance in frequency parameters may partly be explained by the different assessment instruments used, the different intervals between assessments and different follow-up periods. The increasing trends for hallucinations, delusions/delusional misidentification, aggression, wandering/agitation, aberrant motor behaviour/motor hyperactivity, and apathy are in line with findings of studies on the course of NPS in nursing home patients with dementia, especially for wandering/agitation and apathy.[15,46] Apparently a universal course of NPS exists regardless of the setting of patients with dementia. Although the development and course of NPS is a result of complex interactions between psychological, environmental and biological factors.[47-49] Sleep disturbance, agitation/aggression and depression/dysphoria are the symptoms that causes caregivers the most emotional distress.[5]. Apathy is the symptom that gives a negative impact on the quality of the relationship between patient with dementia and caregiver and is a predictor for relationship change.[6]

Strengths and limitations

In this systematic review, we used an extensive search strategy to identify relevant studies. We pre-tested the search strategy in a pilot assessment and we searched all relevant databases without language restriction. Finally, we independently extracted data and assessed the quality of included studies with a validated checklist of predefined criteria, which has been used in previous prognostic reviews.[17,21] We presented our results together with a quality score of each study to visualize the susceptibility of each study for bias, because the quality of the individual study influences outcomes.

There are also limitations to this review that should be acknowledged. Pooling of data was impossible due to the heterogeneity of the characteristics of the community-dwelling patients studied and the methods used. The presence of selection bias in all studies limits the generalizability of the results for the individual patients, but general trends in NPS have been found for the overall population. In two studies a small part (5.9 % and 8.9 %) of the sample was institutionalized. This could also influence the generalizability of the results. Furthermore, we included 22 studies from the USA and Europe and 1 study from Japan. Unfortunately, we have not been able to include any studies from Africa or South America. It is quite likely that the pattern of NPS and caregivers' response may differ among various ethnic and cultural groups, especially between developing and developed countries. This also limits the generalizability of the results. The median number of participants enrolled in the cohorts of the included studies in this review is 170 with a wide range of 30 - 2288 study participants. Five studies enrolled less than 100 patients into the cohort.[31-34,42] These low numbers of participants in the cohorts limit the strength of the evidence concerning outcomes.

In the included 23 studies, several diagnostic criteria were used and even more different assessment instruments. There was a wide range in duration of follow-up and in six studies loss to follow-up was more than 20 % per year. Therefore, the interpretation and comparability of these studies has been difficult. Further studies on the course of NPS which are large enough to follow up a substantial amount of patients over longer periods of time and which will use established assessment instruments will improve comparability and will give more information on the persistence and resolution of NPS. Together with important prognostic factors such as type and stage of dementia this will give important recommendations for professional long-term care for community-dwelling patients with dementia.

CONCLUSIONS

Delusions/delusional misidentification, wandering/agitation, aberrant motor behaviour/motor hyperactivity and apathy are the most common NPS. For hallucinations, delusions/delusional misidentification, paranoia, aggression, wandering/agitation, aberrant motor behaviour/motor hyperactivity, disinhibition, apathy, and sleep disturbance increasing trends in point prevalence rates have been found. The increasing trends of several NPS in the course of dementia require a preventive approach of professional caretakers. For such an approach, a timely diagnosis and adequate professional support to prevent or diminish these problems is necessary.

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Supplementary Table 1. Overview of computerized search strategy: terms used in PubMed.

("Dementia"[MeSH] OR Alzheim*[All Fields] OR "CADASIL"[All Fields] OR "Dementia"[All Fields] OR "Lewy Body"[All Fields] OR Pick*[All Fields] OR "Prion Diseases"[All Fields])

AND

("Community Health Services"[MeSH] OR "General Practice"[MeSH] OR "General Practitioners"[MeSH] OR "Independent Living"[MeSH] OR "Primary Health Care"[MeSH] OR "Community Based Care"[All Fields] OR "Community-Based Care"[All Fields] OR "Community Dwelling"[All Fields] OR "Community-Dwelling"[All Fields] OR "Community Health Services"[All Fields] OR ("Community"[All Fields] AND "Healthcare"[All Fields]) OR "Family Doctor"[All Fields] OR "Family Doctors"[All Fields] OR "Family Physician"[All Fields] OR "Family Physicians"[All Fields] OR "Family Practice"[All Fields] OR "Family Practitioner"[All Fields] OR "Family Practitioners"[All Fields] OR "General Practice"[All Fields] OR "General Practitioner"[All Fields] OR "General Practitioners"[All Fields] OR "Home Care Services"[All Fields] OR "Independent Living"[All Fields] OR "General Medicine"[All Fields] OR "Primary Care"[All Fields] OR "Primary Health Care"[All Fields] OR "Public Health"[All Fields])

AND

("Cohort Studies"[MeSH] OR "Cohort"[All Fields] OR "Concurrent"[All Fields] OR "Follow up"[All Fields] OR "Follow-up"[All Fields] OR "Longitudinal"[All Fields] OR "Prospective"[All Fields])

AND

("Activities of Daily Living"[MeSH] OR "Affect"[MeSH] OR "Aggression"[MeSH] OR "Anxiety"[MeSH] OR "Appetite"[MeSH] OR "Behavioral Symptoms"[MeSH] OR "Chronic Disease"[MeSH] OR "Cognition Disorders"[MeSH] OR "Communication"[MeSH] OR "Communication Disorders"[MeSH] OR "Comorbidity"[MeSH] OR "Cooperative Behavior"[MeSH] OR "Delusions"[MeSH] OR "Depression"[MeSH] OR "Depressive Disorder"[MeSH] OR "Eating Disorders"[MeSH] OR "Environment"[MeSH] OR "Euphoria"[MeSH] OR "Geriatric Assessment"[MeSH] OR "Geriatric Psychiatry"[MeSH] OR "Hallucinations"[MeSH] OR "Hearing Loss"[MeSH] OR "Irritable Mood"[MeSH] OR "Language Disorders"[MeSH] OR "Marital Status"[MeSH] OR "Mental Disorders"[MeSH] OR "Mood disorders"[MeSH] OR "Natural History"[MeSH] OR "Neurobehavioral Manifestations"[MeSH] OR "Neuropsychological Tests"[MeSH] OR "Neuropsychology"[MeSH] OR "Pain"[MeSH] OR "Personality"[MeSH] OR "Psychiatric Status Rating Scales"[MeSH] OR "Psychomotor Agitation"[MeSH] OR "Psychotic Disorders"[MeSH] OR "Quality of Life"[MeSH] OR "Race Relations"[MeSH] OR "Risk Factors"[MeSH] OR "Severity of Illness Index"[MeSH] OR "Sexual behavior"[MeSH] OR "Sleep Disorders"[MeSH] OR "Social Behavior Disorders"[MeSH] OR "Vision Disorders"[MeSH] OR "Activities of Daily Living"[All Fields] OR "Affect"[All Fields] OR "Aggression"[All Fields] OR "Agitation"[All Fields] OR "Anxiety"[All Fields] OR "Appetite"[All Fields] OR "Behavioral Symptom"[All Fields] OR "Behavioral Symptoms"[All Fields] OR "Behavioural Symptom"[All Fields] OR "Behavioural Symptoms"[All Fields] OR "Chronic Disease"[All Fields] OR "Chronic illness"[All Fields] OR "Cognition Disorder"[All Fields] OR "Cognition Disorders"[All Fields] OR "Communication"[All Fields] OR "Cooperative Behavior"[All Fields] OR "Cooperative Behaviour"[All Fields] OR "Delusions"[All Fields] OR "Depression"[All Fields] OR "Depressive Disorder"[All Fields] OR "Depressive Disorders"[All Fields] OR "Eating Disorder"[All Fields] OR "Eating Disorders"[All Fields] OR "Environment"[All Fields] OR "Euphoria"[All Fields] OR "Geriatric Assessment"[All Fields] OR "Geriatric Psychiatry"[All Fields] OR "Hallucinations"[All Fields] OR "Hearing"[All Fields] OR "Irritable Mood"[All Fields] OR "Language Disorder"[All Fields] OR "Language Disorders"[All Fields] OR "Marital Status"[All Fields] OR "Mental Disorder"[All Fields] OR "Mental Disorders"[All Fields] OR "Mood Disorder"[All Fields] OR "Mood Disorders"[All Fields] OR "Natural History"[All Fields] OR "Neurobehavioral Manifestation"[All Fields] OR "Neurobehavioral Manifestations"[All Fields] OR "Neurobehavioural Manifestation"[All Fields] OR "Neurobehavioural Manifestations"[All Fields] OR "Neuropsychological Tests"[All Fields] OR "Neuropsychology"[All Fields] OR "Pain"[All Fields] OR "Personality"[All Fields] OR "Psy-

chiatric Status Rating Scales"[All Fields] OR "Psychomotor Agitation"[All Fields] OR "Psychotic Disorder"[All Fields] OR "Psychotic Disorders"[All Fields] OR "Quality of Life"[All Fields] OR "Race Relations"[All Fields] OR "Risk Factors"[All Fields] OR "Severity of Illness Index"[All Fields] OR "Sexual Behavior"[All Fields] OR "Sexual Behaviour"[All Fields] OR "Social Behavior Disorder"[All Fields] OR "Social Behavior Disorders"[All Fields] OR "Social Behaviour Disorder"[All Fields] OR "Social Behaviour Disorders"[All Fields] OR "Sleep Disorder"[All Fields] OR "Sleep Disorders"[All Fields] OR "Vision"[All Fields])

CHAPTER 4

Neuropsychiatric symptoms and psychotropic drug use in patients with dementia in general practices

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ABSTRACT

Background

Neuropsychiatric symptoms (NPS) frequently occur in community-dwelling patients with dementia and they are also frequently prescribed psychotropic drugs. The prescription of psychotropic drugs has been found to be associated with the level of NPS. Data on NPS in patients with dementia in general practices are scarce.

Objectives

The aim of this study was to assess the prevalence rates of NPS and psychotropic drug use in patients with dementia in general practices.

Methods

We analyzed data from the baseline measurement of a prospective cohort study in a sample of (Dutch) patients in general practices. Prevalence rates of NPS and subsyndromes assessed with the Neuropsychiatric Inventory (NPI) and of psychotropic drug use were calculated. Prevalence rates of individual NPS are presented both as clinically relevant symptoms (NPI symptom score ≥ 4) and as prevalence rates of symptoms with symptom score > 0.

Results

Of the 117 patients, more than 90% had at least one symptom and more than 65% had at least one clinically relevant symptom. The most common NPS were agitation/aggression, dysphoria/depression and irritability/lability. The most common clinically relevant NPS were aberrant motor behaviour, agitation/aggression and apathy/indifference. Only 28.7% of the patients used at least one, 7.0% used at least two different and 1.7% used at least three different types of psychotropic drugs (excluding anti-dementia medication).

Conclusions

NPS are highly prevalent in patients with dementia in general practices, but psychotropic drug use is rather low. The most common clinically relevant NPS were aberrant motor behaviour, agitation/aggression and apathy/indifference.

INTRODUCTION

Dementia is a syndrome that affects memory, thinking, behaviour and the ability to perform everyday activities.[1] Most people with dementia reside in the community. In the Netherlands, it is estimated that there are 260.000 people with dementia of whom approximately 70% are community-dwelling i.e., not live in a long-term care facility (LTCF). Of these, 60% live with their informal caregiver and 40% alone.[2,3]. Over the course of the disease most of them will experience some type of neuropsychiatric symptoms (NPS).[4] NPS include psychiatric and behavioural symptoms, such as delusions, hallucinations, depressive symptoms, anxiety, euphoria, agitation, aggression, apathy, and disinhibition.

Recent studies in various countries reported NPS prevalence rates for community-dwelling people with dementia that ranged from 44% to 96% measured with the Neuropsychiatric Inventory (NPI).[5-21] Apathy, agitation/aggression, dysphoria/depression, irritability/lability, anxiety and aberrant motor behaviour were the most common NPS.[5-11,13-16] Prevalence rates of clinically relevant symptoms (NPI symptom score ≥ 4) are lower: 44% to 81%, compared to NPI symptom score > 0: 88% to 96%.[5-11]

Half of the former studies conducted on NPS in community-dwelling people with dementia were community-based studies, but the number of people who were living at home versus those living in a LTCF were either not given or up to one-third appeared to be living in a LTCF. The other half of the studies were conducted on ambulatory patients with dementia visiting outpatient memory, (old age) psychiatry, neurological and geriatric clinical centres or dementia services, which is considered secondary care. Three to 36% of these study populations also lived in a LTCF. In the Netherlands, general practitioners (GPs) provide basic medical care for people who live at home. For LTCF there are specifically trained medical doctors called elderly care physicians.[22,23] Only a small proportion of people in general practice in the Netherlands are referred to secondary care. Therefore, it is likely that a study population visiting outpatient clinical centres have more severe and frequent symptoms than the total group of people with dementia in general practices. For GPs, it is important that accurate data of NPS of patients with dementia in general practices are available. To date only one German study reported prevalence rates of NPS in general practices.[11,13]

Psychotropic drugs, such as antipsychotics, are frequently prescribed in patients with dementia with agitation, psychosis and anxiety. The prevalence of psychotropic drug use is related to the prevalence of NPS.[11,24] Almost 66% of the people with dementia in primary care in Germany use at least one psychotropic drug and the use of antipsychotics is associated with higher NPI scores.[11] In Finland 53% of the people with dementia use at least one and 20% use at least two psychotropic drugs with a prevalence rate of antipsychotic use of 20 - 22%.[24,25] There is only limited evidence for the effectiveness of psychotropic drugs in the treatment of NPS in people with dementia and psychotropic drugs cause serious adverse effects, like extrapyramidal symptoms, accelerated cognitive decline, stroke and death.

Only some atypical antipsychotic drugs have shown benefit in the treatment of aggression in people with Alzheimer's disease over a period of up to 12 weeks.[26] Selective serotonin re-uptake inhibitors or serotonin-specific reuptake inhibitors (SSRIs) have been proposed as an alternative pharmacological approach to antipsychotics based on evidence that the serotonergic system is involved in the etiology of NPS in dementia.[27] For example citalopram compared with placebo significantly reduces agitation and caregiver distress. However, cognitive and cardiac adverse effects of citalopram may also limit its practical application.[28]

NPS, especially depression, are predictors of institutionalization.[29,30] They are also associated with psychological distress in informal caregivers.[31-34]

To date, only one study reported prevalence rates of NPS and psychotropic drug use in general practices. The DelpHi-MV study, a cohort study in general practices in Germany, found that 43.8 % of the patients had one or more clinically relevant NPS in the previous 4 weeks and almost 66 % of the study population used at least one psychotropic drug including anti-dementia medication.[11,13] Thus, data are scarce while they are very relevant for general practices, because the general practitioner (GP) is most often the first physician consulted for dementia-related problems and NPS frequently lead to institutionalization, high rates of psychotropic drug use and psychological distress in their informal caregivers.

Therefore, the aim of this study was to assess the prevalence of NPS and the prevalence of psychotropic drug use in patients with dementia in general practices.

METHODS

This is a cross-sectional analysis of baseline measurements from a prospective naturalistic cohort study with a follow-up of 18 months. All participants were living at home and cared for by an informal caregiver. This study has been described in detail previously.[35] We invited all 192 known GPs in 114 general practices in the region West- and Middle-Brabant. These practices are representative for the Dutch general practices because the practice/GP ratio in West- and Middle-Brabant (59 %) is comparable to the ratio of the Netherlands (58 %).[36] Eventually, 37 GPs in 18 general practices participated in this study. These 18 general practices in the study are representative for the Dutch general practices because the percentages of single-handed/two-person/group practices seem to be rather comparable (22 % to 28 % single handed, 33 % to 39 % two-person practice, 44 % to 33 % group practice) and because the mean number of patients per practice is comparable (2062 versus 2200).

Patients and informal caregivers

We successively screened the 18 participating practices between January and July 2012 to identify and recruit dyads of patients and informal caregivers. Eligible patients were selected with a search in the electronic medical files. It took 7 months to visit all practices, selection was

done at one specific moment in time. These patients and their caregivers were approached by mail. The GP contacted patient or informal caregiver by telephone to stimulate participation in the study. Inclusion criteria for patients were: living at home and registered in the GP's electronic medical file with a diagnosis of dementia. Dutch GPs code all diagnoses in their files according to the International Classification of Primary Care (ICPC).[37] According to the ICPC dementia is coded as P70 and memory disturbance as P20. Patients living in a LTCF or with an estimated life expectancy of less than three months were excluded. This research project was presented for medical ethics review at the regional Committee on Research Involving Human Subjects (CMO). The committee judged that this project, according to the Dutch legislation, could be carried out without formal approval by the CMO. Patients, or their legal representatives, and caregivers gave written informed consent.

Assessment instruments

Clinical characteristics of patients and informal caregivers were collected by a trained research assistant during an interview with the patient and the informal caregiver at their home. NPS of the patients were assessed with the Neuropsychiatric Inventory (NPI) ranging from 0 to 144.[17,21,38] Based on previous studies we categorized the NPI in three behavioural subsyndromes: mood/apathy (depression, apathy, nighttime behaviour disturbances, and appetite and eating abnormalities), psychosis (delusions and hallucinations), and hyperactivity (agitation, euphoria, irritability, disinhibition, and aberrant motor behaviour). Anxiety was regarded as a separate symptom.[39] Cognition of the patient was assessed with the Mini-Mental State Examination (MMSE) ranging from 0 to 30.[40]

Data about psychotropic drug use were obtained on the day of assessment during the interview with the patient and the informal caregiver. All drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system: antipsychotics (N05A), antiepileptic medication (N03A), antidepressants (N06A), anxiolytics (N05B), hypnotics (N05C) and anti-dementia medication (N06D).[41] For antipsychotics we made a distinction between typical/classical, (first-generation antipsychotics), and atypical, (second-generation antipsychotics). For antidepressants, we made a distinction between selective serotonin reuptake inhibitors (SSRI's) and tricyclic antidepressants. Anti-dementia medication included the use of an acetylcholinesterase inhibitor (AChEI: rivastigmine and galantamine) or a N-methyl-d-aspartate receptor antagonist (NMDAR: memantine).[42]

Prevalence of NPS

The prevalence of NPS was calculated by dividing the number of participants who exhibit NPS in the previous 4 weeks by the number of participants in our study population. Each symptom score of the NPI was defined by a frequency (F) times severity (S) score. Generally a symptom score of 4 or higher is considered clinically relevant.[6-8] Prevalence rates of

individual NPS are presented both as clinically relevant symptoms (NPI symptom score ≥ 4) and as prevalence irrespective of clinical relevance (NPI symptom score > 0).

Psychotropic drug use

The prevalence of psychotropic drugs and combinations of these were calculated by dividing the number of participants who use one or more psychotropic drugs by the number of participants in our study population.

Data analysis

We summarized the demographic and clinical characteristics of the participants by descriptives. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) 23.0. For missing items for the NPI we used ipsative mean imputation, which substitutes the missing items by the mean of the remaining items within the individual.[43,44] We accepted 1 missing item in the NPI for the NPI total score and no missing items for the NPI subsyndromes.

RESULTS

The participating general practices in our study are representative for the Netherlands for the types of general practices. We do not have data about characteristics such as age, gender and socioeconomic status of the total patient population of the participating practices. We have incomplete data of the age distribution in the 18 participating practices. In 10 of these practices the percentage of patients aged 75 and older is 22.5 %. In total 243 patients with

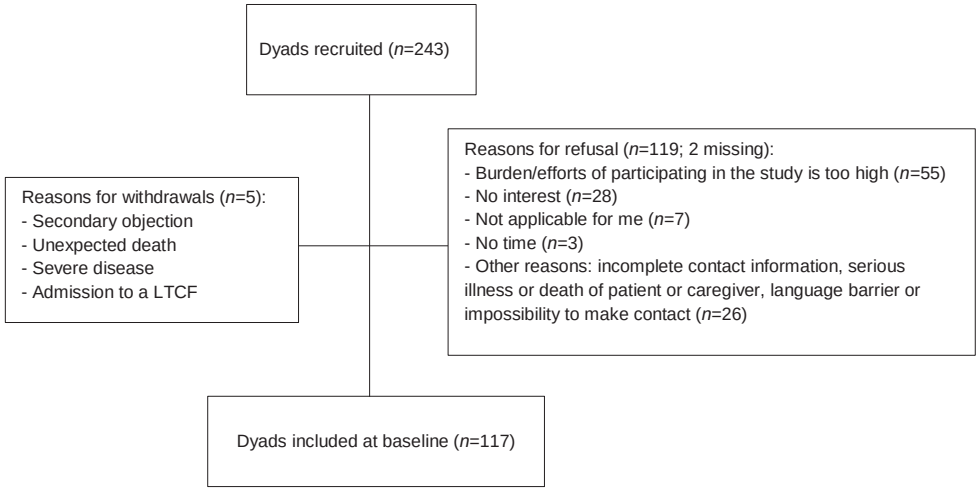

Figure 1. Recruitment of patients with dementia in general practice (2012)
Dyads: patient and caregiver; LTCF: Long term care facility; *n*: number of participants

dementia were identified of whom 117 (48%) were included (Figure 1). The mean age of the 126 patients who refused (*n* = 121) or withdrew (*n* = 5) their consent was 79.2 years (SD 6.8) and 67% were female. The mean age of the informal caregivers who refused or withdrew their consent (missing data *n* = 31) was 66.0 years (SD 14.0, range 28 - 92) and 67% were female (missing data *n* = 2). The relation of the informal caregiver with the patient (missing data *n* = 4) was 49% spouse, 45% child and 6% others. The 126 patients who refused or withdrew their consent were more often female; informal caregivers of these patients were more often child. Two patients were admitted to a LTCF after informed consent and just before baseline assessment. They entered the study and the baseline questionnaires were filled out as before institutionalization.

Clinical characteristics of the patients and informal caregivers

Patients of the study population had a mean age of 78.6 years (SD 7.1) and 52% were female (Table 1). Only 4% of these patients had an age less than 65 years. Mean NPI total score was low (15.7, range 0 - 77). Use of health care services were: case manager (29.3%), day care centres (34.2%), home care services (47.9%) and domestic care (47.9%).

Informal caregivers of the patients had a mean age of 67.3 years (SD 13.3, range 32 - 92) and 68.4% were female, 65.0% were spouse, 29.1% child or child-in-law and 5.9% were others, like grandchild, sibling, friend/acquaintance, neighbor or nephew or niece.

Prevalence of NPS

Almost all patients (92.2%) had one or more NPS, whereas 65.5% had one or more clinically relevant NPS. Prevalence rates of NPS are presented in Figure 2. The most common NPS (NPI symptom score > 0) were agitation/aggression (54.3%), dysphoria/depression (52.6%) and irritability/lability (48.3%). The most common clinically relevant NPS (NPI symptom score ≥ 4) were aberrant motor behaviour (28.4%), agitation/aggression (23.3%) and apathy/indifference (21.6%). Prevalence rates of NPI subsyndromes for NPI symptom score > 0 and clinically relevant NPS were: mood/apathy 81.0% and 47.0%, psychosis 23.3% and 9.6%, hyperactivity 80.2% and 48.7%, respectively.

Psychotropic drug use

Prevalence rates of psychotropic drug use are presented in Table 1. Almost half (47.0%, *n* = 54) of the patients in our study population did not use psychotropic drugs at all, 53.0% (*n* = 61) used at least one, 13.9% (*n* = 16) used at least two and four patients (3.5%) used three different psychotropic drugs. When leaving out anti-dementia medication 71.3% (*n* = 82) used no psychotropic drugs at all, 28.7% (*n* = 33) used at least one, 7.0% (*n* = 8) used at least two different psychotropic medications and two patients (1.7%) used three different psychotropic drugs. Of the six patients who used antiepileptics, one was for focal epilepsy, two for leg pain.

Table 1. Characteristics of patients with dementia and informal caregivers (*n* = 117) in general practice (2012)

Patients	**Participants (*n* = 117)**	**Refusals/withdrawals (*n* = 126)**
Age (years)		
Mean ± SD	78.6 ± 7.1	79.2 ± 6.8
Range	57 - 91	63 - 92
Gender (*n* (%))		(*n* = 89)
Male	56 (47.9)	42 (33.3)
Female	61 (52.1)	84 (66.7)
Race (*n* (%))		
Caucasian	115 (98.3)	
Other	2 (1.7)	
Level of profession (*n* (%))		
Elementary occupation	23 (19.7)	
Lower occupation	22 (18.8)	
Secondary profession	48 (41.0)	
Higher profession	18 (15.4)	
Scientific profession	6 (5.1)	
Marital status (*n* (%))		
Married	80 (68.4)	
Widow	33 (28.2)	
Divorced	1 (0.9)	
Unmarried	3 (2.6)	
Use of care services (*n* (%))		
Case manager	34 (29.3)	
Day care centres	40 (34.2)	
Home care services	56 (47.9)	
Domestic care	56 (47.9)	
Psychotropic medication (*n* (%))	(*n* = 114)	
No psychotropic medication	54 (47.0)	
Antipsychotics	11 (9.6)	
Typical or classic	5 (4.3)	
Atypical	7 (6.1)	
Antiepileptics	6 (5.2)	
Antidepressants	20 (17.4)	
Non-tricyclic/SSRIs	19 (16.5)	
Tricyclic	1 (0.9)	
Anxiolytics	3 (2.6)	
Hypnotics	2 (2.6)	
Anti-dementia	39 (33.6)	
AChEI	39 (33.6)	
NMDAR	2 (1.7)	

Table 1. Characteristics of patients with dementia and informal caregivers (*n* = 117) in general practice (2012) (continued)

Patients	**Participants (*n* = 117)**	**Refusals/withdrawals (*n* = 126)**
MMSE-score	(*n* = 97)	
Mean ± SD	19.5 ± 5.6	
Range (0 - 30)	0 - 27	
Score 20+ (Mild) (*n* (%))	63 (57.8)	
Score 10 - 19 (Moderate) (*n* (%))	31 (28.4)	
Score 0 - 9 (Severe) (*n* (%))	15 (13.8)	
NPI total score	(*n* = 116)	
Mean ± SD	15.7 ± 15.4	
Range (0 - 144)	0 - 77	
Informal caregivers		
Age (years)		(*n* = 95)
Mean ± SD	67.3 ± 13.3	66.0 ± 14.0
Range	32 - 92	28 - 93
Gender (*n* (%))		(*n* = 124)
Male	37 (31.6)	41 (33.1)
Female	80 (68.4)	84 (66.9)
Relationship to the patient (*n* (%))		(*n* = 122)
Spouse	76 (65.0)	60 (49.2)
Child/child-in-law	34 (29.1)	55 (45.1)
Other	7 (5.9)	7 (5.7)

n: number of participants; SSRIs: Selective serotonin re-uptake inhibitors; AChEI: acetylcholinesterase inhibitor; NMDAR: N-methyl-d-aspartate receptor antagonist; MMSE: Mini-Mental State Examination; NPI: Neuropsychiatric Inventory

DISCUSSION

We found that NPS are very common in people with dementia in general practices. More than 90 % of the study population had at least one NPS and more than 65 % had at least one clinically relevant NPS. The most common NPS were agitation/aggression, dysphoria/depression and irritability/lability. The most common clinically relevant NPS were aberrant motor behaviour, agitation/aggression and apathy/indifference. Almost 29 % of the patients used at least one, 7.0 % used at least two different and 1.7 % used at least three psychotropic drugs (excluding anti-dementia medication).

Compared to the DelpHi-MV study, the prevalence of all symptoms of the NPI in our study are higher. The most common NPS in this study were dysphoria/depression 36.8 %, apathy 32.2 %, agitation/aggression 31.0 %, which is, except for apathy, in line with the findings of our study.[13] In the DelpHi-MV study GP practices screened patients aged 70 years and older for dementia and only 81 of the 176 (46 %) people with dementia in this cohort were

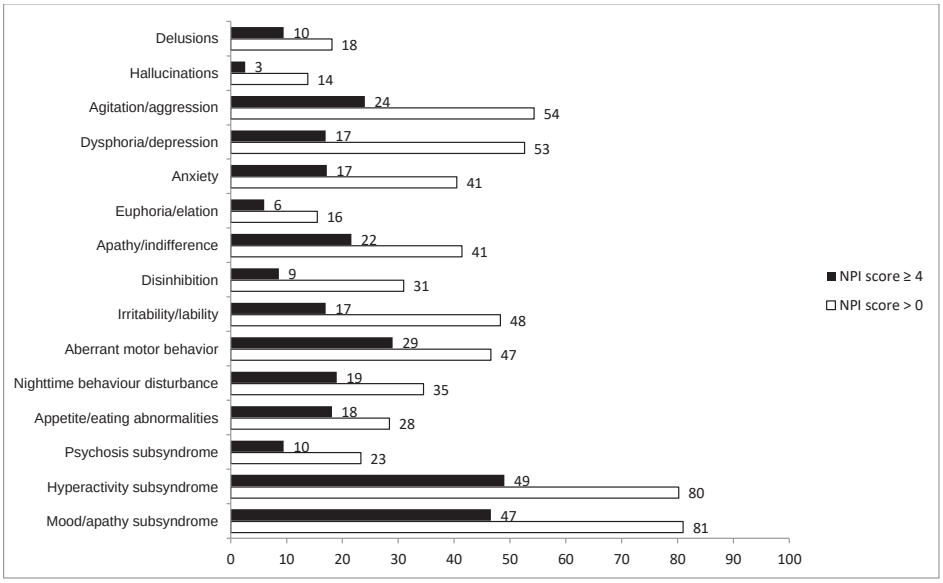

Figure 2. Prevalence of neuropsychiatric symptoms in patients with dementia (*n* = 116) in general practice (2012)
Neuropsychiatric Inventory (NPI) score > 0: percentage who exhibit the symptom on the NPI (*n* = 116); NPI score ≥ 4: percentage with clinically relevant score on the NPI (*n* = 115); Psychosis subsyndrome: delusions and hallucinations; Hyperactivity subsyndrome: agitation, euphoria, disinhibition, irritability, and aberrant motor behaviour; Mood/apathy subsyndrome: depression, apathy, nighttime behaviour disturbances, and appetite and eating abnormalities

already diagnosed before start of the study. Because of this under-reporting of GPs the study population in our study is probably in a more advanced stage of the disease. The mean MMSE score in our study (19.5 ± 5.6) is lower than in the DelpHi-MV study (20.87 ± 5.6).

Except for delusions and hallucinations, all other symptoms and subsyndromes on the NPI in our study were more prevalent than in the DelpHi-MV study. The most common clinically relevant symptoms in the DelpHi-MV study were apathy 15.3 %, aberrant motor behaviour 11.4 %, anxiety 10.2 %, which is, except for anxiety in line with our findings.[11] On the other hand, compared to the MAAstricht Study of BEhaviour in Dementia (MAASBED) study, a prospective Dutch study on a cohort of psychiatric-based clinics, the prevalence rates we found were lower for the majority of the clinically relevant symptoms and subsyndromes on the NPI (10 out of 15) except for agitation/aggression, disinhibition, aberrant motor behaviour, nighttime behaviour disturbance and the hyperactivity subsyndrome. Especially for delusions and hallucinations (psychosis subsyndrome), dysphoria/depression, apathy/indifference and the mood/apathy subsyndrome our prevalence rates were much lower. Mean MMSE score in the MAASBED study was lower: 18.09 (4.68), as compared to our study as we expected in an ambulatory psychiatry-based study.[10]

Psychotropic drug use in our study (28.7% at least one excluding anti-dementia medication) is higher compared to the findings of the Dutch study of Hamers et al (16.0%) in 2016. However, this study was conducted on people with cognitive impairment, not specifically with a diagnosis of dementia. And secondly, they were all supported by a case manager, compared to 29.3% in our study. Psychotropic drug use including anti-dementia medication (53.0% at least one) in our study is lower compared to the DelpHi-study (66%). Use of antipsychotics in our study (9.6%) is relatively low compared to the studies in Germany (10.6 to 13.6%), Finland (20 to 22.1%) and the United States of America (USA) (27%).[11,13,24,25,45] Only in Sweden the antipsychotic use is lower (4.2%).[46] The use of antiepileptics (5.2%) in our study is lower than in Germany; use of antidepressants (17.4%) is higher than in Germany (14.0 to 15.3%), but lower than in Sweden (22.9%) and Finland (28%).[11,13,25,45,46] The use of anxiolytics (2.6%) and hypnotics (2.6%) in our study is much lower than in Sweden (6.9% and 13.3% respectively).[46] Use of anti-dementia medication (33.6%) is similar to the studies in Germany (25.8 to 42%) and low compared to Sweden (75.4%), where the use of AChEI is recommended in the national guidelines for all people with Alzheimer's disease.[11,13,46] In this Swedish study it was found that patients taking an AChEI were treated with less antipsychotics and anxiolytics than those not taking an AChEI. Overall, in our study psychotropic drug use is relatively low compared to other studies, specifically if you take into account the high prevalence rates of NPS we found. Dutch GPs and their guidelines are generally very reticent in prescribing psychotropic drugs.[36]

Strengths and limitations

The sample of patients and informal caregivers in this study was heterogeneous with patients in all stages of dementia and they were included from general practices. The participating general practices in our study are representative for the Dutch general practices. Data included psychotropic drug use.

A limitation to our study is the rather low participation of general practices (114 invited, 18 participated) and high refusal rate of patients and informal caregivers indicating that burden of participating in the study is too high. Due to this there is a risk that we have studied a selective group of patients with relatively low levels of NPS. On the other hand, GPs often wait before diagnosing dementia which may have biased our sample towards a more severe spectrum of people with dementia and NPS. The difference in clinical characteristics between the participants and those who refused or were withdrawn, also gives a risk of selection bias. The percentage of patients aged over 75 in the participating general practices (22.5%) is probably higher than in the Dutch general population (9.6%).[36] This overestimates the number of patients with dementia, NPS and psychotropic drug use compared to the average general practice in the Netherlands.

Finally, caregivers who experience high levels of psychological distress may score the NPS of the person with dementia they care for as more severe. Higher frequency of NPS is associ-

ated with higher levels of psychological distress.[34] This results in caregiver-rating bias, which could have affected the level of NPS to a more severe spectrum.[16,47]

Implications

We expected less severe and frequent NPS in patients with dementia in general practices compared to ambulatory patients visiting outpatient clinical centres, but this study showed that a high proportion of patients with dementia in general practices have at least one (clinically relevant) NPS. The prevalence of psychotropic drug use in our study is low compared to other studies but still almost 29 % of the patients with dementia has a prescription for at least one psychotropic drug. The GP is often the first person to be consulted for patients who are worried that they may have dementia or for dementia-related problems like NPS. A timely diagnosis of dementia is important to be able to provide adequate post-diagnostic support, such as psycho-education, access to treatment and psychosocial interventions, peer support, advance care planning and advance directives.[48] Many psychosocial interventions for people with dementia and their informal caregivers have been developed in the last decades and they have proven to be more effective and give less adverse effects than prescribing psychotropic drugs.[49-51] Cognitive stimulation or multicomponent interventions, in which cognitive stimulation is combined with reminiscence and relaxation or support, or behavioural interventions performed by individual work with the informal caregiver have been shown to be effective on NPS.[49] Multicomponent interventions as cognitive stimulation combined with reminiscence or physical exercise or ADL training or support have been shown to be effective in improving the mood of the people with dementia.[49] NPS in people with dementia require a timely diagnosis and adequate professional support to diminish NPS and prevent institutionalization and psychological distress in their informal caregivers.

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CHAPTER 5

The course of neuropsychiatric symptoms in patients with dementia in primary care

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ABSTRACT

Background

During the course of dementia, most people develop some type of neuropsychiatric symptoms (NPS), which result in lower quality of life, high caregiver burden, psychotropic drug use and a major risk of institutionalization. Studies on NPS in people with dementia have been mainly conducted in clinical centres or psychiatric services.

Objectives

To investigate the course of NPS in people with dementia in primary care.

Methods

Analysis of (cumulative) prevalence and incidence, persistence and resolution based on data collected during an assessment at home of a prospective naturalistic cohort study in primary care in a sample of 117 people with dementia and their informal caregivers. Subsyndromes of NPS were assessed with the Neuropsychiatric Inventory (NPI) and Cohen-Mansfield Agitation Inventory. Multivariate analyses were used to detect determinants for the course of NPS.

Results

The mean age of the people with dementia was 78.6 years and 52% were female. Mean Mini-Mental State Examination total score was 19.5, mean NPI total score 15.7. The most prevalent clinically relevant subsyndromes of the NPI were hyperactivity and mood/apathy and the most prevalent individual NPS were aberrant motor behaviour (28%), agitation/aggression (24%) and apathy/indifference (22%). Of the people with dementia 72.3% had one or more symptoms of the mood/apathy and 75.3% of the hyperactivity subsyndrome.

Conclusions

GPs should be aware of NPS in people with dementia and should actively identify them when they visit these patients or when informal caregivers consult them. Timely diagnosing facilitates adequate professional care.

INTRODUCTION

Dementia is a syndrome characterized by deterioration in memory, thinking, behaviour and everyday activities. Worldwide, around 47 million people have dementia, and there are nearly 10 million new cases every year.[1] In the Netherlands, more than 260.000 people have dementia of whom 70% are community-dwelling.[2] Of these, 60% live with their informal caregiver and 40% alone.[3] During the course of dementia most people develop some type of challenging behaviour, also called neuropsychiatric symptoms (NPS).[4]

NPS can be categorized in behavioural subsyndromes: mood/apathy, hyperactivity and psychosis. Mood/apathy and hyperactivity are the most common subsyndromes with delusions, wandering/agitation, aberrant motor behaviour and apathy as the highest prevalent individual symptoms.[4,5] Moreover NPS are persistent although frequency parameters vary considerably across studies.[4] For hallucinations, delusions, paranoia, aggression, wandering/agitation, aberrant motor behaviour, anxiety, irritability, disinhibition, apathy and sleep disturbance increasing trends in point prevalence rates at successive measurements have been found.[4,6]

Almost all studies on the course of NPS in community-dwelling people with dementia were conducted in ambulatory patients visiting outpatient memory, (old-age) psychiatry, neurological or geriatric clinical centres or dementia services.[4] In these studies most participants were living at home. Some were living in long-term care facilities and some studies did not specify whether or not the study population was institutionalized.[4,7-9]

The only Dutch study on the course of NPS in community-dwelling people with dementia, the MAAstricht Study of BE-haviour in Dementia (MAASBED), was conducted in people with dementia enrolled from outpatient psychiatry-based clinics. This study found high incidence and prevalence rates and high persistence after 2 years.[5]

In the Netherlands, basic medical care for community-dwelling older people is provided by general practitioners (GPs). In long-term care facilities medical care is provided by specifically trained medical doctors called elderly care physicians.[10] Only a small proportion of people in general practice are referred to outpatients' memory, (old-age) psychiatry, neurological and geriatric clinical centres, which is considered secondary care. Therefore, it is likely that a study population visiting outpatient clinical centres has more severe and frequent symptoms than the total group of people with dementia in primary care.

The GP is most often the first physician consulted for dementia-related problems and has an important role in prescribing psychotropic drugs, such as antipsychotics, antidepressants, anxiolytics and hypnotics.[11-13] The use of antipsychotics is associated with higher NPI scores.[11] Greater cognitive impairment, higher baseline severity of NPS and increased functional impairment are associated with more NPS; the use of support services, like day and respite care and training courses for caregivers, are associated with less NPS over time.[14-19] Higher frequency of NPS is associated with higher levels of psychological distress in informal

caregivers of people with dementia. However, the evidence is not conclusive as to if some NPS are more stressful for informal caregivers than others.[20-24]

To our knowledge, prospective studies on the course of NPS have not been conducted in patients exclusively from general practices. Such a study would help GPs and other professionals in primary care in the management of their patients with dementia, especially with respect to the planning of follow-up visits and the timing of psycho-education, psychosocial interventions and the provision of care. Therefore, the aim of this study was to investigate the course of NPS and to detect determinants for the course of NPS in people with dementia in primary care.

METHODS

This is a prospective naturalistic cohort study in primary care in the southern part of the Netherlands with a follow-up of 18 months. All participants were living at home and cared for by an informal caregiver at the start of this study. All 192 known GPs in 114 general practices were invited of whom 37 GPs in 18 general practices participated. Patients were assessed at baseline and after 9 and 18 months. Follow-up was continued after admission to a long-term care facility. Details of this study have been described previously.[21,25,26] A trained research assistant collected data during an interview with patient and informal caregiver at home at baseline (T0), at 9 months (T1) and at 18 months (T2)

Patients and informal caregivers

The electronic medical files of the 18 participating practices were screened between January and July 2012. We identified and recruited dyads of patients with a diagnosis of dementia and their informal caregivers. Patients living in a long-term care facility or with an estimated life expectancy of less than 3 months were excluded. Patients, or their legal representatives, and caregivers gave written informed consent. The regional Committee on Research Involving Human Subjects in the Netherlands judged that this project could be carried out without formal approval.

Assessment instruments

Information about age and gender of the patient, about caregivers' age, gender and relation to the patient and about the use of health care services such as day care services, home and domestic care services and case management was collected.[27]

NPS of the patient were assessed with the Neuropsychiatric Inventory (NPI) and the Cohen-Mansfield Agitation Inventory (CMAI). The NPI consists of 12 categories of NPS: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, sleeping disorder and eating disorder. Based on

previous studies we categorized the NPI in three behavioural subsyndromes, relevant for the GP: mood/apathy (depression, apathy, nighttime behaviour disturbances, and appetite and eating abnormalities), psychosis (delusions and hallucinations), and hyperactivity (agitation, euphoria, irritability, disinhibition, and aberrant motor behaviour). Anxiety is regarded as a separate symptom.[28] For each individual symptom, the severity and frequency are scored with structured questions administered to the patients' caregiver. The final score for each symptom is obtained by multiplying severity (score: 1 - 3) with frequency (score: 1 - 4). Symptom scores are combined to an overall score with a range of 0 to 144 with higher scores indicating a more severe symptom burden. In line with previous studies, a score greater than 3 for an individual symptom was defined as clinically relevant.[5,29-31]

The CMAI was developed to assess the frequency of agitated behaviours. It has 29 items scored on a 7-point frequency scale (1 = never, 2 = < once a week, 3 = 1 - 2 times per week, 4 = several times per week, 5 = 1 - 2 times per day, 6 = several times per day, and 7 = several times per hour). Symptom scores are combined to an overall score with a range of 29 to 203 with higher scores indicating a more severe symptom burden.[32-34] In line with a previous study we categorized the items in three subsyndromes: physically aggressive (spitting, cursing/verbal aggression, hitting, grabbing, pushing, strange noises, screaming and scratching), physically non-aggressive (pace/aimless wandering, inappropriate dressing/disrobing, trying to get to a different place, handling things inappropriately, hiding things, hoarding things and general restlessness) and verbally agitated behaviour (constant unwarranted request for attention/help, repetitive sentences/questions, complaining and negativism).[34] A score ≥ 3 was defined as clinically relevant.[34]

Cognition of the patient was assessed with the Mini-Mental State Examination (MMSE) ranging from 0 to 30.[35]

Psychotropic drug use of the patient was classified according to the Anatomical Therapeutic Chemical classification system: antipsychotics (N05A), antiepileptic medication (N03A), antidepressants (N06A), anxiolytics (N05B), hypnotics (N05C) and anti-dementia medication (N06D).[36]

For the assessment of psychological distress of the informal caregivers the Sense of Competence Questionnaire (SCQ) was used (range 27 - 135), a 27-item questionnaire of which higher scores indicate lower feelings of burden.[37,38]

Fourteen of the 18 general practices participated in a special care program called CONCERN (Care Optimization for Non-professional Caregivers of Elderly with dementia and Reduction of Neuropsychiatric symptoms) after baseline measurements. In CONCERN a GP, case manager and an elderly care physician systematically collaborate to improve dementia care in order to reduce NPS.[25] Other participants received care as usual.

Data analysis

Data were analysed using the Statistical Package for Social Science 23.0. We used descriptive statistics for data at T0, T1 and T2. Analysis of variance, Chi Square tests and t-tests were used to analyse differences between patient and caregiver dyads who completed the study and those who were lost to follow-up, and between patients with and without admission to a long-term care facility during follow-up.

We made 3 categories for cognition of the patient: 0 - 9, 10 - 19 and 20 - 30. Six patients had no MMSE in all 3 assessments because assessment was too stressful or because of absence due to stay at day care centres. It was assumed for these patients to have a low MMSE score 0 - 9, because they visited day care centres and used home care services and 4 of these patients were admitted to a long-term care facility after baseline and before T1 measurements. Eight patients were lost to follow-up. Therefore, at baseline the numbers of patients in the different subgroups were: MMSE score 0 - 9; n = 15 (13.8 %); score 10 - 19; *n* = 31 (28.4 %); score 20+; *n* = 63 (57.8 %).

The prevalence (point and cumulative), cumulative incidence, and persistence of each NPS at each assessment were expressed as the percentage of patients with scores greater than 3 on any item of the NPI or subsyndrome. *Point prevalence* was defined as the proportion of patients with a specific NPS at each assessment, *cumulative prevalence* as the proportion of patients developing a specific NPS on at least one assessment, *cumulative incidence* as the proportion of patients who were symptom-free at baseline but developed the specific NPS at subsequent assessments, *persistence* as a NPS present on at least 2 or during all 3 subsequent assessments, regardless of time of first manifestation of the NPS and *resolution* as the proportion of patients who showed a specific symptom at baseline but not at the next assessments.[5]

We used a random intercept mixed model in the multivariate analysis which took into account the clustering of measurements within patients and the clustering of patients within a general practice. Dependent variables were NPI total score and the NPI and CMAI subsyndromes. Independent variables were patients' age and gender, cognition of the patient, psychotropic drug use, patient-caregiver relationship, psychological distress of informal caregiver, use of respite care or personal health care at baseline and participation in CONCERN, all at baseline.

To investigate the course of NPS over time, a model with time as a discrete independent variable was used. We compared a model with interaction terms of the independent variables with time (model 2) with a restricted model without those interaction terms (model 1) using a likelihood ratio test.[39]

RESULTS

In the 18 participating general practices 243 patients with dementia were identified of whom 117 (48%) were included (Figure 1). In total 32 dyads (27.4%) were lost to follow up during the study: 19 dyads (16.2%) between T0 and T1 and 13 dyads (11.1%) between T1 and T2. Twenty-one patients were admitted to a LTCF between T0 and T1 and 4 patients between T1 and T2. Of these 25 admitted patients, 15 completed the study.

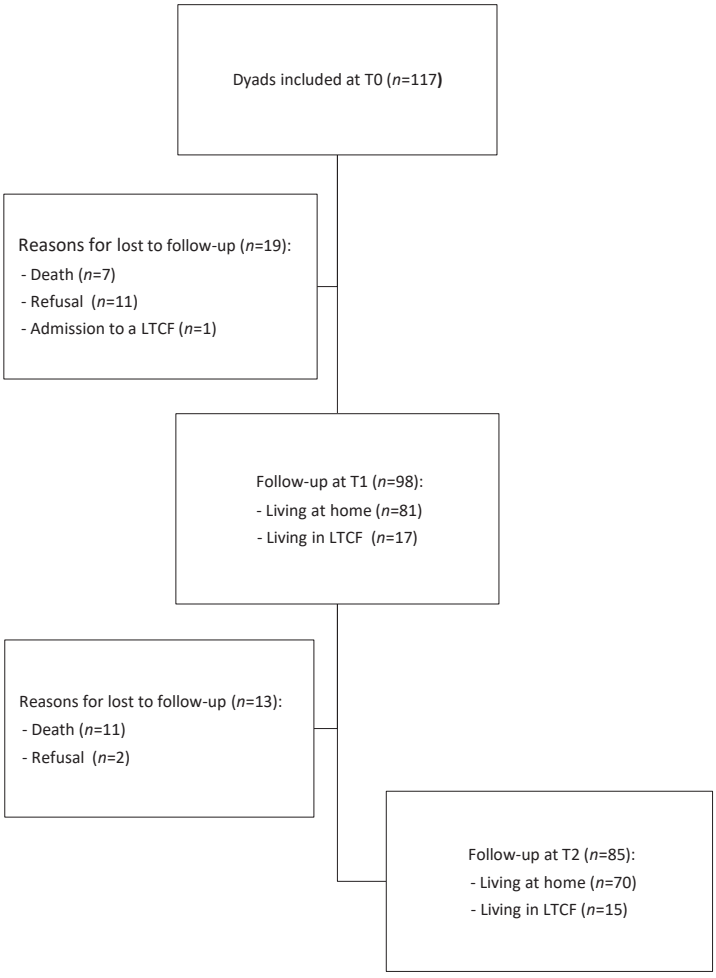

Figure 1. Recruitment of patients with dementia in primary care and follow-up (2012 and 2013).doc Dyads: patient and caregiver; LTCF: Long term care facility; *n*: number of participants; T0: baseline; T1: after 9 months; T2: after 18 months.

Table 1. Characteristics of patients with dementia and informal caregivers (*n* = 117) in primary care (2012)

	Baseline (*n* = 117)	Lost to follow-up[a] Baseline (*n* = 32)	LTCF[b] Baseline (*n* = 25)	Refusal + withdrawn[c] (*n* = 126)
Patient characteristics				
Age, years (SD) [range]	78.6 (7.1) [57 - 91]	80.8 (6.9) [65 - 91]*	80.9 (6.9)[68 - 91]	79.2 (6.8)[63 - 92]
Age subgroup (*n* (%))				
<70 years	15 (12.8%)			
70 - 80 years	55 (47.0%)			
>80 years	47 (40.2%)			
Sex (*n* (%))				
Male	56 (47.9%)	11 (34.4%)	13 (52.0%)	42 (33.3%)
Female	61 (52.1%)	21 (65.6%)	12 (48.0%)	84 (66.7%)
MMSE total score, mean (SD) [range]	19.5 (5.6) [0 - 27] [*n* = 97]	18.4 (6.6) [*n* = 24]	17.81 (4.2) [*n* = 16]	
MMSE score (*n* (%))	[*n* = 109]			
0 - 9	15 (13.8%)			
10 - 19	31 (28.4%)			
20 - 30	63 (57.8%)			
NPI total score, mean (SD)	15.7 (15.4) [*n* = 116]	18.8 (18.9) [*n* = 31]	24.2 (21.0)*	
Psychotropic drug use (*n* (%))[d]				
None	54 (47.0%) [*n* = 115]			
At least one	61 (53.0%)			
At least 2 different	16 (13.9%)			
At least 3 different	4 (3.5%)			
Psychotropic medication	[*n* = 114]			
No psychotropic medication	54 (47.0%)			
Antipsychotics	11 (9.6%)			
Antiepileptics	6 (5.2%)			

Table 1. Characteristics of patients with dementia and informal caregivers (*n* = 117) in primary care (2012) (continued)

	Baseline (*n* = 117)	Lost to follow-up[a] Baseline (*n* = 32)	LTCF[b] Baseline (*n* = 25)	Refusal + withdrawn[c] (*n* = 126)
Antidepressants	20 (17.4%)			
Anxiolytics	3 (2.6%)			
Hypnotics	3 (2.6%)			
Anti-dementia	39 (33.6%)			
Caregiver characteristics				
Age, years (SD) [range]	67.3 (13.3) [32 - 92]	64.9 (16.7) [32 - 92]	63.3 (12.1) [46 - 87]	66.0 (14.0)[28 - 92] [*n* = 95]
Sex (*n* (%))				
Male	37 (31.6%)	11 (34.4%)	4 (16.0%)	41 (33.1%) [*n* = 124]
Female	80 (68.4%)	21 (65.6%)	21 (84.0%)	84 (66.9%) [*n* = 124]
Relationship (*n* (%))			*	
Spouse	76 (65.0%)	18 (56.2%)	11 (44.0%)	60 (49.2%) [*n* = 122]
Child	34 (29.1%)	11 (34.4%)	13 (52.0%)	55 (45.1%) [*n* = 122]
Other	7 (5.9%)	3 (9.4%)	1 (4.0%)	7 (5.7%) [*n* = 122]
SCQ total score, mean (SD) [range]	98.7 (15.9) [40 - 128] [*n* = 115]	98.5 (17.0) [32 - 92]	92.0 (17.0) [58 - 128]*	
Use of care services (*n* (%))				
CONCERN	59 (50.4%)	14 (43.8%)	9 (36.0%)	
Case management	34 (29.3%) [*n* = 116]	9 (29.0%) [*n* = 31]	3 (12.0%)*	
Respite care	40 (34.2%)	10 (31.2%)	12 (48.0%)	
Home care services, including domestic care	69 (59.0%)	23 (71.9%)	22 (88.0%)*	

CONCERN: Care Optimization for Non-professional Caregivers of Elderly with dementia and Reduction of Neuropsychiatric symptoms; LTCF: Long-term care facility; MMSE: Mini-mental State Examination; *n*: number of subjects; NPI: Neuropsychiatric Inventory; SCQ: Sense of Competence Questionnaire.

[a]Lost to follow-up: baseline characteristics of dyads who were lost to follow-up during the study (*n* = 32). [b]LTCF: baseline characteristics of patients who were admitted to a LTCF during the study (n = 25). [c]Refusal + withdrawn: baseline characteristics of dyads who refused (n = 121) or withdrew their consent (n = 5) before start of the study. [d]Psychotropic drug use: antipsychotics, antiepileptic medication, antidepressants, anxiolytics, hypnotics or anti-dementia medication.

* $p < 0.05$.

Characteristics of study population

Characteristics of patients and informal caregivers at baseline and separately for the patients who were lost to follow-up or institutionalized during follow-up are presented in Table 1 according as the patients who refused to participate or were withdrawn. Only 4% of the patients were younger than 65 years. Mean MMSE total score: at baseline 19.5 (SD 5.6; *n* = 97), after 9 months 19.6 (SD 6.9; *n* = 70) and after 18 months 15.1 (SD 9.4; *n* = 63). Mean NPI total score: at baseline 15.7 (SD 15.4; *n* = 116), after 9 months 17.8 (SD 16.7; *n* = 97) and after 18 months 20.3 (SD 15.6; *n* = 85).

Course of NPS

At baseline, aberrant motor behaviour (28.4%), agitation/aggression (23.9%) and apathy/indifference (22.4%) were the most prevalent clinically relevant symptoms, and their prevalence continued to be high or increased throughout the study (Table 2). Irritability/lability prevalence increased throughout the study. Delusions, disinhibition, euphoria/elation and hallucinations were infrequent.

Mood/apathy subsyndrome

The prevalence of the mood/apathy subsyndrome was stable throughout the study. Of the participants with dementia 72.3% had one or more symptom. The high cumulative prevalence could be largely attributed to the symptom apathy/indifference (51.2%). The cumulative incidence was 47.7% for the mood/apathy subsyndrome and 38.8% for the symptom apathy/indifference.

Hyperactivity subsyndrome

Hyperactivity was the most prevalent subsyndrome at each measurement and increased throughout the study. Of the participants with dementia 75.3% had one or more symptom. The high cumulative prevalence could be largely attributed to the symptom aberrant motor behaviour (58.8%). The cumulative incidence was highest for the subsyndrome hyperactivity (55.3%), and in particular for aberrant motor behaviour (47.0%).

Psychosis subsyndrome

Of the psychosis subsyndrome 23.5% of the participants with dementia had one or more symptoms throughout the study.

Persistence and resolution of NPI subsyndromes

Participants with dementia who had one or more symptoms of the hyperactivity or mood/apathy subsyndrome on one assessment were highly likely to still have symptoms at the next assessment. Of the 85 participants with a complete follow-up, 24.7% demonstrated at least one or more clinically relevant symptom of the hyperactivity subsyndrome and 20.0% of the

Table 2. Frequencies of clinically relevant NPI symptoms and subsyndromes (NPS ≥ 4) and CMAI subsyndromes (score ≥ 3) of patients with dementia in primary care (2012)

	Point prevalence			Cumulative prevalence	Cumulative incidence	Persistence (*n* = 85)		
	Baseline (*n* = 117)	9 months (*n* = 97)	18 months (*n* = 85)	(*n* = 85)		2 times	3 times	Resolution
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
NPI								
Mood/apathy	55 (47.4) (*n* = 116)	49 (51.0) (*n* = 96)	41 (50.0) (*n* = 82)	60 (72.3) (*n* = 83)	21 (47.7) (*n* = 44)	35 (41.7) (*n* = 84)	17 (20.0)	6 (15.4) (*n* = 39)
Dysphoria/depression	19 (16.2)	16 (16.7) (*n* = 96)	9 (10.8) (*n* = 83)	25 (30.1) (*n* = 83)	11 (15.9) (*n* = 69)	8 (9.5) (*n* = 84)	0 (0.0) (*n* = 84)	6 (42.9) (*n* = 14)
Apathy/indifference	26 (22.4) (*n* = 116)	33 (34.0)	25 (29.8) (*n* = 84)	43 (51.2) (*n* = 84)	26 (38.8) (*n* = 67)	18 (21.2)	8 (9.4)	7 (41.2) (*n* = 17)
Nighttime behaviour disturbance	22 (19.0) (*n* = 116)	14 (15.1) (*n* = 93)	13 (17.1) (*n* = 76)	25 (32.1) (*n* = 78)	12 (18.5) (*n* = 65)	6 (7.2) (*n* = 83)	2 (2.4) (*n* = 84)	3 (27.3) (*n* = 11)
Appetite/eating abnormalities	22 (18.8)	19 (19.6)	19 (22.6) (*n* = 84)	34 (40.5) (*n* = 84)	19 (27.5) (*n* = 69)	8 (9.4)	2 (2.4)	5 (33.3) (*n* = 15)
Hyperactivity	57 (48.7)	50 (51.5)	50 (58.8)	64 (75.3)	26 (55.3) (*n* = 47)	37 (43.5)	21 (24.7)	4 (10.5) (*n* = 38)
Agitation/aggression	28 (23.9)	23 (23.7)	27 (31.8)	39 (45.9)	22 (32.4) (*n* = 68)	12 (14.1)	8 (9.4)	5 (29.4) (*n* = 17)
Euphoria/elation	7 (6.0) (*n* = 116)	1 (1.0)	2 (2.4)	6 (7.1)	1 (1.3) (*n* = 80)	0 (0.0)	0 (0.0)	4 (80.0) (*n* = 5)
Irritability/lability	19 (16.2)	27 (28.1) (*n* = 96)	23 (27.1)	36 (42.4)	22 (31.0) (*n* = 71)	17 (20.0)	7 (8.2)	3 (21.4) (*n* = 14)
Disinhibition	11 (9.4)	10 (10.3)	6 (7.1)	14 (16.5)	8 (10.1) (*n* = 79)	4 (4.7)	1 (1.2)	4 (66.7) (*n* = 6)
Aberant motor behaviour	33 (28.4) (*n* = 116)	32 (33.0)	36 (42.4)	50 (58.8)	31 (47.0) (*n* = 66)	19 (22.4)	7 (8.2)	3 (15.8) (*n* = 19)
Psychosis	12 (10.3)	18 (18.6)	10 (11.8)	20 (23.5)	13 (16.7) (*n* = 78)	8 (9.4)	3 (3.5)	2 (28.6) (*n* = 7)
Delusions	12 (10.3)	14 (14.4)	9 (10.6)	18 (21.2)	11 (14.1) (*n* = 78)	7 (8.2)	3 (3.5)	3 (42.9) (*n* = 7)
Hallucinations	3 (2.6)	6 (6.2)	4 (4.7)	6 (7.1)	5 (6.0) (*n* = 84)	1 (1.2)	1 (1.2)	0 (0.0) (*n* = 1)
Anxiety	20 (17.1)	18 (18.8) (*n* = 96)	13 (15.3)	28 (33.3) (*n* = 84)	13 (18.8) (*n* = 69)	12 (14.1)	5 (5.9)	6 (40.0) (*n* = 15)
CMAI subsyndromes								
Physically aggressive	28 (23.9)	23 (23.7)	35 (41.2)	58 (49.6)	30 (40.0)	13 (15.3)	33 (38.8)	6 (31.6)
Physically non-aggressive	72 (61.5)	56 (57.7)	60 (70.6)	97 (82.9)	25 (58.1)	8 (9.4)	59 (69.4)	4 (8.5)
Verbally agitated	82 (70.1)	70 (72.2)	60 (70.6)	103 (88.0)	21 (63.6)	48 (56.5)	41 (48.2)	5 (9.3)

CMAI: Cohen-Mansfield Agitation Inventory; *n*: number of subjects; NPI: Neuropsychiatric Inventory; NPS: neuropsychiatric symptoms

Point prevalence: the proportion of patients with specific symptoms at each assessment; Cumulative prevalence: the proportion of patients developing a symptom on at least one assessment over the 18-month study period; Cumulative incidence: the proportion of patients who were symptom-free at baseline but developed the symptom at subsequent assessments; Persistence: symptom was present on at least two subsequent assessments, regardless of time of the first manifestation and persistence of NPS during all 3 assessments; Resolution: the proportion of patients who showed a specific symptom at baseline but not at the next assessments.

mood/apathy subsyndrome at all assessments. Aberrant motor behaviour (22.4%) and apathy/indifference (21.2%) showed the highest persistence for two consecutive measurements.

Euphoria/elation (80.0%) and disinhibition (66.7%) are the clinically relevant symptoms of the hyperactivity subsyndrome which are most likely to be present at baseline but not at the next two assessments. For the mood/apathy subsyndrome these symptoms are dysphoria/depression (42.9%) and apathy/indifference (41.2%) and for the psychosis subsyndrome it is delusions (42.9%). The symptom anxiety (40.0%) is also likely to be present at one measurement but not at the next two assessments.

CMAI subsyndromes

Verbally agitated subsyndrome was the most prevalent subsyndrome of the CMAI at each measurement and remained stable throughout the study. The prevalence rates of symptoms of the physically aggressive and non-aggressive subsyndromes of the CMAI increased between 9 and 18 months of follow-up. Throughout the study 88.0% of the participants with dementia had one or more verbally agitated symptoms, 82.9% one or more symptoms of the physically non-aggressive subsyndrome compared to 49.6% of the physically aggressive subsyndrome. For the CMAI the cumulative incidence was highest for the verbally agitated subsyndrome (63.3%), but the cumulative incidence for the physically non-aggressive subsyndrome was almost as high (58.1%). Participants with dementia who had one or more symptoms of the physically non-aggressive subsyndrome of the CMAI at baseline were highly likely to have symptoms again at the next two assessments (69.4%). This was also high for the verbally agitated subsyndrome (48.2%) and the physically aggressive subsyndrome (38.8%). The symptoms of the physically aggressive subsyndrome of the CMAI were most likely to be present at baseline but not at the next two assessments.

Multivariate analysis of determinants

The majority of the multivariate analysis of determinants did not show statistically significant results. For the NPI subsyndrome mood/apathy, we found a significant different course in time for cognition of the patient ($p = 0.02$), participation in CONCERN ($p = 0.005$) and for respite care ($p = 0.002$) and for the CMAI subsyndrome physically aggressive behaviour for relationship of the informal caregiver to the patient ($p = 0.000$). All results are shown in Table S1 and Figure S1, available as supplementary material.

DISCUSSION

In this prospective naturalistic cohort study in primary care, we found that 72.3% of the participants with dementia had one or more symptoms of the NPI mood/apathy subsyndrome and 75.3% of the hyperactivity subsyndrome. Almost 50% of the participants with dementia

without one or more symptoms of the mood/apathy and hyperactivity subsyndrome at baseline measurements developed these at subsequent measurements. The symptoms aberrant motor behaviour, apathy/indifference and in a slightly lesser degree agitation/aggression occurred frequently and were persistent. Most participants with dementia remained free of symptoms of the psychosis subsyndrome. Euphoria/elation, disinhibition, dysphoria/depression, apathy/indifference, delusions and anxiety are the symptoms that are most likely to resolve. The verbally agitated subsyndrome was the most prevalent subsyndrome of the CMAI, 88.0 % of the people with dementia had one or more verbally agitated symptoms and 82.9 % one or more physically non-aggressive symptoms. We found a different course in time for participation in CONCERN for the NPI subsyndrome mood/apathy specifically between baseline and after 9 months of follow-up, but in our opinion it is not possible to differentiate the relevance of this in clinical practice.

Comparison with the literature

Except for delusions, the most prevalent individual symptoms in our study were aberrant motor behaviour, apathy/indifference and agitation/aggression with increasing point prevalence rates, which is in accordance with former studies.[4]

This study confirms our hypothesis that a study population visiting outpatient clinical centres in the Netherlands have more severe and frequent symptoms than the total group of people with dementia in primary care. In the Dutch MAASBED study there was a higher occurrence of all subsyndromes, but the most prevalent and incident symptoms were similar.[5]

Individual clinically relevant NPS in community-dwelling people with dementia in Australian Memory Clinics and in the DelpHi-Study (Dementia: life- and person-centered help) were less prevalent than among people with dementia in primary care in our study. This is probably a selection issue as the Australian study population partly consisted of people with mild cognitive impairment[6] and in the DelpHi-Study after screening only 46 % of the people with dementia had a diagnosis of dementia before the start of the study.[40]

Strengths and limitations

In this study patients and informal caregivers were included from general practices. The sample was heterogeneous with patients in all stages of dementia. Dyads were followed beyond admission to a long-term care facility. The lost to follow-up rate during 18 months was low.

Limitations of our study are the rather low participation of general practices (114 invited, 18 participated) and the difference between the participants and non-participants which indicates selection bias. Moreover, general practices and dyads who participated in CONCERN are different from those who did not and this also might result in selection bias. This might affect the prevalence, incidence and persistence of symptoms. Another limitation is that there are three assessments during the follow-up period of 18 months. Variations in

NPS between two successive assessments are unknown. Finally, there were missing data for the MMSE at baseline. We assumed that 6 patients without MMSE scores in all 3 measurements have low MMSE scores (0 - 9) because they visited day care centres and used home care services and four of these patients were admitted to a LTCF after baseline and before T1 measurements. This may have led to misclassification bias.

For the CMAI we categorized the items in three subsyndromes in line with a previous study in Dutch nursing homes, because our study population was too small to perform a factor analysis. We assumed that the factor structure would be the same for our Dutch primary care population.

Implications

The results of this study showed that NPS of the subsyndromes hyperactivity and mood/apathy, and specifically aberrant motor behaviour, apathy/indifference and agitation/aggression, are highly prevalent, incident and persistent in Dutch people with dementia in primary care. NPS are associated with psychological distress in informal caregivers of people with dementia in primary care.

Consequently, GPs should be aware of this and should actively identify these symptoms when they visit these patients or when informal caregivers consult them about these patients or for themselves. Timely diagnosing NPS facilitates adequate professional care, that might either train caregivers to prevent those symptoms to deal with them in an effective way or to look for additional assistance. This probably enables people with dementia to remain longer in their own environment and reduce their informal caregivers' psychological distress.

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Table S1. Multivariable analysis of the determinants of clinically relevant NPS over time of patients with dementia (Linear Mixed Model)

	NPI Mood/Apathy				CMAI physically aggressive behaviour			
		Fixed effects				Fixed effects		
All patients including lost to follow-up	**Sign.[a]**	**Estimates**	**95% CI**	**Sign.[b]**	**Sign.[a]**	**Estimates**	**95% CI**	**Sign.[b]**
measurement	0.81							
measurement = 1 (Ref measurement = 3)		1.04	-11.4 - 13.4	0.868		-7.9	-13.2 - -2.7	0.003*
measurement = 2 (Ref measurement = 3)		14.80	2.0 - 27.6	0.024*		-10.9	-16.4 - -5.4	0.000*
Age patient	0.583				0.645			
< 70 years (Ref > 80 years)		2.42	-2.0 - 6.8	0.281		-1.13	-2.7 - 0.5	0.168
70 - 80 years (Ref > 80 years)		-1.04	-4.1 - 2.0	0.504		0.18	-0.9 - 1.3	0.751
Gender patient	0.056				0.088			
Male (Ref female)		3.06	0.1 - 6.0	0.044*		0.79	-0.3 - 1.9	0.155
Relationship	0.530				0.023*			
Spouse (Ref Other)		4.45	-2.0 - 10.9	0.174		-5.22	-7.6 - -2.8	0.000*
Child (Ref Other)		4.44	-1.9 - 10.7	0.166		-6.02	-8.3 - -3.7	0.000*
Cognition patient	0.322				0.033*			
MMSE 0 - 9 (Ref 20 - 30)		3.85	-0.2 - 7.9	0.064		1.50	0.0 - 3.0	0.048*
MMSE 10 - 19 (Ref 20 - 30)		0.49	-2.7 - 3.7	0.768		-0.02	-1.2 - 1.2	0.970
Psychotropic drug use	0.983				0.534			
> 0 (Ref None)		-0.69	-3.4 - 2.0	0.615		0.56	-0.4 - 1.5	0.267
CONCERN	0.177				0.531			
Yes (Ref CONCERN no)		0.18	-2.4 - 2.8	0.890		-0.87	-1.8 - 0.1	0.074
Respite care	0.984				0.739			
Yes (Ref Respite care No)		-3.30	-6.4 - -0.2	0.036*		0.48	-0.7 - 1.6	0.407
Personal health care	0.391				0.416			
Yes (Ref Personal health care No)		1.63	-1.7 - 5.0	0.342		-0.24	-1.5 - 1.0	0.709
SCQ total score	0.000*				0.039*			
		-0.10	-0.2 - 0.0	0.033*		-0.04	-0.1 - 0.0	0.031*

Table S1. Multivariable analysis of the determinants of clinically relevant NPS over time of patients with dementia (Linear Mixed Model) (continued)

	NPI Mood/Apathy				CMAI physically aggressive behaviour			
		Fixed effects				Fixed effects		
All patients including lost to follow-up	**Sign.[a]**	**Estimates**	**95% CI**	**Sign.[b]**	**Sign.[a]**	**Estimates**	**95% CI**	**Sign.[b]**
measurement*age patient	0.194				0.422			
measurement = 1*age patient < 70 years		0.67	-3.9 - 5.3	0.772		1.60	-0.4 - 3.6	0.109
measurement = 1*age patient 70 - 80 years		2.63	-0.6 - 5.8	0.105		0.00	-1.4 - 1.4	0.996
measurement = 2*age patient < 70 years		-3.12	-7.8 - 1.5	0.188		1.51	-0.5 - 3.5	0.139
measurement = 2*age patient 70 - 80 years		0.59	-2.7 - 3.9	0.721		0.27	-1.1 - 1.7	0.704
measurement*gender patient	0.475				0.815			
measurement = 1*gender patient Male		-0.74	-3.8 - 2.3	0.636		-0.41	-1.7 - 0.9	0.539
measurement = 2*gender patient Male		-1.92	-5.1 - 1.2	0.230		-0.13	-1.5 - 1.2	0.848
measurement*relationship	0.572				0.000*			
measurement = 1*relationship Spouse		-3.40	-10.0 - 3.2	0.313		4.96	2.2 - 7.8	0.001*
measurement = 1*relationship Child		-1.72	-8.2 - 4.8	0.602		4.61	1.9 - 7.4	0.001*
measurement = 2*relationship Spouse		-3.09	-10.0 - 3.9	0.381		6.81	3.8 - 9.8	0.000*
measurement = 2*relationship Child		-3.65	-10.4 - 3.1	0.290		7.62	4.7 - 10.5	0.000*
measurement*cognition patient	0.023*				0.407			
measurement = 1*cognition patient MMSE 0 - 9		-3.83	-8.1 - 0.4	0.076		-1.39	-3.2 - 0.4	0.133
measurement = 2*cognition patient MMSE 10 - 19		-1.49	-4.8 - 1.9	0.382		-0.52	-1.9 - 0.9	0.474
measurement = 1*cognition patient MMSE 0 - 9		-5.87	-10.2 - -1.6	0.008*		0.28	-1.6 - 2.1	0.767
measurement = 2*cognition patient MMSE 10 - 19		-4.55	-8.0 - -1.1	0.009*		-0.06	-1.5 - 1.4	0.934
measurement*psychotropic drug use	0.710				0.322			
measurement = 1*psychotropic drug use > 0		0.84	-2.0 - 3.6	0.554		-0.86	-2.0 - 0.3	0.158
measurement = 2*psychotropic drug use > 0		1.16	-1.7 - 4.0	0.420		-0.22	-1.4 - 1.0	0.724

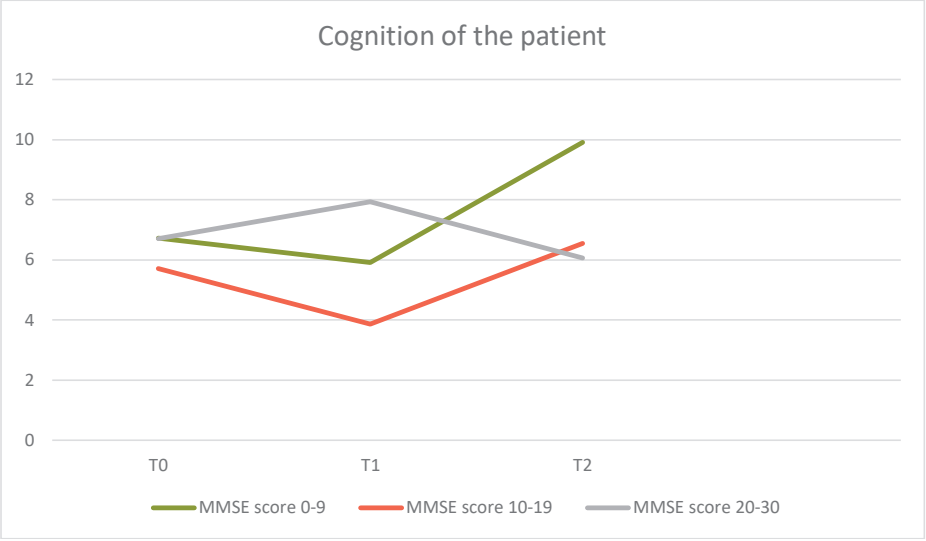
Table S1. Multivariable analysis of the determinants of clinically relevant NPS over time of patients with dementia (Linear Mixed Model) (continued)

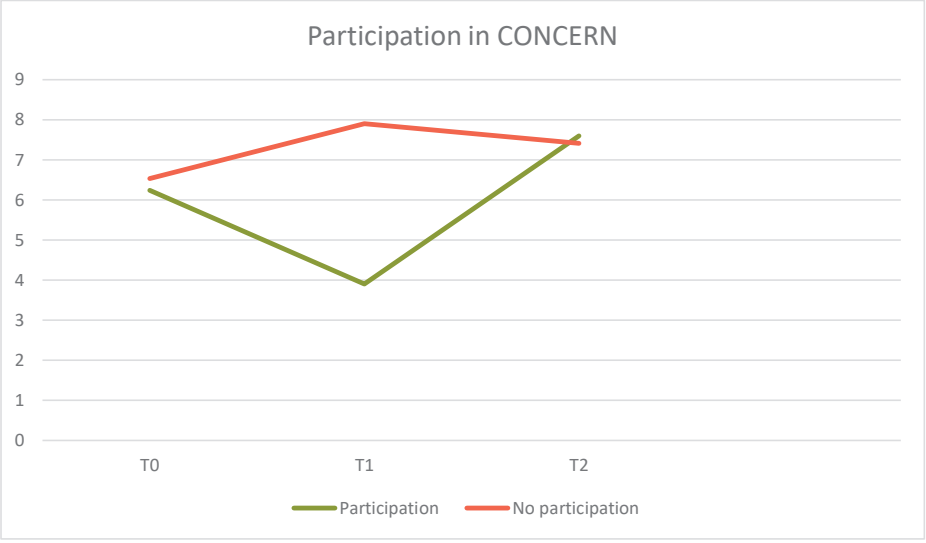
	NPI Mood/Apathy				CMAI physically aggressive behaviour			
		Fixed effects				Fixed effects		
All patients including lost to follow-up	**Sign.[a]**	**Estimates**	**95% CI**	**Sign.[b]**	**Sign.[a]**	**Estimates**	**95% CI**	**Sign.[b]**
measurement*CONCERN	0.005*				0.158			
measurement = 1*CONCERN Yes		-0.48	-3.2 - 2.2	0.727		0.98	-0.2 - 2.1	0.099
measurement = 2*CONCERN Yes		-4.2	-7.0 - -1.4	0.003*		1.04	-0.2 - 2.2	0.087
measurement*respite care	0.002*				0.277			
measurement = 1*respite care Yes		4.11	0.9 - 7.3	0.012*		-0.09	-1.4 - 1.3	0.901
measurement = 2*respite care Yes		5.9	2.6 - 9.1	0.001*		-0.99	-2.4 - 0.4	0.165
measurement*personal health care	0.459				0.340			
measurement = 1*personal health care Yes		-1.79	-5.3 - 1.7	0.313		1.10	-0.4 - 2.6	0.143
measurement = 2*personal health care Yes		0.10	-3.5 - 3.7	0.957		0.58	-1.0 - 2.1	0.463
measurement*SCQ total score	0.050				0.481			
measurement = 1*SCQ total score		-0.01	-0.1 - 0.1	0.873		0.19	0.0 - 0.1	0.349
measurement = 2*SCQ total score		-0.10	-0.2 - -0.0	0.033*		0.02	0.0 - 0.1	0.248

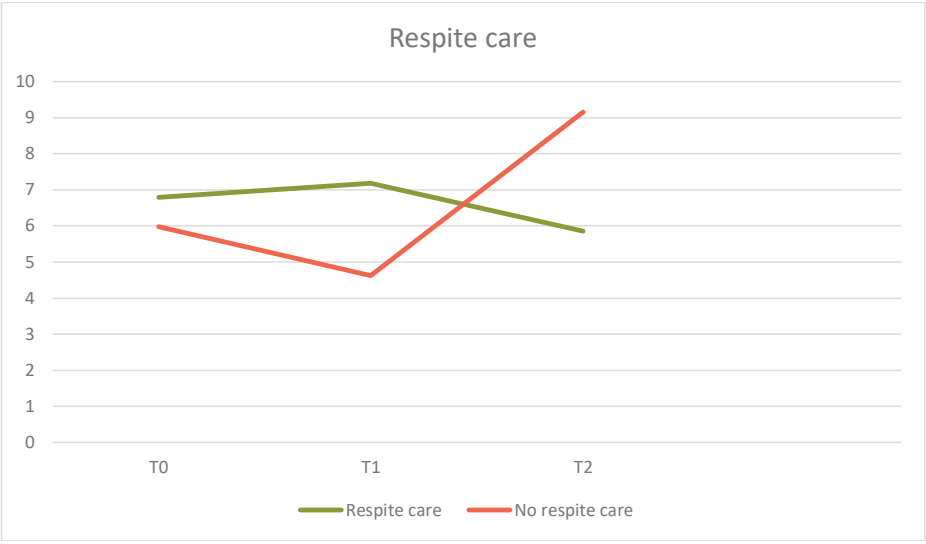
CI: confidence interval; CMAI: Cohen-Mansfield Agitation Inventory; CONCERN: Care Optimization for Non-professional Caregivers of Elderly with dementia and Reduction of Neuropsychiatric symptoms; MMSE: Mini-mental State Examination; NPI: Neuropsychiatric inventory; NPS: Neuropsychiatric symptoms; SCQ: Sense of Competence Questionnaire; Sign: significance; [a]Type III test of fixed effects: F-test; [b]Estimates of fixed effects: t-test;

* statistically significant $p < 0.05$

NPI subsyndrome Mood/apathy score







CMAI subsyndrome Physically aggressive behaviour score

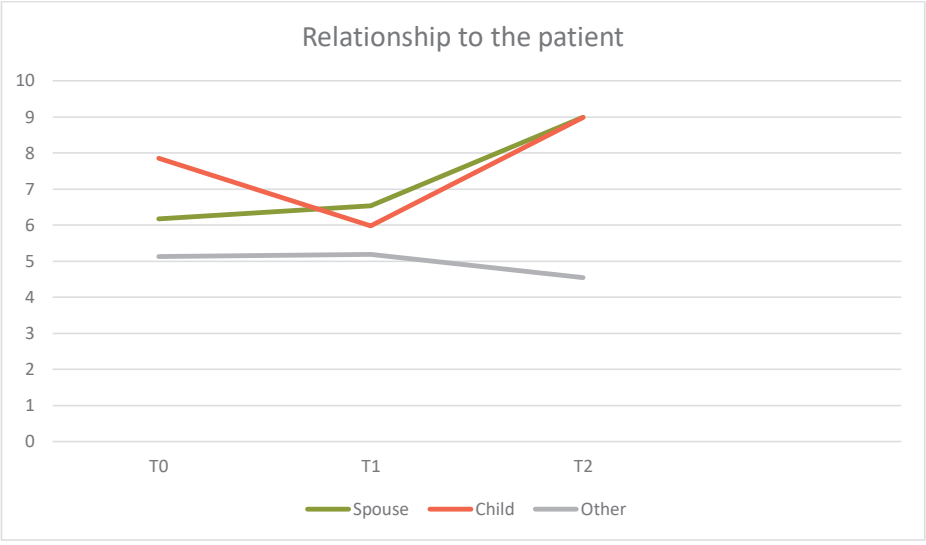


Figure S1. Multivariate analysis of determinants of the course of NPS in patients with dementia in primary care (2012)

CMAI, Cohen-Mansfield Agitation Inventory; MMSE, Mini-mental State Examination; NPI, Neuropsychiatric Inventory; NPS, neuropsychiatric symptoms; T0 = baseline measurements; T1 = after 9 months; T2 = after 18 months

Estimated values of NPI subsyndrome and CMAI subsyndrome scores of the random intercept mixed model with time are displayed on a scale of 0 to 10.

CHAPTER 6

Psychological distress in informal caregivers of patients with dementia in primary care: course and determinants

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ABSTRACT

Background

The course of psychological distress in informal caregivers of patients with dementia has been investigated in longitudinal studies with conflicting outcomes.

Objectives

We investigated the course and determinants of psychological distress in informal caregivers of patients with dementia in primary care.

Methods

In this prospective observational cohort study, data were collected at baseline, after 9 and 18 months. We assessed cognition and neuropsychiatric symptoms (NPS) of the patient (Mini-Mental State Examination and Neuropsychiatric Inventory) and psychological distress (Sense of Competence questionnaire, Center for Epidemiological Studies Depression scale and General Health Questionnaire1-item version) of the informal caregivers. Determinants for the course of psychological distress were caregivers' age, gender and relationship with the patient, patients' cognition and NPS, participation in a care program and admission to long term care facilities (LTCF). With linear mixed models, the course over time for psychological distress and its determinants were explored.

Results

We included 117 informal caregivers, of whom 23.1% had a high risk for depression and 41.0% were identified to be likely to have mental problems at baseline. We found a stable pattern of psychological distress over time. Higher frequency of NPS, informal caregivers' age between 50 - 70 years and being female or spouse were associated with higher psychological distress. For patients who were admitted to a LTCF during the study psychological distress of the informal caregivers improved.

Conclusions

General practitioners should focus on NPS in patients with dementia and on caregivers' psychological distress and be aware of their risk for depression and mental problems, specifically to those who are spouse, female or between 50 - 70 years of age.

INTRODUCTION

Worldwide approximately 47.5 million people have dementia with 7.7 million new cases every year.[1] The total number is expected to increase to 75.6 million in 2030 and almost triple by 2050.[1] In the Netherlands there are 260.000 people with dementia of whom approximately 70% live in the community. Sixty percent of them live with their informal caregiver and 40% alone.[2,3] In the next decades the percentage of people with dementia living in the community will increase due to preference of older people to remain in their own homes for as long as possible and the economic burden associated with residential or nursing home care.[4]

Informal caregivers are at risk for deterioration of their mental health. This psychological distress in informal caregivers includes feelings of burden and depressive and anxiety disorders.[5,6] Prevalence rates of depressive disorders range from 15 to 80% with higher prevalence rates for female caregivers (38% versus 10%).[5-7]

Understanding the course and determinants of psychological distress is important to prevent or diminish it. The course has been investigated in some longitudinal studies with conflicting outcomes: increase, decrease or no changes.[8-15] Most of the longitudinal studies were performed in cohorts of ambulatory patients visiting outpatient clinical centres.[9-14] It is likely that these patients have more neuropsychiatric symptoms (NPS) and psychological distress in informal caregivers is higher.

Determinants of psychological distress have been investigated in cross-sectional studies. Patient characteristics associated with increased distress are NPS, decline in instrumental ADL (IADL) abilities, severity of cognitive impairment, (male) gender and young onset dementia.[16-20] The association of distress with NPS differs with type of NPS and it does not depend on frequency and severity of NPS.[21] Caregiver characteristics associated with more psychological distress in cross-sectional studies are (younger) age, (female) gender, (lower) educational level/socio-economic status, longer duration of caregiving and caregiver-patient relationship.[16,17]

Determinants of the course of psychological distress have also been investigated in longitudinal studies. Higher frequency of NPS, deterioration of dementia and patients' functional decline are related to an increase in psychological distress over time. NPS are the most significant contributors to the course of psychological distress.[8-12,15,19,20] Although depression, aggression, and sleep disturbances are the most frequently identified NPS to impact negatively on caregivers, a wide range of NPS is associated with psychological distress and the evidence is not conclusive as to whether some NPS are more important than others.[22] High baseline burden, living with the patient, decline in IADL of the patient and poor mental health of the caregiver are caregiver characteristics associated with increasing psychological distress over time.[8-12]

In this study, we aimed to investigate the course and determinants of psychological distress in informal caregivers of patients with dementia in primary care. This knowledge is important for the general practitioner (GP) who is most often the first physician consulted for dementia-related problems for both the patient and informal caregiver.

METHODS

This study was a prospective naturalistic observational cohort study with a follow-up of 18 months. In the south of the Netherlands, 192 GPs of 114 general practices were invited to participate of whom 37 GPs in 18 general practices participated. Follow-up was continued after admission to a long-term care facility (LTCF). Detailed information of the design has been published elsewhere.[23]

Patients and informal caregivers

Patients and their informal caregivers were recruited from January until July 2012. Inclusion criteria for patients were living at home and registered in the GP's electronic medical system with codes of International Classification of Primary Care (ICPC) for dementia (P70) or memory disturbance (P20). Patients living in a LTCF or with an estimated life expectancy of < 3 months were excluded. Patients, or their legal representatives, and caregivers gave written informed consent.

Assessment instruments

Baseline demographics were collected by a trained research assistant at patients' homes at baseline (T0), at 9 months (T1) and 18 months (T2). Cognition and NPS of the patient were assessed with the Mini-Mental State Examination (MMSE) ranging from 0 to 30, and with Neuropsychiatric Inventory (NPI) ranging from 0 to 144. The NPI consists of 12 categories of NPS: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, sleeping disorder and eating disorder. For each positive symptom, the severity and frequency are scored on the basis of structured questions administered to the patients' caregiver. The continuous score for each symptom is obtained by multiplying severity (1 - 3) by frequency (1 - 4).[24-27] For the assessment of psychological distress the Sense of Competence Questionnaire (SCQ), the Center for Epidemiological Studies Depression scale (CES-D) and the Likert scoring of the General Health Questionnaire 12-tem version (GHQ-12) were used.[28-38] For the SCQ (range 27 - 135) higher scores indicate lower feelings of burden; for the CES-D (range 0 - 60) and GHQ-12 (range 0 - 36) lower scores indicate better mental health. A difference score of five points on the SCQ was considered clinically relevant.[39] For the CES-D a score ≥ 16 is associated with

higher risk of depression.[32,33] There are no generally accepted cut-off scores for the GHQ-12 Likert scale (0 - 1 - 2 - 3). GHQ-12 scoring for screening (0 - 0 - 1 - 1) has a cut-off score of ≥ 2.[40]

Two items of the SCQ and four of CES-D worded in the positive direction were recoded.[32] For missing items we used ipsative mean imputation for the SCQ, CES-D, GHQ-12 and NPI and last observation carried backward for the MMSE.[39,41] We accepted one missing item for each subscale of the SCQ[42], two missing items in the CES-D (10 % missing) and GHQ-12[34] and one missing item in the NPI (10 % missing). Therefore, we had to exclude two SCQ's, one GHQ-12 and two NPI questionnaires. Six patients had no MMSE because it was too stressful or because of absence due to stay at day care centres. It was assumed for these patients to have a low MMSE score 0 - 9 because they visited day care centres and used home care services and four of these patients were admitted to a LTCF after baseline and before T1 measurements. Eight patients were lost to follow-up. Therefore, at baseline the numbers of patients in the different subgroups were as follows: MMSE score 0 - 9; *n* = 15 (13.8 %); score 10 - 19; *n* = 31 (28.4 %); score 20+; *n* = 63 (57.8 %).

Information on the use of care services, such as day care centres, home care services, domestic care and case management, was collected. Day care centres can provide support and activities for people with dementia and provide respite for informal caregivers. Home care services include personal care and health care. Domestic care includes several household tasks that patients may require help with. In the Netherlands (medical) care for community-dwelling people with dementia is primarily provided by the GP. Further help can be provided by a case manager (CM), which involves assessment, planning and advocacy for people with dementia and their informal caregivers. This is available in all parts of the country. In this study, in 14 of the 18 general practices, a special care program called Care Optimization for Non-professional Caregivers of Elderly with dementia and Reduction of Neuropsychiatric symptoms (CONCERN) was provided. In CONCERN a GP, CM and an elderly care physician systematically collaborate to improve dementia care in order to reduce NPS.[23] Participation in CONCERN was by choice of the patients and caregivers and started after baseline measurements. Other participants received care as usual only by the GP or also by a CM as single component care.

Data analysis

Data were analysed using the Statistical Package for Social Science 20.0. We used descriptive statistics for data at T0, T1 and T2. Analysis of variance, chi-square tests and *t*-tests were used to analyse differences between patient and caregiver (dyads) who completed the study and those who were lost to follow-up, and between patients with and without admission to a LTCF during follow-up.

To take into account the clustering of measurements within patients and the clustering of patients within a general practice, linear mixed models with random intercept were used. Dependent variables were SCQ, CES-D and GHQ-12 (psychological distress). Determinants

were caregivers' age and gender, patient-caregiver relationship, NPS and patients' cognition.[8-12] Other determinants were participation in CONCERN and admission to a LTCF. No linear relationship was found between age of the caregiver and cognition of the patient with the dependent variables. Age of the caregiver was categorized in three subgroups: < 50, 50 - 70 and > 70 years of age because the group 50 - 70 refers to the sandwich generation. Cognition of the patient was categorized in three subgroups each of one third cut off range of seriousness of the MMSE score: 0 - 9, 10 - 19 and 20 - 30.

To investigate course over time of caregiver burden a model with time as an independent variable was used. Interaction terms of time with patient and caregiver characteristics were added to the model to investigate differences in course over time of caregiver burden between subgroups of patients and caregiver dyads. We removed all non-significant interaction terms ($p > 0.05$) manually using a stepwise backward selection procedure.

RESULTS

The flowchart of the study population is shown in Figure 1. The 126 patients who refused or were withdrawn were more often female; informal caregivers of these patients were more often child. Two patients, who were admitted to a LTCF after informed consent and just before baseline assessment entered the study and the baseline questionnaires were filled out for the situation as before institutionalization.

Table 1 shows patient and caregiver characteristics for patients at all measurements. The study population was homogenous concerning race: 98% Caucasian and 2% other. Patients lost to follow up ($n = 32$; 27.4% in 18 months) were older (80.8 versus 77.8 years; $p = 0.038$) and used more care services (65.6% versus 41.2%; $p = 0.018$) at baseline than those who completed the study ($n = 85$).

Twenty-one patients were admitted to a LTCF between T0 and T1 and 4 patients between T1 and T2. Of these 25 patients 15 completed the study. Caregivers of patients admitted to a LTCF during follow-up were statistically different at baseline on relationship ($p = 0.017$): they were less often spouse (44.0% versus 70.7%) and more often child (52.0% versus 22.8%). SCQ mean scores were lower (92.0 versus 100.5; $p = 0.033$) and CES-D mean scores (16.0 versus 9.0; $p = 0.001$) and GHQ-12 mean scores (15.0 versus 10.8; $p < 0.001$) were higher indicating higher psychological distress. Patients admitted to a LTCF used more home care services (88.0% versus 37.0%; $p < 0.001$) and had higher NPI total scores (24.2 versus 13.4; $p < 0.001$) at baseline.

Caregivers who participated in CONCERN had statistically significant lower SCQ mean scores at baseline (95.7 versus 101.7; $p = 0.041$). Patients who participated in CONCERN were different at baseline on gender ($p = 0.033$): they were more often male (57.6% versus

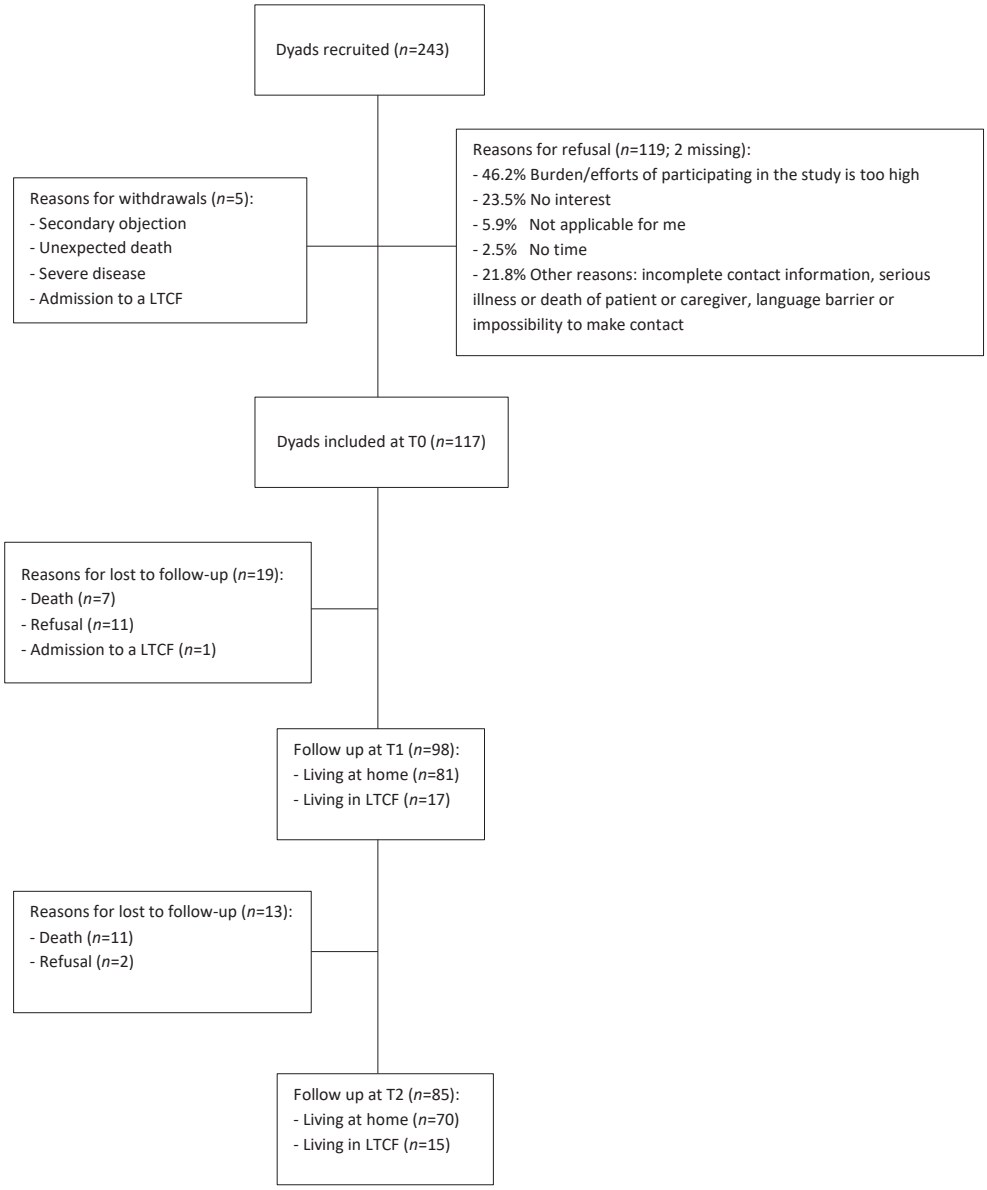

Figure 1. Flowchart study population

Dyads: patient and caregiver; LTCF: Long term care facility; *n*: number of subjects; T0: baseline; T1: after 9 months; T2: after 18 months.

Table 1. Characteristics of patients with dementia and informal caregivers (*n* = 117)

				Lost to follow-up	LTCF	CONCERN	Refusal + Withdrawn
	Baseline (*n* = 117)	**9 months (*n* = 98)**	**18 months (*n* = 85)**	**Baseline (*n* = 32)**	**Baseline (*n* = 25)**	**Baseline (*n* = 59)**	**(*n* = 126)**
Caregiver characteristics							
Age, y (SD) [range][a]	67.3 (13.3) [32 - 92]	68.5 (12.4) [40 - 93]	69.7 (11.7) [43 - 90]	64.9 (16.7) [32 - 92]	63.3 (12.1) [46 - 87]	67.5 (13.0) [32 - 88]	66.0 (14.0)[28 - 92] [n = 95]
Sex							
Male (%)	37 (31.6%)	31 (31.6%)	26 (30.6%)	11 (34.4%)	4 (16.0%)	16 (27.1%)	41 (33.1%) [n = 124]
Female (%)	80 (68.4%)	67 (68.4%)	59 (69.4%)	21 (65.6%)	21 (84.0%)	43 (72.9%)	84 (66.9%) [n = 124]
Relationship					*		
Spouse (%)	76 (65.0%)	65 (66.3%)	58 (68.2%)	18 (56.2%)	11 (44.0%)	41 (69.5%)	60 (49.2%) [n = 122]
Child (%)	34 (29.1%)	28 (28.6%)	23 (27.1%)	11 (34.4%)	13 (52.0%)	15 (25.4%)	55 (45.1%) [n = 122]
Other (%)	7 (5.9%)	5 (5.1%)	4 (4.7%)	3 (9.4%)	1 (4.0%)	3 (5.1%)	7 (5.7%) [n = 122]
Level of profession							
Elementary occupation(%)	20 (17.1%)	16 (16.3%)	16 (18.8%)	4 (12.5%)	4 (16.0%)	14 (23.7%)	
Lower occupation (%)	13 (11.1%)	11 (11.2%)	10 (11.8%)	3 (9.4%)	0 (0.0%)	6 (10.2%)	
Secondary profession (%)	39 (33.3%)	30 (30.6%)	25 (29.4%)	14 (43.8%)	7 (28.0%)	16 (27.1%)	
Higher profession (%)	31 (26.5%)	30 (30.6%)	25 (29.4%)	6 (18.8%)	10 (40.0%)	16 (27.1%)	
Scientific profession (%)	14 (12.0%)	11 (11.2%)	9 (10.6%)	5 (15.6%)	4 (16.0%)	7 (11.9%)	
SCQ, mean (SD) [range]	98.7 (15.9) [40 - 128]			98.5 (17.0) [32 - 92]	92.0 (17.0) [58 - 128]*	95.7 (16.5) [40 - 127]*	
CES-D, mean (SD) [range]	10.5 (7.8) [0 - 40]			12.0 (8.6) [0 - 31]	16.0 (8.9) [1 - 31]*	10.4 (7.2) [0 - 40]	

Table 1. Characteristics of patients with dementia and informal caregivers (*n* = 117) (continued)

				Lost to follow-up	LTCF	CONCERN	Refusal + Withdrawn
	Baseline (*n* = 117)	**9 months (*n* = 98)**	**18 months (*n* = 85)**	**Baseline (*n* = 32)**	**Baseline (*n* = 25)**	**Baseline (*n* = 59)**	**(*n* = 126)**
Patient characteristics							
Age, y (SD) [range]	78.6 (7.1) [57 - 91]	79.2 (7.0) [58 - 92]	79.3 (7.0) [59 - 92]	80.8 (6.9) [65 - 91]*	80.9 (6.9)[68 - 91]	78.3 (7.9) [57 - 91]	79.2 (6.8) [63 - 92]
Sex						*	
Male (%)	56 (47.9%)	49 (50.0%)	45 (52.9%)	11 (34.4%)	13 (52.0%)	34 (57.6%)	42 (33.3%)
Female (%)	61 (52.1%)	49 (50.0%)	40 (47.1%)	21 (65.6%)	12 (48.0%)	25 (42.4%)	84 (66.7%)
MMSE total score, mean (SD)[b]	19.5 (5.6) [n = 97]	19.6 (6.9) [n = 70]	15.1 (9.4) [n = 63]	18.4 (6.6) [n = 24]	17.81 (4.2) [n = 16]	19.7 (5.5) [0 - 27]	
NPI total score, mean (SD)	15.7 (15.4) [n = 116]	17.8 (16.7) [n = 97]	20.3 (15.6)	18.8 (18.9) [n = 31]	24.2 (21.0)*	15.6 (14.6) [0 - 63]	
LTCF (%)[c]		17 (17.3%)	15 (17.6%)	10 (31.2%)			
Use of care services							
CONCERN (%)	59 (50.4%)	48 (49.0%)	45 (52.9%)	14 (43.8%)	9 (36.0%)	59 (100%)	
Case manager (%)[d]	34 (29.3%) [n = 116]	23 (57.5%) [n = 40]	17 (54.8%) [n = 31]	9 (29.0%) [n = 31]	3 (12.0%)*	8 (13.6%)*	
Day care centres (%)[e]	40 (34.2%)	38 (46.3%) [n = 82]	33 (47.1%) [n = 70]	10 (31.2%)	12 (48.0%)	17 (28.8%)	
Home care services (%)[e]	56 (47.9%)	33 (40.2%) [n = 82]	28 (40.0%) [n = 70]	21 (65.6%)*	22 (88.0%)*	24 (40.7%)	
Domestic care (%)[e]	56 (47.9%)	40 (48.8%) [n = 82]	34 (48.6%) [n = 70]	14 (43.8%)	16 (64.0%)	2339.0%)	

n: number of subjects. [a]Age at baseline: <50 12.8%, 50 - 70 35.9% and > 70 years 51.3%. [b]Cognition at baseline (n = 109): score 0 - 9 13.8%, score 10 - 19 28.4% and score 20 - 30 57.8%, range 0 - 27. [c]LTCF: patients with admission to a LTCF with complete data. [d]CM is part of care as usual but not applied to patients with LTCF admission. [e]Day care facilities, home care services or domestic care is not applied to patients with LTCF admission. * $p < 0.05$.

37.9%). Caregivers and patients who participated in CONCERN were less often supported by a CM at baseline (13.8% versus 44.8%; $p < 0.001$).

The percentage of informal caregivers with a clinically relevant difference (≥ 5) on the SCQ between T0-T1 was 69.0% (*n* = 67). Of these informal caregivers 41.2% (*n* = 40) improved and 27.8% (*n* = 27) declined. At baseline 23.1% (*n* = 27) of informal caregivers had a high risk for depression (CES-D score ≥ 16) and 41.0% (*n* = 48) were identified to be likely to have mental problems (GHQ-12 screening 0 - 0 - 1 - 1 score ≥ 2).

Course of SCQ, CES-D and GHQ-12

The mean scores of SCQ, CES-D and GHQ-12 at each assessment for the whole group of dyads showed little change over time in 18 months with only a significantly improved but clinically not relevant SCQ score (3.4 points) between T0 and T1 (Table 2).

Table 2. Estimated marginal means of psychological distress in informal caregivers of patients with dementia (*n* = 117)

	T0			T1				T2			
	n	Mean	95% CI	*n*	Mean	95% CI	Significance T0-T1	*n*	Mean	95% CI	Significance T0-T2
SCQ	115	98.7	96.0 - 101.5	97	102.1	99.2 - 105.0	*P* = 0.019	84	99.8	96.8 - 102.8	*P* = 0.474
CES-D	117	10.3	8.6 - 12.1	98	9.8	7.9 - 11.6	*P* = 0.410	85	11.4	9.5 - 13.3	*P* = 0.142
GHQ-12	116	11.5	10.5 - 12.6	98	11.4	10.4 - 12.5	*P* = 0.864	85	12.2	11.1 - 13.3	*P* = 0.154

CI: confidence interval; *n*: number of informal caregivers; T0: baseline; T1: after 9 months; T2: after 18 months; T0-T1: between baseline and 9 months; T0-T2: between baseline and 18 months.

Multivariate analysis of determinants

Results of the multivariate analysis with linear mixed models are shown in Table 3. The first column of each dependent variable indicates whether there is a significant relation between the determinant and the dependent variable. The fixed effects estimates in the second column and the statistical significance in the fourth column of each dependent variable indicates the difference in score between the subgroup of the determinant and the reference group of the dependent variable and whether this difference is significant.

Informal caregivers' age, gender, relationship to the patient, admission of the patient to LTCF and patients' NPS were statistically significant related to psychological distress. Statistically significant and clinically relevant lower scores of SCQ and statistically significant higher scores of CES-D were found in informal caregivers' age group 50 - 70 years compared to age group > 70 years. Statistically significant lower CES-D and GHQ-12 scores were found in male compared to female informal caregivers. Statistically significant and clinically relevant higher scores of SCQ and statistically significant lower scores of CES-D and GHQ-12 were found in children compared to spouses. Statistically significant and clinically relevant lower

Table 3. Multivariate analysis of the determinants of psychological distress of informal caregivers of patients with dementia (Linear Mixed Model)

	SCQ	Fixed effects SCQ			CES-D	Fixed effects CES-D			GHQ-12	Fixed effects GHQ-12		
	Significance	Estimates	95% CI	Significance	Significance	Estimates	95% CI	Significance	Significance	Estimates	95% CI	Significance
Age	0.005*				0.006*				0.067			
< 50 years (Ref > 70y)		-7.28	-16.6 - 2.0	0.125		1.77	-3.3 - 6.9	0.492		0.17	-2.6 - 2.9	0.901
50 - 70 years (Ref > 70y)		-10.02	-16.0 - -4.0	0.001*		5.05	1.7 - 8.3	0.003*		1.80	0.04 - 3.6	0.045*
Gender	0.172				0.003*				0.001*			
Male (Ref female)		3.41	-1,5 - 8.3	0.172		-4.06	-6.7 - -1.4	0.003		-2.48	-3.9 - -1.0	0.001*
Relationship	0.038*				<0.001*				0.003*			
Child (Ref Spouse)		8.29	1.8 - 14.8	0.014*		-8.59	-12.2 - -5.0	<0.001*		-3.35	-5.3 - -1.4	0.001*
Other (Ref Spouse)		6.67	-3.2 - 16.6	0.183		-4.18	-9.6 - 1.2	0.127		-2.11	-5.0 - -0.8	0.153
Cognition	0.546				0.526				0.178			
MMSE 0 - 9 (Ref 20 - 30)		-2.15	-8.5 - 4.2	0.502		-1.00	-4.5 - 2.5	0.566		0.19	-1.7 - 2.0	0.840
MMSE 10 - 19 (Ref 20 - 30)		-2.51	-7.5 - 2.4	0.315		1.10	-1.6 - 3.8	0.417		1.36	-0.1 - 2.8	0.066
NPI	<0.001*				<0.001*				<0.001*			
		-0.28	-0.4 - -0.2	<0.001*		0.19	0.1 - 0.2	<0.001*		0.10	0.07 - 0.13	<0.001*
CONCERN	0.301				0.533				0.232			
Yes (Ref CONCERN no)		-2.22	-6.5 - 2.0	0.301		-0.74	-3.1 - 1.7	0.533		-0.76	-2.0 - 0.5	0.232
LTCF	0.001*				0.027*				0.026*			
No (Ref LTCF yes)		-8.55	-13.4 - -3.6	0.001*		2.63	0.3 - 5.0	0.027*		1.72	0.2 - 3.2	0.026*

CI: confidence interval; * statistically significant $p < 0.05$.

scores of SCQ and statistically significant higher scores of CES-D and GHQ-12 were found in informal caregivers of patients who continued to live at home during the study compared to informal caregivers of patients who were admitted to a LTCF during follow-up. NPI total score is negatively related to SCQ total score and is positively related to CES-D and GHQ-12 total score.

Although informal caregivers' age and relationship to the patient were significantly correlated ($p < 0.001$) the correlation coefficient was medium (Cramer's V 0.55). Age of the informal caregivers and relationship to the patient both contributed to the model. This indicates that relationship to the patient is important in informal caregivers between 50 - 70 years.

After multivariate analyses entering time and an interaction of time with the other determinants in the model and a stepwise backward selection procedure only the interaction term of gender with time remained in the model with outcome GHQ-12 ($p = 0.037$) indicating a different course in time for male and female (higher scores at all three assessments) caregivers.

DISCUSSION

In this naturalistic prospective observational cohort study, we found a stable pattern of psychological distress over time among 117 informal caregivers of patients with dementia in primary care. Sixty-nine percent of informal caregivers had a clinically relevant difference score on the SCQ between T0 and T1 of which 41.2% improved and 27.8% declined. At baseline, 23.1% of informal caregivers had a high risk for depression and 41.0% were identified to be likely to have mental problems. NPI total score at baseline was low [15.7 standard deviation (SD) 15.4]. Especially compared to the Dutch MAASBED study in psychiatric-based clinics in which a total NPI score of 21.6 (SD 20.8) was found.[43]

Multivariate analysis showed that higher frequency of NPS as well as informal caregivers' age, gender and relationship to the patient were associated with higher psychological distress. Female informal caregivers have higher levels of psychological distress compared to male informal caregivers. Informal caregivers aged 50 - 70 have higher levels of psychological distress compared to those aged > 70 years. Spouses have higher levels of psychological distress than children. Relationship to the patient is important in the informal caregivers' age group 50 - 70 years. For patients who were admitted to a LTCF during the study psychological distress of the informal caregivers improved. At baseline these informal caregivers were more often spouse and had higher levels of psychological distress. The patients whom they cared for had more NPS and used more home care services. In the multivariate model with an interaction of time we only found a different course over time for GHQ-12 for gender, which we therefore considered as a finding of coincidence.

Mean SCQ scores in other Dutch studies with community-dwelling people differ from our findings. Janssen *et al.*[31] found higher mean baseline SCQ scores of 107.7 in their population of 93 primary care patients with higher mean MMSE-scores (22.4). Graff[44] found mean SCQ scores of 89.7 at baseline in the occupational therapy group and 90.4 in the control group. Even though in this randomized controlled trial patients with a score > 12 on the geriatric depression scale and with severe NPS were excluded. Janssen *et al.* and Graff found similar mean CES-D and GHQ-12 scores.[31,45]

The stable pattern of levels of burden that we found is in line with the 1-year follow-up study of Heru and the 2-year follow-up study that Berger conducted on outpatient referrals to a memory clinic.[9,13] Berger found that severe depression decreased over time; the total percentage of caregivers with slight and moderate depression increased over the same period.[9] A stable level of depressive symptoms in informal caregivers in longitudinal studies has also been described.[46,47] Four other prospective studies in outpatients of memory and dementia clinics with 1- or 2-year follow-up found a (slight) increase of psychological distress over time.[10,12,15] One other longitudinal study with a follow-up of 3 years identified three different groups: initially high but decreasing burden, moderate but increasing burden and low burden that increased slightly.[11] None of the other longitudinal studies reported data on informal caregivers of patients with admission to a LTCF during the study.

The relation between high frequency of NPS and caregiver burden is in line with former longitudinal studies.[9-12,15,20] In our study cognition was not a determinant for psychological distress, which is in line with the findings of Aguera-Ortiz and Brodaty.[10,12] However, Berger[9] found a significant correlation between caregivers' psychological distress and cognitive status and dementia severity. Conde-Sala and Brodaty also found a relation between informal caregivers' gender and relationship to the patient and psychological distress.[11,12] They also found that living with the patient/being spouse[11] and being a female informal caregiver[12] is related to higher psychological distress.

Strengths and limitations

Patients and informal caregivers in this study were included from general practices. It was a heterogeneous sample with patients in all stages of dementia and dyads were followed beyond admission to a LTCF. There was a low rate of lost to follow-up during 18 months.

Limitations to our study are the rather low participation of general practices (114 invited, 18 participated), the large proportion of general practices that provide CONCERN and that 46.2 % of the patients and informal caregivers who refused to participate indicated that burden/efforts of participating in the study is too high. This may have resulted in a selective group of informal caregivers with relatively low levels of psychological distress. However, caregivers who participated in CONCERN had statistically significant higher levels of psychological distress (lower SCQ mean scores) and were less often supported by a CM at baseline.

Another limitation in our study is the difference between the participants and non-participants. However, we do not know if other longitudinal studies on psychological distress also had this risk of selection bias, because none of the other studies did present the number of non-participants or the characteristics of them.

The lack of information on other caregiver characteristics such as the number of daily hours spent, the duration of caregiving and the nature of the caregiving role (sole caregiver or shared responsibility) is also a limitation. Informal caregivers who are spending more daily hours on caregiving for a longer period of time are likely to have more psychological distress[9,11,19], whereas sharing responsibility might reduce it.[11] Thirdly, there were missing data, especially for the MMSE at baseline. Also, the baseline characteristics of the patients who were lost to follow-up during the study were different from those who completed the study: they were older and used more care services. Both give selection bias. Finally, caregiver-rating bias could have affected the relationship between NPS and psychological distress. Caregivers who experience high levels of psychological distress may score the NPS of the person with dementia they care for as worse.[48]

Implications

The results of this and previous studies showed that in spite of low NPI total scores, NPS is significantly related to psychological distress. Therefore, NPS should be proactively assessed by the GP as well as on caregivers' psychological distress. Specifically, to those who are spouse, female and between 50 - 70 years of age, which are associated with higher levels of psychological distress. GPs should be aware of the informal caregivers' risk for depression and mental problems. The group of informal caregivers between 50 and 70 years correspond to the sandwich generation of people who care for their aging parents or spouse while supporting their own children and probably taking care of grandchildren as well. Informal caregivers encounter other life phase specific problems including relational difficulties, family conflict, employment and financial issues.[4] GPs should pay attention to these problems, especially because of the availability of effective psychological and psychosocial interventions to reduce informal caregivers' psychological distress such as education programs, respite care, support groups and cognitive-behavioural therapy.[4,49]

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CHAPTER 7

General discussion

GENERAL DISCUSSION

The aim of this thesis was to investigate the prevalence of neuropsychiatric symptoms (NPS) and psychotropic drug use, as well as the course and determinants of NPS in people with dementia and the psychological distress in their informal caregivers in primary care. In the following, a summary of the main findings, the methodological considerations, the generalizability of the findings, the impact for dementia care in general practices and recommendations for education and future research are discussed in more detail.

SUMMARY OF THE MAIN FINDINGS

What is known from earlier research about the prevalence and course of neuropsychiatric symptoms in community-dwelling people with dementia?

We conducted a systematic review in which we included 23 prospective cohort studies for data analysis. NPS in these studies were assessed by 15 different assessment instruments. Twelve studies presented data for patients per assessment, including those lost to follow-up. Studies showed a lot of variation concerning duration of follow-up (1 - 6 years), timing between assessments and the total number of assessments (2 - 12). Consequently, the results of the studies varied considerably. Overall, we found that NPS are highly prevalent, incident and persistent. Virtually all patients with dementia showed NPS during a period of 1 - 6 years. We presented the data in 3 subgroups: a subgroup with affective symptoms (mood/apathy), a subgroup with hyperactivity symptoms and a subgroup with psychotic symptoms. NPS in the affective subgroup were the most prevalent, NPS in the psychotic subgroup the least prevalent. On symptom level our review showed that delusions, wandering/agitation, aberrant motor behaviour/motor hyperactivity, and apathy were the most common. We found increasing point prevalence rates in consecutive assessments for hallucinations, delusions, paranoia, aggression, wandering/agitation, aberrant motor behaviour/motor hyperactivity, disinhibition, apathy and sleep disturbance in some studies and decreasing point prevalence rates in consecutive assessments for depression and anxiety in some other studies. There were a lot of similarities between the occurrence of NPS in community-dwelling people with dementia and those living in nursing homes, especially concerning wandering/agitation and apathy.

What is the prevalence of neuropsychiatric symptoms and psychotropic drug use in people with dementia in general practice?

Our study showed that NPS are very common in people with dementia in general practice. At baseline, more than 90% of the study population had at least one NPS and 66% had at least one clinically relevant (NPI symptom score ≥ 4) NPS. The most common NPS were

agitation/aggression, depression and irritability. The most common clinically relevant NPS were aberrant motor behaviour, agitation/aggression and apathy.

Fifty-three percent of the people with dementia used psychotropic medication (including ant-dementia medication). Almost 29% of the patients used at least one, 7% used at least two different and 2% used at least three psychotropic drugs (excluding anti-dementia medication). Antipsychotics were prescribed to 10%, antidepressants to 17% and anti-dementia medication to 34% of the patients.

What is the course of neuropsychiatric symptoms and which are the determinants for the course of neuropsychiatric symptoms in people with dementia in primary care?

Over a period of 18 months, our prospective study showed that in people with dementia several NPS, as assessed by the neuropsychiatric inventory (NPI), were highly prevalent, incident and persistent and that some NPS were more likely to resolve. The majority of people with dementia showed one or more symptoms of the mood/apathy or the hyperactivity subsyndrome (72% versus 75%) over 18 months. For people with dementia with one or more symptoms at baseline, these persisted for 18 months in 20% and 25%, respectively. Approximately half of the patients with dementia without symptoms of the mood/apathy or hyperactivity subsyndrome at baseline developed these symptoms at subsequent measurements (48% versus 55%). The clinically relevant symptoms aberrant motor behaviour, apathy and to a slightly lesser degree agitation/aggression occurred frequently in a period of 18 months (59%, 51% and 46%) and apathy, agitation/aggression and irritability (9%, 9% and 8%) were the most persistent for at least 18 months. On the other hand, most patients with dementia remained free of symptoms of the psychosis subsyndrome. Euphoria, disinhibition, depression, delusions, also apathy and anxiety were the symptoms that were most likely to resolve during at least 18 months after baseline.

Verbally agitated symptoms, as assessed by the Cohen-Mansfield Agitation Inventory (CMAI), were the most prevalent over a period of 18 months, closely followed by physically non-aggressive symptoms (88% versus 83%). These symptoms were also very likely to occur after baseline (cumulative incidence 64% versus 58%) and to persist over a period of 18 months (48% versus 69%)

For the course of NPS we found a different course in time for cognition of the patient, participation in CONCERN, use of respite care and for the relationship of the informal caregiver to the patient. As we used a likelihood ratio test, we do not consider these results as a coincidence, but in our opinion, it is not possible to differentiate the relevance of this in clinical practice due to the small effect sizes.

What is the course of psychological distress in informal caregivers of people with dementia in primary care and which are its determinants?

Our study about informal caregiver distress showed that at baseline, 23% of informal caregivers of people with dementia in primary care had a high risk for depression, as assessed with the Center for Epidemiological Studies Depression scale (CES-D). Forty-one percent scored above the cut-off score ≥ 2 indicating a high risk of psychological symptoms according to the General Health Questionnaire 12-item version (GHQ-12). Over a period of 18 months the total group of these informal caregivers showed a stable pattern of psychological distress. Multivariate analysis showed that higher frequency of NPS in the people with dementia as well as informal caregivers' age, gender and relationship to the patient were associated with higher levels of psychological distress. Higher levels of psychological distress were associated with being a female informal caregiver, being between 50 - 70 years old and being a spouse. The psychological distress of the informal caregivers improved when the patient they cared for was admitted to a long-term care facility (LTCF) during the study. At baseline these informal caregivers were more often spouse and had higher levels of psychological distress. The patients whom they cared for had more NPS and used more home care services.

Caregivers' age and gender, patient-caregiver relationship, NPS, cognition of the patient, participation in CONCERN and admission to a LTCF were not significantly associated with the course of psychological distress.

METHODOLOGICAL CONSIDERATIONS

Change of study design

This study was originally designed as a cluster randomized controlled trial (RCT). The aim was to test a new approach for optimization of care delivery for people living at home with dementia and NPS and their informal caregivers using an individually tailored, multidisciplinary care program and to evaluate its effectiveness. In this care program called Care Optimization for Non-professional Caregivers of Elderly with dementia and Reduction of Neuropsychiatric symptoms (CONCERN), a general practitioner (GP), case manager and an elderly care physician systematically collaborate to improve the care for patients with dementia in order to reduce NPS. It was intended that the elderly care physician reviewed the diagnosis of dementia and differentiated in a specific clinical diagnosis of dementia. The inclusion criteria for this cluster RCT were: age 65 years or older, living at home, informal caregiver available, NPS being a problem for patient and/or informal caregiver (NPI-Q (severity) score > 1 and /or NPI-Q caregiver distress scale > 2 on one or more items). Patients were excluded when life expectancy was less than 3 months, the person with dementia was living in a LTCF or on a waiting list for admission to a LTCF and when a case manager was already

involved or when the patient and informal caregiver were already referred to secondary care for treatment of the NPS. Assessments were chosen at baseline and after 9 and 18 months to be able to implement CONCERN and to measure its effectiveness.

We included patients from the GPs' electronic medical system with a diagnosis of dementia. During inclusion, the necessary information to properly include or exclude patients with dementia appeared often not to be available. Subsequently, during recruitment the majority of the patients and/or informal caregivers declared that there were no NPS at all. And finally, several patients with dementia and their informal caregivers were willing to participate in the study but did not want the involvement of a case manager or already were attended by a case manager on a regular basis. Because of the prospect of not being able to include a sufficient number of participants in the study, we decided to change the design from a cluster RCT into a prospective cohort study. There were 14 general practices, of which the GPs already agreed to participate in this study and to implement CONCERN and we added 4 more general practices, of which the GPs were willing to participate in this prospective cohort study, but not in CONCERN. Not all patients in the 14 participating practices were actually involved in CONCERN because participation was the choice of the patients and their caregivers. We did not evaluate whether CONCERN was implemented correctly in the general practices. In the data analysis of this prospective cohort study, we used participation in CONCERN as a separate variable in the multivariate analyses. For the prospective cohort study, the 3 chosen assessments for the original cluster RCT during the follow-up period of 18 months is a limitation, because variations in NPS between two successive assessments remain unknown.

Influence of bias

Selection bias occurs when individuals or groups in a study differ systematically from the population of interest.[1] In general, selection bias can have varying effects, and the magnitude of its impact and the direction of the effect is often hard to determine.[2] There are several sources for selection bias in our study: the rather low participation rate of general practices, the difference in clinical characteristics between the participants and those who refused or were withdrawn before the start of the study and the high refusal rate of dyads indicating that the burden of participating in the study is too high. The low participation rate of general practices could have resulted in a selection of GPs who are familiar with and interested in people with dementia. The consequence of this could be that patients who were consulting these GPs have been appropriately assessed and diagnosed and that more people in a less advanced stage of dementia are denoted in the GPs' electronic medical system.[3,4] Patients who refused or were withdrawn before start of the study were more often female (67 % versus 52 % of the study participants) and the relationship of the informal caregiver to the patient was less often spouse (49 % versus 65 % of the study participants) and more often child (45 % versus 29 % of the study participants). This might indicate that informal

caregivers of female patients and informal caregivers who were related to the patient as child experienced less motivation to participate in this study. There was also a high refusal rate of participants (50%) and almost half of them indicated that burden of participating in the study was too high. It is difficult to determine the impact and the effect of this on our outcomes, because this could have biased our study population into several directions: to patients with less or more advanced stages of dementia and NPS and to informal caregivers experiencing lower or higher levels of psychological distress.[5] The most important factors are the low participation rate of GPs and high refusal rate of dyads due to high burden for participation in the study. We assume that the first factor did not influence the results of our study because the prevalence and incidence of NPS are not dependent on whether the GP is interested in or well-equipped for dementia related problems. The second source for selection bias (high burden for participation in the study) probably results in an underestimation of prevalence and incidence of NPS in primary care.

Attrition bias occurs when there is an unequal loss to follow-up or losses of different types of participants from study groups.[6] There is a rule of thumb for RCTs that less than 5% attrition leads to little bias and more than 20% poses serious threats to validity.[7] In RCTs expecting loss to follow-up rates are 5 to 15% over a 1-year follow-up period.[7] Loss to follow-up is also inevitable in most cohort studies. In the past, suggested acceptable follow-up rates were: 50% is adequate, 60% is good and 70% is very good,[8] although others suggested a minimum acceptable follow-up rate of 80%.[9] On the other hand, when loss to follow-up is (completely) at random, attrition bias is unlikely to occur with levels of loss to follow-up up to 60%.[10] In a recent study in primary care it was also found that attrition in cohort studies of older people does not inevitably indicate bias.[11] In our prospective cohort study, the rate of lost to follow-up was 16% after 9 months and 27% after 18 months (18% after one year) of which 50% was due to death of patient participants.[12] With regard to the mean age of 79 years and to the participation of patients with dementia with a limited life expectancy we consider our rate of follow-up of 73% as acceptable. At baseline, the characteristics of the patients who were lost to follow-up during the study were different from those who completed the study: they used more home care services and were on average 2 years older. This might indicate that these patients were in a more advanced stage of dementia at the start of the study and more at risk to die over the 18-months study period. In the light of the high mortality rate in this population, which is to be expected, we consider the attrition rate in our study as acceptable and not threatening the validity of the study results.

Misclassification bias occurs when a study participant is categorized into an incorrect category.[13] For the multivariate analyses with the linear mixed models we categorized cognition in 3 subgroups each one third cut-off range of severity of the MMSE score: 0 - 9, 10 - 19 and 20 - 30. Six patients had a missing MMSE in all 3 measurements, because it was too stressful or because of absence due to stay at day care centres during the interview. We assumed for these 6 patients to have a low MMSE score 0 - 9 because they visited day care

centres and used home care services and 4 of these patients were admitted to a LTCF after baseline and before T1 measurements. This may have led to misclassification bias, but our assumption is an example of the use of a worst-case scenario, which is partly underlined by the facts that these patients visited day care centres and used home care services and that 4 of these patients were admitted to a LTCF after baseline and before T1 measurements. It is possible that the worst-case scenario has led to exaggerated estimations of prevalence and incidence of NPS in the category MMSE score 0 - 9, but we assume that the precise influence of this bias is minimal.

Caregiver-rating bias occurs when caregivers who experience high levels of psychological distress themselves score the NPS of the person with dementia they care for as more severe.[14] It is to be expected that more NPS are associated with higher levels of psychological distress in their informal caregivers, but the effect of caregiver rating bias is that the association is stronger. Thus, the caregiver-rating bias could have resulted in an overestimation of the prevalence of NPS.[14,15] Our data based on informal caregiver ratings should therefore be interpreted with a little caution. An alternative for informal caregiver rating is observation by a research assistant. The NPI warrant collecting information on NPS in the previous 4 weeks. Observation would be very time-consuming and expensive in the accomplishment of such assessments. So, we have to accept the potential caregiver-rating bias in our study.

In conclusion, we consider the high refusal rate of dyads indicating that the burden of participating in the study was too high as the most important bias. As a result - and considering all sources of bias together - we assume that our prevalence and incidence rates are an underestimation of the caregiver-ratings of NPS in primary care.

Generalizability to other general practices

All patients in our study population were registered in the GPs' electronic medical file with a diagnosis of dementia.[16] GPs often wait before diagnosing dementia, although an in-home geriatric primary care intervention can help to identify dementia in relatively early stages.[3] In various Western countries only 20 to 50 % of people with dementia have a formal diagnosis[3,17-23]; in the Netherlands this is 25 %.[3]

This study was performed in the southern part of the Netherlands. Although the sample of GPs is representative for the average Dutch general practice concerning the number of the GPs and mean number of patients per practice its generalizability is questionable because of the participation in CONCERN for the majority (14 out of 18) of the general practices. Data on the age distribution of the patient population in the participating general practices indicate that the percentage of patients aged 75 and older (23 %) is higher in the participating general practices than in the general Dutch population (10 %). This may also overestimate the number of patients with dementia, NPS and psychotropic drug use compared to the average general practice in the Netherlands, as these practices might be more organized in assessing elderly patients and in particular people with dementia .[24]

Finally, the results of this study are only generalizable to other countries with a similar primary care system (gate-keepers and general coordinators of primary care) like Great Britain and Denmark.[25,26]

Comparability with other studies

As far as we know, there is only one other study on people with dementia and NPS with a study population that has been recruited from general practices.[27] From this longitudinal study in Germany only cross-sectional data have been published. Compared to this study, the prevalence of all symptoms of the NPI in our study are higher. The most common NPS in the German study were depression (37 %), apathy (32 %) and agitation/aggression (31 %), which is, except for apathy, in line with the findings of our study (agitation/aggression 54 %, depression 53 % and irritability 48 %).[27] Concerning apathy (41 %) our study shows that after aberrant motor behaviour (47 %), together with anxiety (41 %) it is the fifth prevalent individual symptom. For the most common clinically relevant symptoms (NPI symptom score ≥ 4) the findings in Germany were: apathy (20 %), aberrant motor behaviour (15 %) and anxiety and appetite and eating change (both 13 %). The prevalence of agitation/aggression (12 %) is low compared to our results: aberrant motor behaviour 29 %, agitation/aggression 23 % and apathy 22 %. In the German study, GPs started with screening patients aged 70 years and older for dementia and only 109 of the 248 (44 %) people with dementia in this cohort had already been diagnosed before start of the study. Therefore, the study population of the German study probably contained more people with a slightly less advanced stage of dementia (mean MMSE score in our study (19.5 ± 5.6) compared to the German study (20.9 ± 5.6)) and consequently could have lower prevalence rates of NPS.

On the other hand, compared to a prospective Dutch study on a cohort of psychiatric-based clinics (MAASBED) the prevalence rates in our study were lower for the majority of the clinically relevant symptoms and subsyndromes on the NPI (10 out of 15), except for agitation/aggression, disinhibition, aberrant motor behaviour, night-time behaviour disturbance and the hyperactivity subsyndrome.[28] Our prevalence rates were much lower, especially for delusions and hallucinations (psychosis subsyndrome), dysphoria/depression, apathy/indifference and the mood/apathy subsyndrome.[28] In the MAASBED study dementia was in a slightly more advanced stage (lower MMSE scores 18.0 ± 4.7) and, as we expected in a cohort of psychiatry-based clinics, there was a higher prevalence, incidence and persistence of NPS in all subsyndromes, but the most prevalent and incident individual symptoms were similar to our study.[28]

IMPACT FOR DEMENTIA CARE AND MANAGEMENT IN GENERAL PRACTICES

Worldwide, the numbers of people with dementia will increase in the next decades.[29] In the Netherlands, most people with dementia (70%) live in the community and are cared for by their GP.[30,31] The GP has an important role in detecting dementia and disclose the diagnosis to the patient and the informal caregivers. The GP is also most often the first physician consulted for dementia related problems like NPS and psychological distress in the informal caregivers.

We found that NPS are very common in people dementia in primary care. Moreover, people with dementia develop new NPS and some of these symptoms appear to be persistent. NPS of people with dementia are associated with higher levels of psychological distress in their informal caregivers. We also found that psychotropic drug use in primary care is much lower than in LTCF (63 - 75%), although still 53% of the people with dementia use at least one psychotropic drug, including anti-dementia medication.[32-34] However, use of anti-dementia medication in LTCF is much lower (1 - 14%) than in our study (34%).[32-34]

GPs should be aware that NPS are very common in people with dementia and should proactively identify NPS in people with dementia and psychological distress in their informal caregivers in order to coordinate and facilitate adequate professional care. In addition, psychotropic drugs should be appropriately prescribed. Medication reviews provide a possible strategy to achieve this and reduce psychotropic drug use in LTCF as well as in primary care.[35,36] The subsyndromes of NPS can facilitate the GP in the detection, analysis and management of NPS in people with dementia in primary care.

The Dutch GP guideline for dementia recommends to identify the care needs of people with dementia and their informal caregivers, to give information and psycho-education and to create a care plan after the diagnosis of dementia. The guideline also provides common directions for non-pharmacological (psycho-education, individual coaching, cognitive behaviour therapy, physical activity, occupational therapy and day care services) as well as for pharmacological interventions in case of NPS occur in people with dementia. For NPS that cannot be overcome with non-pharmacological or psychosocial interventions it is recommended to refer to specialists in dementia care, for example the elderly care physician and/or geropsychologist.

According to the Dutch Elderly Care Physician guidelines for NPS in dementia it is recommended to methodologically and multidisciplinary analyze NPS and to use validated assessment instruments like the NPI and CMAI.[37] As well as, to actively assess psychological distress in informal caregivers related to the NPS. Carrying capacity and competencies of the informal caregiver, and environmental characteristics are factors that offer good clues for interventions.[38] There is limited evidence for the effectiveness of psychotropic drug use in case of NPS and particular attention should be paid to possible adverse effects.[39,40] The prescription of psychotropic drugs is only indicated when non-pharmacological interven-

tions are not effective and symptoms are severe: antidepressants in case of depression, anxiolytics in case of anxiety, antipsychotics in case of severe hallucinations or delusions and in case of agitation or aggression and melatonin or trazodone in case of nighttime behaviour disturbance.[37] This guideline is not yet widely implemented in primary care, but provides concrete directions for detecting, analyzing and managing NPS and psychological distress as well as for appropriately prescribing psychotropic drugs. In our opinion, cooperation between specialists in elderly care, like elderly care physicians, and GPs is most indicated in the management of NPS and the prescription of psychotropic drugs.

The coordination of dementia care in general practices is a very important point to consider. Many GPs are supported by practice nurses in their general practices. They help the GPs with case finding of frail elderly, such as people with dementia and detecting the consequences of dementia, and proactive care planning in daily practice. Other health care workers and social care professionals are also often involved in the care for people with dementia, like case managers, home care services, facilities for respite care or transfer nurses involved in waiting list management. Dementia care in primary care can therefore be highly fragmented and people with dementia and their informal caregivers sometimes have to deal with many different care professionals, irrespective of the legal frameworks for the organization and financing of their dementia care.[31] This is an important argument for an active role of the GP who often has a longstanding relationship with these people with dementia and their informal caregivers. We consider the GP as the ideally situated professional to be the primary contact for them. Practice nurses could also play an important role in this process.

In the ideal collaborative dementia care program in primary care timely delivering the appropriate and right combination of components after diagnosis and disclosure of diagnosis (psychosocial interventions, appropriate prescription of psychotropic drugs, case management and coordination and advanced care planning) to the dementia patient and informal caregiver is crucial. This will require a stepped-care approach where the intensity of care varies according to the level of patient disability.[41]

To determine the content of (multidisciplinary) care and coordination for people with dementia in a general practice the stepped care model provides 3 different modules: level 1: for people with dementia who are well-functioning; level 2: people with dementia with functional impairment, but stable situation; level 3: people with dementia with significant functional impairment in a complex setting. In level 1, the GP or practice nurse monitors the people with dementia and visits them yearly. Telephone consultations in between the yearly visits could also play a role. In level 2, the practice nurse functions as a case manager, an individual care plan is set up and the elderly care physician is present at the multidisciplinary meetings together with the GP. In level 3, the elderly care physician takes responsibility for the individual care plan, the GP remains the primary practitioner and the primary contact with the person with dementia and their informal caregivers.

RECOMMENDATIONS FOR EDUCATION

In the last few decades GPs have become more aware of people with dementia and their knowledge of dementia has increased. Although timely diagnosis and disclosure of the diagnosis in general practices can still improve, the time has come to make GPs more aware of the consequences of dementia for the people themselves and for their informal caregivers. To increase the awareness of NPS in people with dementia and psychological distress in their informal caregivers in GPs and their practice nurses, educational courses should be provided nationwide. GPs and their practice nurses should also be given concrete directions for detecting, analyzing and managing NPS and psychological distress as well as for appropriately prescribing psychotropic drugs. The use of validated assessment instruments to detect NPS, like the NPI and CMAI could be helpful in this process. NPS will often not spontaneously be mentioned by the people with dementia and their informal caregivers and possibly even denied. A proactive approach is necessary to detect NPS and psychological distress. In order to be able to appropriately prescribe psychotropic drugs GPs and their practice nurses should have knowledge on possible non-pharmacological or psychosocial interventions.

RECOMMENDATIONS FOR FUTURE RESEARCH

The first recommendation for future research would be to investigate the effectiveness of a collaborative stepped-care approach for dementia care in general practices taking into account the intensity of the care needed for people with dementia and their informal caregivers. Based on the complexity of the situation (the level of NPS and psychological distress), the functional impairment and the patient and caregiver needs, the multidisciplinary team could operate in a periodic consultancy model, ongoing co-management mode or as the main care provider. Outcome measures that are person- and goal-centered (patient reported outcome measures) should be used to effectively measure the effectiveness of such an intervention.[42] Also aspects like personality, coping and mutual relationship should be chosen to get more insight into the factors that have association with the outcome measures on NPS and psychological distress.[43,44] Such an intervention should be unrolled nationwide in order to achieve a good sample size and encourage unambiguous dementia care and management in all general practices.

The second recommendation is a trial for appropriate psychotropic drug use in people with dementia in primary care following the example of a similar study in Dutch nursing homes.[36,45] In a pilot study the proportion of inappropriate psychotropic drug use in people with dementia in primary care should be determined. The consecutive intervention should consist of a structured and repeated biannual medication review, preferably multidisciplinary by a pharmacist, GP, elderly care physician and practice nurse. The main goal of such a study

would be to improve the proportion of people with dementia with appropriate psychotropic drug use.

Finally, the implementation of the 2 described recommendations for future research should be conducted conform the Consolidated Framework for Implementation Research (CFIR) in order to be able to effectively realize these interventions.[46]

CONCLUDING REMARKS

In conclusion, this thesis adds important knowledge about the occurrence of NPS and psychotropic drug use and the course of NPS in people with dementia in primary care and about psychological distress in their informal caregivers.

- NPS are very common in people with dementia in general practice. Over a period of 18 months several NPS are highly prevalent, incident and persistent, especially in the hyperactivity and mood/apathy subsyndrome. The most common clinically relevant individual NPS are aberrant motor behaviour, agitation/aggression and apathy.
- Fifty-three percent of the people with dementia used at least one psychotropic drug, 14% use at least two different and 4% use at least three psychotropic drugs, including anti-dementia medication. Excluding anti-dementia medication, almost 29% of the patients use at least one, 7% use at least two different and 2% use at least three psychotropic drugs.
- Informal caregivers of people with dementia in primary care have a high risk for depression and are likely to have mental problems. Female informal caregivers, informal caregivers aged 50 - 70 years and being a spouse is associated with higher levels of psychological distress.

GPs or their supporting practice nurses should be aware of this and should actively identify NPS in people with dementia and psychological distress in their informal caregivers in order to coordinate and facilitate adequate professional care.

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APPENDIX

ENGLISH SUMMARY

Most people with dementia live in the community and are cared for by their general practitioner (GP). The GP is most often the first physician consulted for dementia related problems. During the course of dementia most people develop some type of behavioural symptoms, also called neuropsychiatric symptoms (NPS). Psychotropic drugs are often prescribed in this process, which can cause serious adverse effects. NPS are associated with psychological distress in informal caregivers. Almost all studies on the course of NPS in community-dwelling people with dementia were conducted in ambulatory patients with dementia visiting outpatients' memory, (old-age) psychiatry, neurological or geriatric clinical centres or dementia services. Only a limited proportion of people in general practice in the Netherlands are referred to secondary care. Therefore, it is likely that a study population visiting outpatient clinical centres has more severe and frequent symptoms than the total group of people with dementia in general practice. For GPs, it is important that accurate data of NPS and psychotropic drug use of patients with dementia in general practices are available in order to enlarge their awareness and initiate timely and adequate professional care. Therefore, the general aim of this thesis is to investigate the prevalence of NPS and psychotropic drug use, as well as the course and determinants of NPS in people with dementia and the psychological distress in their informal caregivers in primary care. In **chapter 1** the background for the aims and research questions of this thesis are further addressed.

In **Chapter 2** we describe the design of our prospective naturalistic observational cohort study with a follow-up of 18 months. Thirty-seven GPs in 18 general practices in the southern part of the Netherlands participated in this study. In the electronic medical files of these practices we identified and recruited 117 dyads of patients with a diagnosis of dementia and their informal caregivers. Dyads were assessed at baseline and after 9 and 18 months. Follow-up was continued after admission to a nursing home. In 14 of the participating general practices, a multicomponent collaborative care program named CONCERN (Care Optimization for Non-professional Caregivers of Elderly with dementia and Reduction of Neuropsychiatric symptoms) was provided. In this care program the GP, elderly care physician and a dementia case manager focus on optimization of care for people with dementia and their informal caregivers. The primary outcome measures of this study are the Neuropsychiatric Inventory (NPI) score for the NPS and Sense of Competence (SCQ) score for psychological distress in the informal caregivers.

In **Chapter 3** existing literature is reviewed to get more insight into the course of community-dwelling people with dementia. Previous research indicates that NPS in general are highly prevalent, incident and persistent although the results of the studies varied considerably. The difference in results between studies may partly be explained by the different assess-

ment instruments used, the different intervals between assessments and different follow-up periods. Former research shows that virtually all patients with dementia show NPS during a period of 1 - 6 years. NPS in the affective subgroup are the most prevalent, NPS in the psychotic subgroup the least prevalent. Delusions, wandering/agitation, aberrant motor behaviour/motor hyperactivity, and apathy are the most common individual NPS. The most common NPS in community-dwelling people with dementia are also the most common symptoms in people with dementia in nursing homes, especially wandering/agitation and apathy.

Chapter 4 reports on the prevalence of NPS and psychotropic drug use at baseline. NPS were very common in people with dementia in general practice: 66% had at least one clinically relevant NPS (NPI score ≥ 4). The most common clinically relevant NPS were aberrant motor behaviour, agitation/aggression and apathy. Fifty-three percent of the people with dementia use psychotropic medication including anti-dementia medication. Excluding anti-dementia medication, almost 29% of the patients used at least one, 7% used at least two different and 2% used at least three psychotropic drugs. Antipsychotics were prescribed to 10%, antidepressants to 17% and anti-dementia medication to 34% of the patients.

In **Chapter 5** the results for the course of NPS over 18 months are presented. Several NPS were highly prevalent, incident and persistent and some NPS were more likely to resolve. The majority of people with dementia showed one or more symptoms of the mood/apathy or the hyperactivity subsyndrome (72% versus 75%) over the follow-up period. For people with dementia with one or more symptoms at baseline, these persisted in 20% and 25%, respectively. Approximately half of the patients with dementia without symptoms of the mood/apathy or hyperactivity subsyndrome at baseline developed these at subsequent measurements (48% versus 55%). The clinically relevant symptoms aberrant motor behaviour, apathy and in a slightly lesser degree agitation/aggression occurred frequently in a period of 18 months (59%, 51% and 46%). Apathy and agitation/aggression were the most persistent symptoms. On the other hand, most patients with dementia remained free of symptoms of the psychosis subsyndrome. Concerning the agitated/aggressive symptoms, the verbally agitated symptoms were the most prevalent over the follow-up period, closely followed by physically non-aggressive symptoms (88% versus 83%). These symptoms were also very likely to occur after baseline (cumulative incidence 64% versus 58%) and to persist over the follow-up period (48% versus 69%). We did not find clinically relevant associations between the independent variables at baseline (patients' age, gender, cognition, psychotropic drug use and use of respite care or personal health care, and informal caregivers' psychological distress, as well as participation in CONCERN) and the course of NPS over time.

Chapter 6 reports on the results for the course of psychological distress of the informal caregivers. At baseline, 23 % of informal caregivers of people with dementia in primary care had a high risk for depression (CES-D) and 41 % were identified to be likely to have psychological symptoms (GHQ-12). The total group of these informal caregivers showed a stable pattern of psychological distress (SCQ). Higher frequency of NPS as well as informal caregivers' age, gender and relationship to the patient were associated with higher psychological distress. Female informal caregivers, informal caregivers aged 50 - 70 years and being a spouse were associated with higher levels of psychological distress. The psychological distress of the informal caregivers improved when the patient they cared for was admitted to a LTCF during the study. We did not find associations between the independent variables at baseline (caregivers' age and gender, patient-caregiver relationship, patients' cognition and NPS, as well as participation in CONCERN and admission to a LTCF) and the course of psychological distress over time.

Finally, in **chapter 7** we provide an overview of our main findings in this thesis and we reflect on our methodological choices. In addition, implications for dementia care in general practices, as well as recommendations for future research are discussed. We conclude that GPS should be aware of the occurrence of NPS in people with dementia and psychological distress in their informal caregivers and actively identify these in order to coordinate and facilitate adequate professional care.

NEDERLANDSE SAMENVATTING

De meeste mensen met dementie wonen thuis en worden begeleid door hun huisarts. De huisarts is meestal de eerste persoon, die geconsulteerd wordt bij aan dementie gerelateerde problemen. Tijdens het beloop van dementie ontwikkelen de meeste mensen een vorm van probleemgedrag, die ook wel neuropsychiatrische symptomen (NPS) worden genoemd. Vaak worden hierbij psychofarmaca voorgeschreven, die ernstige bijwerkingen kunnen geven. NPS zijn ook van invloed op de ervaren psychologische belasting bij mantelzorgers. Bijna alle onderzoeken naar het beloop van NPS bij thuiswonende mensen met dementie zijn uitgevoerd bij ambulante patiënten met dementie van geheugenpoli's, (ouderen)psychiatrische, neurologische of geriatrische klinische centra of andere gespecialiseerde centra voor dementie. In Nederland wordt slechts een klein gedeelte van de patiënten uit een huisartspraktijk doorverwezen naar deze gespecialiseerde centra in de tweede lijn. Het is daarom aannemelijk, dat een onderzoekspopulatie van mensen vanuit klinische centra symptomen hebben, die ernstiger zijn en vaker voorkomen dan in de totale groep van mensen met dementie in de huisartspraktijk. Voor huisartsen is het belangrijk, dat er nauwkeurige gegevens beschikbaar zijn over NPS en het gebruik van psychofarmaca binnen de huisartspraktijk om de bewustwording hiervan te vergroten en om op tijd adequate zorg in te kunnen zetten. Daarom is het doel van dit onderzoek om binnen de huisartspraktijk de aanwezigheid van NPS en psychofarmacagebruik bij mensen met dementie vast te stellen. En daarnaast om het beloop en de beïnvloedende factoren van NPS bij mensen met dementie en die van de psychologische belasting van hun mantelzorgers te onderzoeken. In **hoofdstuk 1** wordt verder ingegaan op de achtergrond van de doelstellingen en onderzoeksvragen van dit proefschrift.

In **hoofdstuk 2** wordt de onderzoeksopzet van onze prospectieve, naturalistische, observationele cohortstudie beschreven. Het onderzoek duurde 18 maanden en er namen 37 huisartsen uit 18 verschillende huisartspraktijken aan deel. In de elektronische medische dossiers van deze huisartspraktijken werden patiënten met dementie en hun mantelzorgers geselecteerd, waarvan er 117 wilden deelnemen aan dit onderzoek. Gegevens van deze patiënten met dementie en gegevens van hun mantelzorgers werden verzameld bij het starten van het onderzoek en na 9 en 18 maanden. Ook wanneer patiënten met dementie werden opgenomen in een zorginstelling werden zij en hun mantelzorgers verder vervolgd in dit onderzoek. In 14 van de deelnemende huisartspraktijken konden de geselecteerde patiënten en hun mantelzorgers eventueel deelnemen aan een zorgprogramma genaamd CONCERN (Care Optimization for Non-professional Caregivers of Elderly with dementia and Reduction of Neuropsychiatric symptoms). In dit zorgprogramma werken huisarts, specialist ouderengeneeskunde en een casemanager dementie samen om de zorg voor mensen met dementie en hun mantelzorgers te verbeteren. De belangrijkste vragenlijsten die gebruikt worden in dit onderzoek, zijn de Neuropsychiatrische vragenlijst (NPI) score voor NPS en de Sense of Competence Questionnaire (SCQ) score voor psychologische belasting bij de mantelzorgers.

In **hoofdstuk 3** wordt de bestaande literatuur beoordeeld en besproken om meer inzicht te krijgen in het beloop van NPS bij thuiswonende mensen met dementie in eerder verricht onderzoek. Eerder onderzoek geeft aan dat NPS in het algemeen heel vaak voorkomen, vaak nieuw ontstaan en blijven bestaan, alhoewel de resultaten van de verschillende onderzoeken sterk uiteenlopen. De verschillen in resultaten tussen de onderzochte studies kunnen gedeeltelijk worden verklaard door het gebruik van verschillende meetinstrumenten, de verschillende tijdsintervallen tussen de momenten waarop de gegevens werden verzameld en de verschillende lengten van studieduur. In eerder onderzoek lieten vrijwel alle mensen met dementie NPS zien tijdens een studieduur van 1 tot 6 jaar. Affectieve symptomen komen het meest voor en psychotische symptomen komen het minst vaak voor. Wanen, dwalen/agitatie, afwijkend motorisch gedrag/motorische hyperactiviteit en apathie zijn de meest voorkomende individuele NPS. De meest voorkomende NPS bij thuiswonende mensen met dementie komen overeen met de meest voorkomende NPS bij mensen met dementie in zorginstellingen. Dit geldt met name voor dwalen/agitatie en apathie.

Hoofdstuk 4 beschrijft de resultaten van het uitgevoerde onderzoek in de huisartspraktijk naar de aanwezigheid van NPS en het gebruik van psychofarmaca bij het eerste meetmoment van het onderzoek. NPS komen vaak voor bij mensen met dementie in de huisartspraktijk: 66 % had ten minste één klinisch relevant symptoom (NPI score ≥ 4). De meest voorkomende klinisch relevante NPS zijn: doelloos repetitief gedrag, agitatie/agressie en apathie. Van de mensen met dementie gebruikt 53 % psychofarmaca inclusief medicijnen tegen dementie. Wanneer medicijnen tegen dementie niet worden meegerekend dan gebruikt bijna 29 % van de patiënten ten minste één, 7 % ten minste twee en 2 % ten minste drie verschillende psychofarmaca. Antipsychotica worden voorgeschreven bij 10 %, antidepressiva bij 17 % en medicijnen tegen dementie bij 34 % van de mensen met dementie.

In **hoofdstuk 5** worden de resultaten gepresenteerd over het beloop van NPS tijdens de 18 maanden van het onderzoek in de huisartspraktijk. Meerdere NPS kwamen veel voor, ontstonden nieuw of bleven bestaan en sommige NPS verdwenen vaker. In het onderzoek zijn NPS onderverdeeld in subgroepen. Het merendeel van de mensen met dementie liet één of meer symptomen zien in de subgroep stemming/apathie en in de subgroep hyperactiviteit (72 % versus 75 %) tijdens het onderzoek. Bij mensen met dementie met één of meer symptomen bij het eerste meetmoment van het onderzoek, bleven deze bij 20 % tot 25 % van de mensen met dementie tijdens de gehele duur van het onderzoek bestaan. Ongeveer de helft van de mensen met dementie, die geen symptomen hadden in de subgroep stemming/apathie en hyperactiviteit bij het eerste meetmoment van het onderzoek, vertoonden deze symptomen wel bij één van de volgende meetmomenten (48 % versus 55 %). De klinisch relevante symptomen doelloos repetitief gedrag, apathie en in iets mindere mate agitatie/agressie kwamen vaak voor tijdens de 18 maanden (59 %, 51 % en 46 %) van het onderzoek.

Apathie en agitatie/agressie waren de symptomen, die het meest frequent bleven bestaan. Veel mensen met dementie hadden geen symptomen uit de subgroep psychose. Wanneer deze symptomen van agitatie/agressie nader worden bekeken, dan blijkt dat de subgroep met verbaal geagiteerde symptomen het meest voorkomt tijdens de duur van het onderzoek, evenals de subgroep met fysiek niet-agressieve symptomen (88 % versus 83 %). Deze symptomen ontstonden ook vaak voor het eerst na de start van het onderzoek (64 % versus 58 %) of bleven bestaan tijdens de duur van het onderzoek (48 versus 69 %). Er is geen klinisch relevant verband gevonden tussen de onafhankelijke variabelen bij de start van het onderzoek (leeftijd, geslacht en cognitie van de patiënt, gebruik van psychofarmaca, gebruik van respijtzorg of persoonlijke verzorging van de patiënt, psychologische belasting van de mantelzorgers en deelname aan het zorgprogramma CONCERN) en het beloop van NPS in de tijd.

Hoofdstuk 6 beschrijft de resultaten naar het beloop van psychologische belasting bij de mantelzorgers in de huisartsenpraktijk. Bij de start van het onderzoek hadden 23 % van de mantelzorgers van mensen met dementie een hoog risico op depressie (gemeten met de CES-D) en bij 41 % van hen was het waarschijnlijk, dat ze psychologische symptomen hadden volgens de GHQ-12. De totale groep van mantelzorgers liet een stabiel niveau zien van psychologische belasting tijdens het onderzoek (SCQ). Er is een verband tussen de mate van NPS bij de patiënt en de ervaren psychologische belasting bij de mantelzorger. Er is ook een verband tussen de leeftijd en het geslacht van de mantelzorger en de relatie met de patiënt en de mate van ervaren psychologische belasting. Vrouwelijke mantelzorgers, mantelzorgers in de leeftijd van 50 tot 70 jaar en echtgenoten/partners ervaren meer psychologische belasting. De ervaren psychologische belasting nam af, wanneer de patiënt waar zij zorg voor droegen werd opgenomen in een zorginstelling tijdens het onderzoek. Er is geen klinisch relevant verband gevonden tussen de onafhankelijke variabelen bij de start van het onderzoek (leeftijd en geslacht van de mantelzorger, relatie tussen patiënt en mantelzorger, cognitie en NPS bij de patiënt deelname aan het zorgprogramma CONCERN en opname in een zorginstelling) en het beloop van psychologische belasting bij de mantelzorgers in de tijd.

Ten slotte wordt in **hoofdstuk 7** een overzicht gegeven van de belangrijkste bevindingen uit dit proefschrift en is er een beschouwing opgenomen over de gekozen methodologie. De consequenties van deze bevindingen voor de zorg voor mensen met dementie en hun mantelzorgers in de huisartspraktijk worden bediscussieerd en aanbevelingen voor toekomstig onderzoek worden gedaan. De eindconclusies zijn, dat huisartsen alert moeten zijn op de aanwezigheid van NPS bij mensen met dementie en op de psychologische belasting hiervan bij de mantelzorgers. En dat huisartsen NPS en psychologische belasting bij de mantelzorgers actief moeten opsporen om op tijd adequate professionele zorg te kunnen inzetten.

ABBREVIATIONS

AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
(i)ADL	(instrumental) activities of daily living
CES-D	Center for Epidemiological Studies Depression Scale
CI	confidence interval
CM	case manager
CMAI	Cohen-Mansfield Agitation Inventory
CMO	Committee on Research Involving Human Subjects (Commissie Mensgebonden Onderzoek)
CONCERN	Care Optimization for Non-professional Caregivers of Elderly with dementia and Reduction of Neuropsychiatric symptoms
CSDD	Cornell scale for depression in dementia
DelpHi-MV	Dementia life- and person-centered help in Mecklenburg - Western Pomerania
Dyad	patient and caregiver
GHQ	General Health Questionnaire
GP(s)	general practitioner(s)
LASER-AD	London And the South East Region – Alzheimer's Disease
LBD	dementia with Lewy bodies
LTCF	long-term care facilities
MAASBED	MAAstricht Study of BEhaviour in Dementia
MMSE	Mini-Mental State Examination
n	number of participants
NMDAR	N-methyl-d-aspartate receptor antagonist
NPI(-Q)	Neuropsychiatric Inventory (- Questionnaire)
NPS	neuropsychiatric symptoms
p	calculated probability
PPA	patients per assessment
RCT	randomized controlled trial
REAL.FR	Réseau sur la Maladie d'Alzheimer Français
SCQ	Sense of Competence Questionnaire
SD	standard deviation
SSRIs	selective serotonin re-uptake inhibitors or serotonin-specific reuptake inhibitors
VaD	vascular dementia

CURRICULUM VITAE

Petra Borsje werd geboren op 20 oktober 1972 in Spijkenisse. In 1991 behaalde ze het vwo-diploma op de Blaise Pascal te Spijkenisse. Aansluitend studeerde ze geneeskunde aan de Erasmus Universiteit te Rotterdam. In november 1995 behaalde ze het doctoraalexamen, nadat ze haar afstudeeronderzoek op de afdeling kinderlongziekten in het Sophia Kinderziekenhuis in Rotterdam had afgerond. Voorafgaande aan de coschappen deed ze begin 1996 een onderzoeksstage bij de Department of Pharmaceutical Sciences and Drug Research aan de Punjabi University in Patiala, India. Na de reguliere coschappen, volgde ze in het voorjaar van 1998 een keuzecoschap in het Tshilidzini Hospital in Shayandima, Zuid-Afrika. Het artsexamen behaalde ze in juli 1998.

Na werkzaam te zijn geweest als arts-assistent niet in opleiding op de afdeling interne geneeskunde in het Groene Hart Ziekenhuis in Gouda, bij de GGD in Gouda en verpleeghuis De Riethoek in Gouda startte ze in september 2000 met de verpleeghuisartsopleiding bij GERION in het VU medisch centrum. Zij werkte tijdens haar opleiding in verpleeghuis Schiehoven en verpleeghuis Antonius IJsselmonde in Rotterdam en in verpleeghuis De Plantage in Brielle. In januari 2003 werd zij geregistreerd als verpleeghuisarts, deze functie heet sinds 2009 specialist ouderengeneeskunde.

Van september 2005 tot en met december 2006 volgde zij de Kaderopleiding Psychogeriatrie bij GERION in het VU medisch centrum. Zij is ingeschreven in het register voor kaderartsen psychogeriatrie. Vanaf september 2016 is zij stafdocent bij de Kaderopleiding Psychogeriatrie. Van 2007 tot en met 2011 was zij lid van de congrescommissie van Verenso, de beroepsvereniging voor specialisten ouderengeneeskunde, vanaf januari 2011 als voorzitter.

Als specialist ouderengeneeskunde is zij na haar registratie werkzaam geweest in verpleeghuis De Plantage in Brielle en van 2007 tot en met 2010 als zelfstandig specialist ouderengeneeskunde voor meerdere zorginstellingen in het zuidwesten van Nederland. Van 2011 tot en met 2014 werkte zij voor Thebe in de regio Zuid-Oost. Een deel van deze aanstelling was beschikbaar voor het uitvoeren van het onderzoeksproject, wat uiteindelijk tot dit proefschrift heeft geleid. Aansluitend was zij 2 jaar werkzaam voor Laurens vanuit locatie Antonius Binnenweg, onder andere op een afdeling voor jonge mensen met dementie. Vanaf januari 2017 is zij weer zelfstandig werkzaam vanuit haar eigen Praktijk Borsje. Zij werkt samen met verschillende huisartsen als consulent en/of medebehandelaar in de thuissituatie of vanuit kleine, al dan niet particuliere, zorgorganisaties.

Petra is getrouwd met Sebastiaan en samen met hun twee kinderen, Anne en Thijs, wonen ze in Spijkenisse. In haar vrije tijd houdt ze van wandelen, hockeyen en verre reizen maken.

LIST OF PUBLICATIONS

This thesis:

Borsje P, Wetzels RB, Lucassen PLBJ, Pot AM, Koopmans RT. Neuropsychiatric symptoms in patients with dementia in primary care: a study protocol. BMC Geriatrics 2014;14:32.

Borsje P, Wetzels RB, Lucassen PL, Pot AM, Koopmans RT. The course of neuropsychiatric symptoms in community-dwelling patients with dementia: a systematic review. International Psychogeriatrics 2015;27(3):385-405.

Borsje P, Hems MAP, Lucassen PLBJ, Bor H, Koopmans RTCM, Pot AM. Psychological distress in informal caregivers of patients with dementia in primary care: course and determinants. Family Practice 2016;33(4):374-381.

Borsje P, Lucassen PLBJ, Wetzels RB, Pot AM, Koopmans RTCM. Neuropsychiatric symptoms and psychotropic drug use in patients with dementia in general practices. Family Practice 2018;35(1):22-28.

Borsje P. Lucassen PLBJ, Bor H, Wetzels RB, Pot AM, Koopmans RTCM. The course of neuropsychiatric symptoms in patients with dementia in primary care. Family Practice 2018, December 4. [Epub ahead of print]

Other publications:

Borsje P, de Jongste JC, Mouton JW, Tiddens HAWM. Aerosol Therapy in Cystic Fibrosis: A Survey of 54 CF Centers. Pediatr Pulmonol 2000;30(5):368-376.

Borsje P, Verburg D. Atypische presentatie van preseniele ziekte van Alzheimer. Tijdschrift voor verpleeghuisgeneeskunde 2009;34(4):141-144.

DANKWOORD

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