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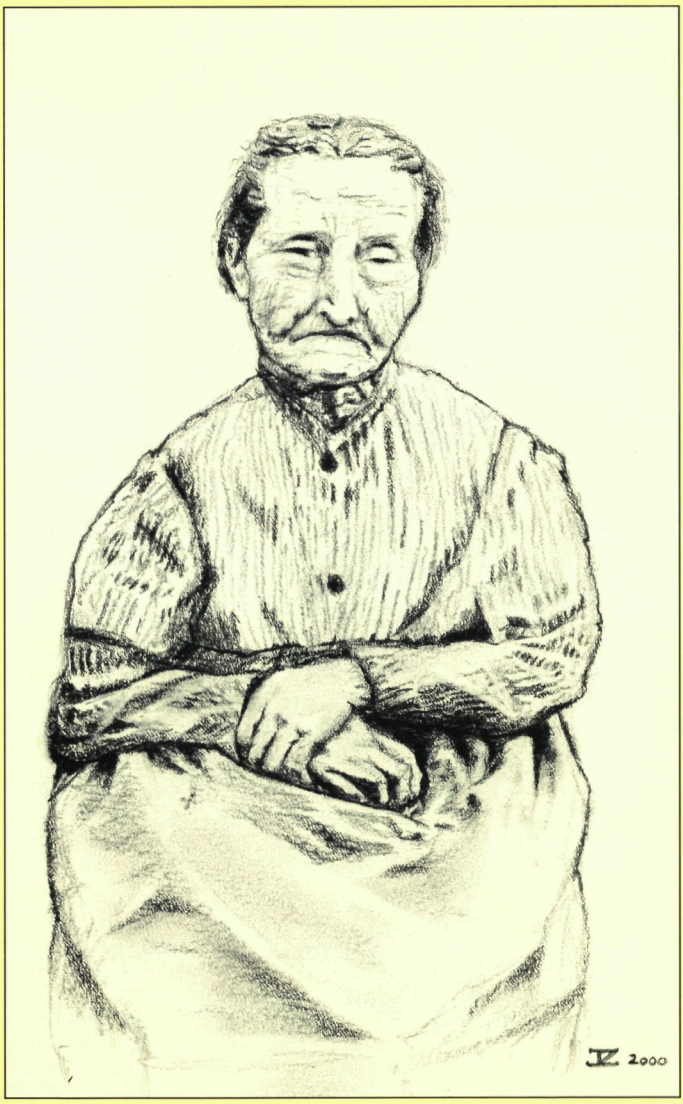
DEPRESSION IN DEMENTIA

A Longitudinal Study in Residents of Homes for the Elderly



J.G.E. Janzing

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A Longitudinal Study in Residents of Homes for the Elderly

Een wetenschappelijke proeve op het gebied
van de Medische Wetenschappen.

Proefschrift

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aan de Katholieke Universiteit Nijmegen,
volgens besluit van het College van Decanen in het
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DEPRESSION IN DEMENTIA

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CONTENTS

Chapter 1

Introduction, aim and outline of the study

INTRODUCTION

In his "Leerboek der Psychiatrie" *(Textboek of Psychiatry)* Jelgersma describes the change of mood in "dementia senilis" as follows (Jelgersma 1926):

> '....De gevoelsprocessen nemen aan den algemeenen achteruitgang der geestvermogens evenzeer deel. De belangstelling vermindert en voor nieuwe dingen wordt al spoedig bijna in het geheel niets meer gevoeld. Deze algemeene vermindering van den gevoelstoon, die bij den normalen mensch de groote drijver voor alle handelingen is, moet er natuurlijk veel toe bijdragen, de apathie van den patient te vermeerderen. De lijder wordt dan ook tot niets meer gedreven, geheele dagen kan hij stil voor zich heen zitten broeden, niets interesseert hem meer of drijft hem tot handelen. Hij heeft geen wenschen meer en spant zich dus ook nergens voor in. De hoogere gevoelens gaan natuurlijk het eerst verloren; daardoor worden de lagere duidelijker en openbaren deze zich minder geremd. De patient luistert meer naar zijne directe lichamelijke behoeften, uit zich ongegeneerder, kan zich niet meer beheerschen tegenover de dagelijksche kleine moeilijkheden. Het lichamelijk welbevinden, het eten, het rooken, de toestand der digestieorganen neemen een veel grotere plaats in dan vroeger, terwijl de slagen van het noodlot, het verlies van nabestaanden, het verdriet van anderen veel minder indruk gaan maken....'
>
> *(Translated from Dutch)*
> '... The emotional processes participate just as greatly in the general deterioration of the mental functions. There is a loss of interest and very soon, there is almost no feeling at all for new things. This general decline in the tone of feeling, which in normal people is otherwise the great initiator of all actions, obviously makes a great contribution to increasing the apathy of the patient. The sufferer is inert, he may sit brooding quietly for days, nothing will interest him or stir him into action. He no longer has any desires and therefore makes no effort at all. The higher feelings are naturally lost first; that is why the lower ones become more apparent and emerge more unashamedly. The patient listens more closely to his direct physical needs, expresses himself without embarrassment, can no longer take charge over small daily troubles Physical well-being, eating, smoking and the state of the digestive organs occupy a far greater vista than before, whereas the strikes of fate, the loss of relatives and the sorrow of others make far less impression...'

Systematic research shows that symptoms of depression occur frequently in patients with dementia (Wragg & Jeste 1989, Janzing et al. 1993). A number of possible explanations are available for the relationship between depression and dementia.

1. Depression can be considered as a reaction to the presence of progressive dementia. For a long time it has been suggested that patients with beginning dementia become depressive when they realize the deterioration in their cognitive functions (Reifler et al. 1982).
2. Depression might have a biological basis. Accordingly, it is the consequence of dysfunction of the brain. The specific nature of the symptomatology depends on the localisation of the defects or the diminished function of specific neurotransmitter systems (Kral 1983, Cummings 1986).
3. A combination of both the aforementioned hypotheses is possible: a proportion of the depressive symptoms may be reactive and a proportion biologically based.

4. There may not be any specific relationship between dementia and depression. According to this hypothesis there is no difference in the nature and the frequency of the symptoms between elderly subjects with and without dementia (Wragg & Jeste 1989).

Many factors complicate the study of psychiatric symptoms in patients with dementia. Owing to their disturbed cognitive functions, it is often difficult to interview these patients. In longitudinal studies, investigators have to anticipate high drop-out rates because of mortality and morbidity. Furthermore, various confounders potentially influence the relationships between psychiatric symptoms and dementia (e.g. the subject's physical health). Finally, there is also evidence of an overlap between the symptoms of depression and those of dementia. The DSM-IV manual refers to this subject as follows (American Psychiatric Association 1994):

....'in elderly persons, it is often difficult to determine whether cognitive symptoms (e.g. disorientation, apathy, difficulty concentrating, memory loss) are better accounted for by a dementia or by a major depressive episode. A thorough medical evaluation and an evaluation of the onset of the disturbance, temporal sequencing of depressive and cognitive symptoms, course of illness and treatment response are helpful in making this determination. The premorbid state of the individual may help to differentiate a major depressive episode from a dementia. In a dementia, there is usually a premorbid history of declining cognitive function, whereas the individual with a major depressive episode is much more likely to have a relatively normal premorbid state and abrupt cognitive decline associated with the depression.'.....

AIM

The aim of this study was to gain more insight into the relationship between depression and dementia. Cohorts of subjects with and without dementia, living in homes for the elderly, were observed during a 12 month period. The study had a controlled prospective design.

OUTLINE

Chapter 2 reviews the literature regarding psychiatric comorbidity (depression, psychosis and behavioural disturbances) in subjects with dementia.

In Chapter 3 the presence of symptoms of DSM-III-R major depressive episode are investigated in subjects with severe dementia, mild dementia and no dementia.

In Chapter 4 the prevalences of a number of GMS-AGECAT-derived depression measures are studied in subjects with and without dementia.

In Chapter 5 the effects of GMS-AGECAT-derived depression measures on the mortality of subjects with dementia are reported.

Chapter 6 presents a study on the course of depression in subjects with and without dementia.

Chapter 7 gives a general discussion of the results of this thesis.

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Chapter 2

The prevalence of psychiatric comorbidity in Dementia of the Alzheimer Type (DAT); A review of the literature.

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ABSTRACT

This article offers a critical review of the published research concerning the prevalence of depressions, psychotic symptoms and disorders of behaviour in patients with Dementia of the Alzheimer Type (DAT). For any of these types of psychopathology there is much diversity in the reported prevalences. Controlled studies seem to indicate that patients with DAT have an increased prevalence of psychotic symptoms and disorders of behaviour but not of depressions. Higher rates of disorders of behaviour are encountered in patients with more serious dementia.

Information about the relationship between the prevalences of depressions or psychotic symptoms and the stage of the dementia is less equivocal. There is much variation in the applied diagnostic methods and the studied populations. No attention was paid to the overlapping symptoms of DAT and psychopathology. The conclusion is that up till now the knowledge concerning the prevalence of psychopathology in DAT is very global.

INTRODUCTION

The dementia syndrome (Schulte 1989) is characterized by a decline in short and long term memory in addition to one of the following symptoms: a disturbance of abstract thinking, impaired judgement, apraxia, aphasia, agnosia and a change of personality. The disturbances interfere with work, social activities and relationships. They do not exclusively occur during the course of delirium.
Dementia of the Alzheimer Type (DAT) is the most prevalent type of dementia. The diagnosis can be made if the onset of dementia is insidious, the course is progressively deteriorating and other causes of dementia have been excluded (American Psychiatric Association 1987).
In accordance with other types of dementia, DAT may be accompanied by psychiatric disorders like depression, psychosis and behavioural disturbances. Up to the present, psychiatric comorbidity has attracted less attention than the cognitive impairment. Its importance can be illustrated as follows:

1. Psychiatric comorbidity complicates the care for patients with dementia. (O'Connor et al. 1990, Pot and van Dyck 1992). Prospective studies have shown that it is a risk factor for admittance in nursing homes (Steele et al. 1990, O'Donnell et al. 1992).
2. Although for DAT there is no causal therapy available, comorbid psychiatric disorders may respond to symptomatic treatments (Schulte 1989).
3. Since DAT possibly includes a heterogenic group of illnesses, psychiatric symptomatology could be used to identify subtypes of dementia (Burns et al. 1990a)

Several studies report prevalences of psychopathology in dementia. They are summarized in this review.

METHODS

The articles from 1981 until 1992 on prevalences of depression, psychotic symptoms and behavioural disturbances in DAT were selected using Medline. Case studies and reviews without new results were excluded.

RESULTS

Depression.

A total of 23 studies report prevalences of depression in DAT. The prevalences ranged from 0 to 85%. The diagnostic methods can be divided in three groups. Most investigators make a DSM-III-R diagnosis of major depression (American Psychiatric Association 1987). Others use depression symptom rating scales. Examples are the Hamilton Rating Scale for Depression (Hamilton 1960), the

Zung (Zung 1965) and the Schedule for Affective Disorders and Schizophrenia (Endicot and Spitzer 1978). Finally there are instruments which have been specifically developed for the diagnosis of psychiatric disorders in dementia such as the Cornell Scale for Depression in Dementia (Alexopoulos et al. 1988), the Columbia University Scale for Psychopathology in Alzheimer's disease (CUSPAD; Devanand et al. 1992) and the Behavioral and Emotional Activities Manifested in Dementia (BEAM-D; Sinha et al. 1992).
The diagnosis of depression is based on anamnesis, heteroanamnesis and observation. MacKenzie et al. (1989) showed that the source of information affects the results. Based on anamnesis, the prevalence of DSM-III major depression was 13.9%. The prevalence rose to 50% if the same criteria were applied to the heteroanamnestic information.
Only 5 studies compare the depression prevalences of subjects with and without dementia. The prevalences ranged from 11.4 to 18% in DAT-patients and from 0 to 21% in the controls. Depression is more frequent in DAT-patients than in controls in three studies (Lazarus et al. 1987, Patterson et al. 1990, Fischer et al. 1990). In contrast, Burke et al. (1989) found more depression in the controls. No difference was found in the study of Knesevich et al. (1983). The variation in these results may be due to the composition of the control groups: a lower prevalence of depression can be expected in paid and healthy volunteers (0%; Lazarus et al. 1987) than in patients referred to a geriatric research centre (21%; Burke et al. 1989).

Several studies investigated if the prevalences of depression changed with the severity of dementia (Mini Mental State Examination score (MMSE; Folstein et al. 1975). In most of them no relationship was found (Breen et al. 1984; Reifler et al. 1986; Krishnan et al. 1988; MacKenzie et al. 1989; Cooper et al. 1990; Patterson et al. 1990; Weiner et al. 1991). Depression was more frequent in mild dementia in two studies (Pearson et al. 1990; Fischer et al. 1990). On the other hand, Rovner et al. (1990) and Devanand et al. (1992) found increased prevalences of depression in the more severe stages of dementia. Again, the information on which the diagnosis of depression was based influenced the results. The patients with mild cognitive disturbance reported more depressive symptoms than those with severe dementia. However, the numbers of depressive symptoms observed by investigators and reported by informants were not related to the severity of dementia.

Psychotic symptoms: delusions, hallucinations and misidentification syndromes.

Prevalences of psychotic symptoms in DAT-patients are reported in 13 studies. The diagnosis is based on anamnesis, heteroanamnesis and observation. A variety of instruments is available for standardized data collection: the Present State Examination (Wing et al. 1974), the Geriatric Mental State (GMS; Copeland et al. 1976), the Diagnostic Interview Schedule (DIS; Robins et al. 1981), the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX; Roth et al. 1986), the Scale of psychosis in AD (Reisberg et al. 1985), the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD; Reisberg et al. 1987) and the

Behavioral and Emotional Activities Manifested in Dementia (BEAM-D; Sinha et al. 1992).
Delusions are defined according to the DSM-III-R criteria (American Psychiatric Association 1987). The prevalence of delusions ranged from 10.6 to 52%. Especially paranoid delusions are frequent in DAT patients. They mostly refer to theft (Cummings et al. 1987; Drevets and Rubin 1989; Patterson et al. 1990; Burns et al. 1990a; Lopez et al. 1991; Deutsch et al.1991; Jeste et al. 1992; Devanand et al. 1992).
A hallucination is described as the hearing of voices or the perception of objects or persons in the absence of an external stimulus. Also the interaction between a patient and non-existent objects is considered as indicative for hallucinations. In 3.3 to 36% of the DAT-patients hallucinations are observed. Visual hallucinations are the most prevalent type followed by acoustical hallucinations. Hallucinations in other modalities are rare (Drevets and Rubin 1989; Patterson et al 1990; Burns et al. 1990a; Lopez et al. 1991; Deutsch et al. 1991; Jeste et al. 1992; Devanand et al. 1992).
Misidentification syndromes are reported in three studies (Drevets and Rubin 1989; Burns et al. 1990b; Deutsch et al. 1991). A misidentification syndrome is diagnosed when the patient does not recognize familiar persons and sees them as intruders, recognizes a different person in his own mirror image or if he believes that persons on television are really present (Burns et al.1990b).
The prevalence of misidentification syndromes varies from 9 to 36% in DAT-patients.
Control groups of persons without cognitive impairment participated in only two studies. Psychotic symptoms were less common in controls than in DAT patients. They were completely absent in the healthy volunteers of Drevets and Rubin (1989). Patterson et al. (1990) reported that psychotic symptoms are rare in partners of DAT patients.
It is unclear if the prevalence of psychotic symptoms is related to the severity of dementia (MMSE score). Five studies found no significant association (Cummings et al. 1987; Teri et al. 1988; Burns et al. 1990a; Burns et al. 1990b; Sinha et al. 1992). The prevalence of psychotic symptoms increased with the severity of dementia in four studies (Patterson et al. 1990; Cooper et al. 1990; Devanand et al. 1992; Jeste et al. 1992). In agreement, Drevets and Rubin (1989) conclude that psychotic symptoms are more common in patients with severe dementia (according to the Clinical Dementia Rating scale, (CDR; Hughes et al. 1982). They found the highest levels of psychotic symptoms in patients with moderate dementia (CDR=2). Their finding that the prevalence did not increase further in patients with severe dementia (CDR=3) was explained by underdiagnosis of psychotic symptoms due to incoherent speech in these patients.

Behavioural disturbance.

Ten studies report prevalences of behavioural disturbances in DAT-patients. Definitions of behavioural disturbances are lacking in most studies. The conceptual vagueness is increased by the fact that several authors bring different

symptoms together in clusters. Cooper et al. (1990) present combined prevalences of anger and agitation and of personality change and apathy. Rubin et al. (1987a) label self-centeredness, loss of concern for others, crude behaviour and loss of emotional control as 'self centered behaviour'. The diagnosis of behavioural disturbances is based on heteroanamnesis and observation. The diagnostic methods vary from neuropsychiatric evaluation to standardized instruments like the Blessed Dementia Scale (Blessed et al. 1968), the behavioral problems checklist (Teri et al. 1989), the Stockton Geriatric Rating Scale (Mere and Baker 1966), the Behavioral Pathology in Alzheimer's Disease (BEHAV-AD; Reisberg et al. 1987) and the Behavioral and Emotional Activities Manifested in Dementia (BEAM-D; Sinha et al. 1992).

Aggression, agitation, apathy and wandering are the most frequently reported disturbances of behaviour in DAT. The prevalences vary from 11 to 35% for aggression; from 24 to 53.4% for agitation; from 21 to 43.4% for apathy and from 3 to 26.5% for wandering. Behavioural disturbances are rarely diagnosed in controls without dementia (Rubin et al. 1987a, Patterson et al. 1990).
Several cross-sectional studies report that the prevalences of behavioural disturbances are positively associated with the severity of dementia (Teri et al. 1988; Burns et al. 1990d; Cooper et al. 1990; Sinha et al. 1992). In agreement, longitudinal studies found that behavioural disturbances became more common with the decline of cognitive function (Rubin et al. 1987b).

DISCUSSION

It is difficult to study psychiatric comorbidity in DAT. Two conceptual problems play a role. First it can be hard to differentiate psychopathology from dementia itself. Wellknown are problems to distinguish between depression and dementia (American Psychiatric Association 1987; Heeren 1988; van Tilburg 1992). Symptoms like disorientation, apathy, concentration disturbances and impairment of memory can appear in the context of both syndromes. The investigator's interpretation of these overlapping symptoms may influence the prevalence rates of psychiatric comorbidity. In the studies described in this review this problem is not discussed.
Secondly, the psychiatric comorbidity in DAT is described with concepts and criteria derived from psychiatric disturbances in subjects without cognitive impairment. For instance, the criteria of DSM-III-R for major depression are applied to study depression in DAT. So, it is suggested they have the same appearance in patients with and without DAT. The legitimacy of this assumption is questionable. Changes in cognitive function in subjects with dementia are likely to influence the nature, the experience and the presentation of psychopathology. In addition the assessment of symptoms based on the subject's introspection (for instance anhedonia) will be more difficult as the severity of cognitive impairment increases.

Apart from conceptual issues differences in methodology caused variation in the prevalence rates. First, it is important what population is studied. Higher prevalences of psychiatric symptoms can be expected in patients attending a psychiatric clinic than in DAT patients who take part in a community study. Moreover, there are differences in in- and exclusion criteria. So patients with a psychiatric history or patients with severe dementia are included in some but excluded from other studies. A further cause of variability is the diagnosis of dementia. In most studies the criteria for primary degenerative dementia of the Alzheimer Type according to the DSM-III-R criteria (American Psychiatric Association 1987) or the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhan et al. 1984) are used. These criteria have only been operationalized to a limited extent. Therefore the investigator's interpretation plays an important role.

Finally differences in diagnostic methods led to variability of results. The diagnostic instruments differ in the nature of symptomatology which is assessed, the period in which the symptoms are measured and the origin of the information.

CONCLUSION

1. Depression, psychotic symptoms and disturbances of behaviour are common in DAT-patients. There is a marked variation in the prevalence rates. Because of important methodological differences it is concluded that the specific prevalence rates can not be generalised.
2. In contrast to depression, psychotic symptoms and disturbance of behaviour are rare in subjects without cognitive disturbance. However the number of controlled studies is small.
3. The prevalence of behavioural disturbance increases with the severity of dementia. The relationship between the stage of dementia and the prevalences of depression or psychotic symptoms is unclear.
4. Psychiatric symptoms and symptoms of dementia can not always be differentiated. The concepts and criteria derived from 'functional' psychiatry have been applied without further consideration.

Taken together the actual knowledge on psychopathology in DAT is very global. Future research should be directed to find solutions for the above mentioned conceptual problems.
A number of areas and research methods have attracted limited attention.
1. Little is known about the prevalence of psychiatric comorbidity of DAT in populations outside specialized research centres and clinics.
2. Longitudinal studies and controlled studies have been rarely performed. Longitudinal designs are important to get insight into the relationship between the course of dementia and the development of psychiatric symptoms. Controlled

studies can help to measure the specific influence of DAT on the prevalence of psychiatric comorbidity.

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Chapter 3

Mood and motivation disturbance in elderly subjects with and without dementia: a replication study.

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INTRODUCTION

Using principal component analysis, Forsell et al. (1993) divided the DSM-III-R criteria for major depressive episode (American Psychiatric Association 1987) in a sample of elderly subjects with and without dementia into two factors. The factor of motivation disturbance consisted of loss of interest, psychomotor change, loss of energy and thinking or concentration disturbance. The factor of mood disturbance consisted of dysphoria, appetite disturbance, feelings of guilt and suicidal ideation.
Scores for mood disturbance were highest in subjects with mild dementia and low in those with more severe stages of dementia. In contrast, scores for motivation disturbance increased proportionally with the severity of dementia.
The importance of these findings is twofold.
First, although different divisions of depressive symptoms were used in earlier studies (Lazarus et al. 1987, Patterson et al. 1990, Troisi et al. 1993), the two-factor model is the first which is empirically based.
Second, the positive relationship between motivation disturbance and dementia severity suggests that an important part of the depressive symptomatology in the sample of Forsell et al. was organically based. This finding may have implications for diagnosing depression in demented subjects.

The present study was designed to see if the results of Forsell et al. could be generalised to a population of residents of homes for the elderly.

METHODS

Subjects

The study was performed at 6 homes for the elderly in the region of Nijmegen, the Netherlands. Informed consent was obtained from the residents themselves and in case of severe cognitive impairment from their close relatives.
Subjects without dementia and subjects with mild and severe dementia were selected using the following design:

Step 1: screening

All residents underwent the Mini Mental State Examination (MMSE, Folstein et al. 1975) and the Short Blessed Test (SBT, Katzman et al. 1983). In subjects with scores indicative of normal cognitive function (MMSE$\geq$24 and SBT$\leq$6) or cognitive impairment (MMSE $\leq$24 and SBT >6) further diagnosis took place according to step 2.

Step 2: further diagnosis

Based on information elicited with the Clinical Assessment Battery (CAB) of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris et al. 1989) it was considered whether the subjects fulfilled the DSM-III-R criteria for dementia (American Psychiatric Association 1987).
The demented subjects in the present study had both DSM-III-R dementia and cognitive impairment in step 1. They were classified as mildly demented (MMSE scores from 18 to 24) or severely demented (MMSE scores from 0 to 17) (Weissman et al. 1985).
The subjects without dementia did not fulfil the DSM-III-R criteria for dementia and had normal cognitive function in the screening phase.

Exclusion criteria were: inability to be tested (severe deafness, severe visual handicap, severe aphasia, too demented), CVA and normal cognitive function in the screening phase, Parkinson's disease, chorea, alcoholism, mental retardation, participation of the partner and missing data on depressive symptoms.

Depressive symptoms

The criteria of DSM-III-R major depressive episode were assessed with the Geriatric Mental State (GMS, Copeland et al. 1976).

Statistics

Chi-square analysis and one-way ANOVA were used for comparisons of demographic variables. The associations between depressive symptoms were expressed as Pearson's correlation coefficients. A principal component analysis with varimax rotation was carried out on the nine symptoms of major depressive episode. The relationship between scores on clusters of depressive symptoms and dementia severity was studied using regression analysis and analysis of covariance. The threshold for significance was $P<0.05$.

RESULTS

201 residents met the inclusion criteria: 110 subjects without dementia, 56 with mild dementia and 35 with severe dementia. Their demographic characteristics are presented in table 1.

Table 1. Demographic characteristics

	No dementia (n=110)	Mild dementia (n=56)	Severe dementia (n=35)
Age in years* (mean(sd))	83.2 (6.6)	87.1 (5.6)	85.1 (5.4)
Sex (%)			
Men	11.8	17.9	8.6
Women	88.2	82.1	91.4
Education in years (mean(sd))	7.0 (2.0)	6.9 (1.6)	7.3 (2.5)
Marital Status (%)			
Married	4.6	7.1	0.0
Widowed	80.9	83.9	85.7
Divorced	0.9	1.8	2.9
Unmarried	13.6	7.1	11.4

* Oneway ANOVA $p<0.001$

The three groups were comparable regarding education, sex and marital status. They differed significantly in age (subjects without dementia 83.2 sd=6.6 years, mild dementia 87.1 sd=5.6 years, severe dementia 85.1 sd=5.4 years; one-way ANOVA $F=7.6$ $p<0.001$). Therefore all further comparisons between groups were adjusted for age.

There were low prevalences of DSM-III-R major depressive episode in all groups: 0.9% (1 subject) in the controls, 0.0% (0 subjects) in the mildly demented and 5.2% (2 subjects) in the severely demented subjects. The symptoms dysphoria and feelings of guilt had the lowest prevalences (2.0% and 4.0% respectively). Highly prevalent were psychomotor change (17.9%), thinking or concentration disturbance (14.4%) and loss of energy (13.4%).

The associations between the individual depressive symptoms and all other depressive symptoms were studied for the total sample. The highest Pearson's correlation coefficients were found for loss of energy ($r=0.42$ $p<0.005$), loss of interest ($r=0.39$ $p<0.005$) and appetite disturbance ($r=0.37$ $p<0.005$). Only the association between sleep disturbance and the other depressive symptoms was insignificant ($r=0.06$).

Table 2 presents the results of the principal component analysis with varimax rotation of the symptoms of DSM-III-R major depressive episode. In agreement with Forsell et al. (Forsell et al. 1993) two factors were drawn. Symptoms with factor loadings greater than 0.40 were dysphoria, appetite disturbance, feelings of guilt and thoughts of death on the first factor and loss of interest, psychomotor change, loss of energy and thinking or concentration disturbance on the second. Sleep disturbance had low factor loadings on both factors. The factors were identical to those found by Forsell et al. (Forsell et al. 1993). They accounted for 26.6% en 16.7% of the variance respectively.

Table 2 *Factor loadings of symptoms of DSM-III-R Major Depressive Episode in 201 subjects with and without dementia*

Symptom	Mood disturbance	Motivation disturbance
Dysphoria	0 72	-0 06
Loss of interest	0 03	0 78
Appetite disturbance	0 68	0 22
Sleep disturbance	0 23	-0 09
Psychomotor change	-0 20	0 63
Loss of energy	0 20	0 69
Feelings of guilt	0 51	0 29
Thinking/concentration	0 12	0 45
Thoughts of death	0 81	0 13

Finally the associations between the factor scores and dementia severity were studied. There was a positive linear association between the factor scores of motivation disturbance and dementia severity (regression coefficient adjusted for age B=0.52; 95% CI: 0.37-0.67 p<0.0001). There was no linear relationship between the factor scores of mood disturbance and dementia severity. The scores on this factor were comparable for controls, mildly and severely demented subjects (analysis of covariance adjusted for age F=1.08 p=0.34).

DISCUSSION

The present study replicated the depressive factors found by Forsell et al. (1993) in a sample of residents of homes for the elderly. The residents can be considered as the most vulnerable elderly living in society (Van Loveren-Huyben and Van der Bom 1983).
The prevalence of major depressive episode was considerably lower than in the subjects of Forsell et al. (1.5% [range 0-5.2%] and 5.7% [range 4-14%] respectively). The lower syndrome rate in our subjects is reflected by the lower correlation coefficients between the depressive symptoms. It may be explained by a number of factors including demographic characteristics and better care facilities at homes for the elderly.

The principal component analysis revealed identical factors of motivation and mood disturbance. Together they explained a comparable percentage of variance. Scores for motivation disturbance increased in proportion to the severity of dementia. There was no significant relationship between the factor scores for mood disturbance and the severity of dementia. Forsell et al. (1993) who found different factor scores for mood disturbance according to the stage of dementia, reported the highest scores in subjects with mild dementia. This discrepancy between our studies can probably be attributed to different sample characteristics.

The replication of the main results of Forsell et al. in a sample consisting of residents of homes for the elderly with a relatively low prevalence of major depressive episode supports the validity of their two-factor model.

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Chapter 4

Depression in subjects with and without dementia; a comparison using GMS-AGECAT.

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ABSTRACT

Background
The results of comparisons of depression between subjects with and without dementia are inconclusive. Confounders may have played a role.

Method
Ninety-one subjects with DSM-III-R dementia and 110 controls without dementia were recruited from homes for the elderly using an identical procedure. The prevalences of AGECAT depressive syndromes, subsyndromes and factors of depressive symptoms were compared adjusting for confounders.

Results
Both groups had similar prevalences of AGECAT depressive syndromes, subsyndromes and overall rates of depressive symptoms. Subjects with dementia had significantly more 'motivation symptoms'. The scores of 'mood symptoms' were similar for both groups.

Conclusion
The results indicate that not (sub)syndrome measures of depression but the profile of depressive symptomatology is affected by dementia.

INTRODUCTION

Depressive disorders occur frequently in elderly subjects with dementia (Wragg & Jeste 1989, Janzing *et al,* 1993). Comparisons of depression in subjects with and without dementia have led to heterogenous results (see table 1). Apart from sample differences confounders may have played a role. Subjects with and without dementia differed in physical health and motivation, variables which are associated with depression (Beekman *et al,* 1995, Forsell *et al,* 1993). Furthermore partners of subjects with dementia served as controls while they have an increased risk for depression (Morris *et al,* 1988). In the present study, GMS-AGECAT (Copeland *et al,* 1976, 1988) was used for the assessment of depressive syndromes, subsyndromes and depressive symptoms. The prevalences of depression of subjects with and without dementia were compared adjusting for possible confounders.

Study	Subjects with dementia	Controls	Measure	Comparison of syndromes of depression	Comparison of symptoms (total rates)	Difference in the nature of symptomatology in subjects with dementia
Knesevich et al 1983	30 referred DAT patients	30 healthy volunteers	HDRS Zung	Not performed	HDRS more symptoms in subjects with dementia Zung comparable scores	More "problems with work & activities"
Lazarus et al 1987	44 referred DAT patients	42 healthy and paid volunteers	HDRS	Not performed	More symptoms in subjects with dementia	More intrapsychic symptoms (comparable in vegetative symptoms)
Burke et al 1988	44 referred DAT patients	58 healthy volunteers	Feighner symptoms	Not performed	Self report comparable scores Collateral source higher scores in subjects with dementia	More loss of interest, loss of energy, difficulty thinking, difficulty con centrating and psychomotor change
O'Connor et al 1990	58 community based with DSM III R dementia	286 community based with low MMSE scores	DSM III R major depression	Comparable prevalences (demented 5 1%, controls 9 4% N S)	Not performed	Less sleeping disorders more indiciveness and slowed thinking
Patterson et al 1990	34 referred DAT patients	21 spouses of DAT subjects	Cornell Scale for Depression	Not performed	Comparable total scores	More agitation, retardation, physical complaints and loss of interest
Fischer et al 1990	55 DAT + 37 MID referred patients	30 volunteers homes for the elderly	HDRS	Not performed	More symptoms in subjects with dementia	Not performed
Forsell et al 1993	213 community based with DSM III R dementia	430 community based subjects	symptoms of DSM III R major depression	Not performed	Not performed	Less mood related symptoms more motivation related symptoms
Troisi et al 1993	26 referred DAT patients	26 volunteers including partners	DSM III R major depression HDRS	Comparable prevalences (demented 23%, controls 11 5% N S)	Comparable HDRS scores	More vegetative symptoms (comparable intrapsychic symptoms)
Forsell et al 1998*	306 community based with DSM III R dementia	795 community based subjects	DSM IV major depression	Higher prevalence in demented subjects 11 8% than in controls 3 9%	Not performed	More loss of energy, thinking/concentration difficulties, loss of interest and psychomotor disturbance

* including the sample of Forsell et al 1993
DAT Dementia of the Alzheimer Type
MID Multi Infarct Dementia
HDRS Hamilton Depression Rating Scale

METHODS

Subjects

The study was approved by the Ethics Committee of the University Hospital. It was carried out at 6 homes for the elderly in the region of Nijmegen, the Netherlands. Informed consent was obtained from the residents themselves and in the case of severe cognitive impairment from close relatives. Subjects with and without dementia were selected using the following two-step design:

Step 1: screening of cognitive functions

The residents were examined with the Mini Mental State Examination (MMSE) (Folstein *et al,* 1975) and the Short Blessed Test (SBT) (Katzman *et al,* 1983). Subjects with scores indicative of a normal cognitive function (MMSE $\geq$24 and SBT$\leq$6) or cognitive impairment (MMSE$\leq$24 and SBT >6) completed step 2.

Step 2: diagnosis of dementia

In step 2 the Clinical Assessment Battery (CAB) of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was administered (Morris *et al,* 1989). Fulfilment of the DSM-III-R criteria for dementia (American Psychiatric Association, 1987) was based on the information obtained with this instrument. Subjects with dementia had a diagnosis of DSM-III-R dementia and cognitive impairment according to the screening instruments. Subjects without dementia with a normal cognitive function at screening served as controls.

The criteria for exclusion were: inability to be tested (severe deafness, a severe visual handicap, severe aphasia, too demented), a history of CVA with normal cognitive function at screening, a history of Parkinson's disease, choreatic disease, alcoholism, mental retardation, participation of the partner (so that partners of subjects with dementia could not serve as controls) and missing symptoms of depression.

Measures of depression

All subjects had a full psychiatric assessment using the Geriatric Mental State (Copeland *et al,* 1976). The measures of depression were derived from AGECAT, the computerised diagnostic package of the GMS-AGECAT system (Copeland *et al,* 1988) and were based on the syndrome clusters (AGECAT stage I) and symptom components (AGECAT preliminary stage).

a. Depressive syndromes. According to AGECAT, subjects can be classified as: 'not depressed', 'a subcase of depression' (subsyndromal depression) or 'a case of depression' (syndromal depression).

b. Depressive symptom score. For each subject the total number of positively rated AGECAT depression symptoms was computed (maximum score: 44).
c. Factors of depressive symptoms. Principal Component Analysis with varimax rotation divided the AGECAT-depressive symptoms in two factors. The factors explained 22% of the total variance and had sufficient Crohnbach's alpha's (>0.75).

The first factor ('motivation symptoms') contained the following items: fatigue; subjective slowing in thinking; subjective slowing in movements; lack of energy; reduced activity; slowness or anergy does not lift with pleasant activities; sits around because of anergia; loss of interest; sudden recent loss of interest; loss of interest because depressed.
The items of the second factor ('mood symptoms') were: worried about almost everything; worries; depressed mood; wanting to cry; life not worth living; wishes to be dead; sleep disturbance; tremulous feelings; loneliness; dissatisfaction.

The final factor scores were the sums of the positively rated items per factor (for both factors maximumscores of 10).

Statistics
Chi-square tests and Student's t-tests were used for comparisons of the demographic variables. Logistic regression analysis and analysis of covariance were carried out to compare the prevalences of depressive syndromes and symptoms of demented subjects and controls.

RESULTS

Subjects
From the total population of 601 residents, 201 subjects were eligible: 91 subjects with and 110 subjects without dementia. A total of 194 residents (32.3%) refused to participate, 33 (5.5%) were unavailable after the screening phase (11 moved, 17 died, 5 too ill), 76 (12.6%) did not fulfil the selection criteria and 97 (16.1%) were excluded (12 untestable, 37 CVA with normal cognitive functioning at screening, 7 Parkinson's disease, 3 choreatic disease, 9 alcoholism, 3 mental retardation, 10 partners of participants and 16 had insufficient numbers of depressive symptoms).
The demographic characteristics of the participants are listed in table 2.

Table 2. Demographic characteristics of subjects with dementia and controls

	With dementia n=91	Controls n=110
Age (y)[1]	86.3 (sd=5.6)	83.2 (sd=6.6)
Education (y)	7.0 (sd=2.0)	7.0 (sd=2.0)
Sex		
Men	13 (14.3%)	13 (11.8%)
Women	78 (85.7%)	97 (88.2%)
Marital Status		
Married	4 (4.4%)	5 (4.6%)
Widowed	77 (84.6%)	89 (80.9%)
Divorced	2 (2.2%)	1 (0.9%)
Unmarried	8 (8.8%)	15 (13.6%)
Physical Illness or handicap[2]	53 (58.2%)	27 (24.5%)
Somatic complaints[3]	11 (12.1%)	27 (24.5%)
MMSE[4]	18.0 (sd=4.4)	26.7 (sd=1.6)

[1] t=-3.57 p<0.001
[2] Chi^2=22.2 p<0.00001
[3] Chi^2=4.3 p<0.05
[4] t=18.01 p<0.001

Subjects with dementia were significantly older, had more physical illnesses or handicaps but reported less somatic complaints than subjects without dementia. Education, sex-ratio and marital status were comparable for both groups.

The following analyses were adjusted for the effects of age, sex, physical illness or handicaps and somatic complaints.

Syndromes

In table 3 the prevalences of AGECAT depression syndromes and subsyndromes are listed. More than a third of both the subjects with and without dementia were AGECAT subcases of depression. Case level depression was found in 12 subjects (13.2%) with dementia and in 12 controls (10.9%). Adjusting for possible confounders, the prevalences of depressive subcases and cases were comparable in the two groups.

Table 3. AGECAT depressive syndromes in subjects with and without dementia

	With dementia N=91 N (%)	Without dementia N=110 N (%)	Odds Ratio's (95% CI) for dementia[1]
No depression	48 (52.7)	56 (50.9)	0 98 (0.52-1.84)
Depressive subcase	31 (34.1)	42 (38.2)	0.89 (0.46-1.70)
Depressive case	12 (13.2)	12 (10 9)	1.35 (0.52-3.53)

[1]Logistic regression adjusted for the effects of age, sex, physical illness or handicaps and somatic complaints

Symptoms

The scores of the depressive symptoms and the depressive factor scores are shown in table 4. The total numbers of depressive symptoms were similar in the two groups. Subjects with dementia had more 'motivation symptoms'. The scores on the factor 'mood symptoms' did not differ significantly.

Table 4. *Depressive symptom scores and factor scores of subjects with and without dementia*

	With dementia N=91 Median (P25,P75)	Without dementia N=110 Median (P25,P75)	Significance[a]
Depressive symptom score	6 (4,11)	6 (4,10)	n.s.
Motivation symptoms	1 (0,3)	0 (0,1)	P<0.05
Mood symptoms	2 (1,4)	3 (1,5)	n.s.

[a]Covariance analysis after square root transformation adjusting for the effects of age, sex, physical illness or handicaps and somatic complaints

DISCUSSION

Design

In the present study measures of depression of subjects with and without dementia were compared accounting for possible confounders.
The analyses were adjusted for the effects of objective and subjective physical health characteristics. Differences in motivation to participate were limited by selecting subjects with and without dementia from the same population according to an identical procedure. Partnership of a subject with dementia served as a criterium for exclusion.

(Sub)syndromes

Subjects with and without dementia had comparable prevalences of AGECAT depressive cases. These prevalences agree with those found in the community (Copeland *et al,* 1987, Van Ojen *et al,* 1995). In earlier studies subjects with dementia showed similar or increased rates of depressive syndromes compared

to controls (O'Connor *et al,* 1990, Troisi *et al,* 1993, Forsell & Winblad, 1998). However, only the restrictive criteria of major depression according to DSM-III-R and DSM-IV were applied.

This study is the first one in which subsyndromal depression is compared. Subsyndromal depression is highly prevalent, especially in elderly samples (Copeland *et al,* 1992., Judd *et al,* 1996, Ernst, 1997). It is associated with significant functional impairment and disability (Judd *et al,* 1994, Judd *et al,* 1996) and predicts syndromal depression (Copeland *et al,* 1992., Howarth *et al,* 1992). Subcases of depression were found in more than a third of both the subjects with and without dementia. These comorbid prevalences of subsyndromal depression can not be compared with those of the final diagnoses in other studies (Copeland *et al,* 1992).

Symptoms

Both groups had similar total amounts of depressive symptoms. In subjects with dementia both higher (Knesevich *et al,* 1983, Lazarus *et al,* 1987, Fischer *et al,* 1990) and equal (Patterson *et al,* 1990, Troisi *et al,* 1993) scores on depression rating scales have been reported. Those results were not adjusted for possible confounders.

Principal component analysis divided the AGECAT depressive symptoms into factors of 'motivation symptoms' and 'mood symptoms'. These factors clearly resemble the factors of 'motivation disturbance' and 'mood disturbance' as demonstrated in the symptoms of DSM-III-R major depressive episode (Forsell *et al,* 1993, Janzing *et al,* 1999).
Subjects with dementia had more 'motivation symptoms' than subjects without dementia. The prevalences of 'mood symptoms' were similar for both groups. Also these findings are in agreement with those of the aforementioned studies (Forsell *et al,* 1993, Janzing *et al,* 1999).

Limitations

Because residents of homes for the elderly belong to the most vulnerable elderly living in society, the results of the present study cannot simply be generalised to other populations of elderly subjects. A total of 32.3% of the residents refused to participate. This rate is in the same order as that reported in a number of population-based studies (Copeland *et al,* 1987, Skoog *et al,* 1993, Henderson *et al,* 1993). An overrepresentation of depression and dementia cannot be excluded in this group.

Conclusion

The present study gives further support to evidence that depression symptoms in elderly subjects can be divided into factors with and without a specific relationship to dementia. In contrast to the profile of depressive symptomatology, the prevalences of AGECAT depressive syndromes and subsyndromes seem to be unaffected by dementia.

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Chapter 5

The relationship between depression and mortality in elderly subjects with less severe dementia.

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ABSTRACT

Background
Little is known about the effects of depression on the mortality rates of elderly subjects with dementia.

Methods
Logistic regression analysis, adjusting for possible confounders, was used to study the associations between GMS-AGECAT derived syndrome and symptom measures and 12 month mortality rates in a cohort of 73 elderly subjects who met the DSM-III-R criteria of dementia with a median MMSE score of 19.

Results
Twenty-three subjects (32%) died within the 12 months follow-up period. A baseline diagnosis of syndromal or subsyndromal depression was associated with increased mortality. At the symptom level mortality was predicted by higher scores on the factor 'mood symptoms'. The effects of interactions between depression measures and severity of dementia were not significant.

Conclusions
Short-term mortality in elderly subjects with less severe dementia is predicted by the presence of (sub)syndromal depression and by mood symptoms. The effects of depression and severity of dementia on the mortality rates seem to be largely independent.

INTRODUCTION

Depression is associated with excess mortality in elderly subjects (Davidson *et al.* 1988; Jorm *et al.* 1991; Henderson *et al.* 1997). Although it is known that depression frequently co-occurs with dementia (Wragg & Jeste 1989; Burns 1991; Janzing *et al.* 1993) the relationship between mortality and depression in subjects with dementia has attracted little attention.

In a sample consisting of patients with Alzheimer's disease, Burns et al. (1991) found increased mortality rates associated with comorbid depression. Only a diagnosis of 'observed depression' could be made in their subjects because of the severity of dementia.
Up to now it is unknown whether these results can be generalized to subjects with less severe dementia. In addition, the effects of depression measures, in which anamnestic information is included, have not been investigated.

In the present study the associations between various measures of depression and one year mortality were examined in subjects with milder dementia. The following questions were addressed:
1. To what extent are depressive syndromes and symptoms associated with mortality?
2. Are the effects of depression on mortality influenced by the severity of dementia?

METHOD

Subjects

The study took place in six homes for the elderly in the region of Nijmegen, the Netherlands. Informed consent was obtained from the subjects themselves or in the case of severe cognitive impairment from close relatives.
Subjects were residents who showed evidence of cognitive impairment in the screening phase of the study (Mini Mental State Examination (MMSE) score ≤24 and Short Blessed Test (SBT) score >6) (Folstein *et al.* 1975; Katzman *et al.* 1983). In addition they fulfilled the DSM-III-R criteria for dementia (American Psychiatric Association 1987) based on information gathered with the Clinical Assessment Battery (CAB) of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris *et al.* 1989). The type of dementia was not specified. Heteroanamnestic information was obtained from both staff members of the homes and relatives of the subjects. The baseline total MMSE score was used as the measure of dementia severity (Weissman *et al.*1985).

The following exclusion criteria were applied (Morris *et al.* 1989): inability to be tested (severe deafness, severe visual handicap, severe aphasia, too demented) Parkinson's disease, choreatic disease, alcoholism, mental retardation, inclusion of the partner and missing data on depressive symptoms.

Physical illness

Using information from the general practitioners, a history of the following diagnoses was recorded: locomotor disease, cerebrovascular disease, diabetes mellitus, heart disease, hypertension, pulmonary disease, malignancies. Because no single diagnosis was significantly associated with 12 month mortality the total number of diagnoses was used as a measure of general health.

Measures of depression

The subjects underwent a full psychiatric assessment using the Geriatric Mental State (GMS community version) (Copeland *et al.* 1976). All measures of depression were derived from AGECAT, the computerized diagnostic package of the GMS-AGECAT system (Copeland *et al.* 1988). In AGECAT they are diagnosed independently from the organic syndromes (Copeland *et al.* 1992).

(a) Depressive syndrome measure
According to AGECAT, subjects were classified as 'not depressed', 'subcase of depression' or 'case of depression'.
(b) Depressive symptoms

The total number of positively rated AGECAT depression symptoms was computed (maximum score: 44).
(c) Factors of depressive symptoms
In an earlier phase of the study two factors with a sufficient Crohnbach's alpha (>0.75) and clinical face validity were obtained from an explorative principal component analysis on the AGECAT depressive symptoms of 91 subjects with dementia and 110 subjects without. These factors explained 22% of the total variance and were composed as follows: Factor 1 'motivation symptoms' (items: fatigue; subjective slowing in thinking; subjective slowing in movements; lack of energy; reduced activity; slowness or anergy does not lift with pleasant activities; sits around because of anergia; loss of interest; sudden recent loss of interest; loss of interest because depressed); and Factor 2 'mood symptoms' (items: worried about almost everything; worries; depressed mood; wanting to cry; life not worth living; wishes to be dead; sleep disturbance; tremulous feelings; loneliness; dissatisfaction).

The factors strongly resemble those found by Forsell et al. (1993). The totals of positively rated items per factor were used as the final factor scores (for both factors the maximumscore was 10).

Statistical analysis
Logistic regression analysis was used to study the associations between the baseline measures of depression and 12-month mortality. For this analysis all the continuous variables were dichotomized at their medians. The threshold for significance was $P<0.05$ (two-sided).

RESULTS

At baseline 91 residents were eligible. From these subjects 16 (18%) refused follow-up. From two more subjects, who had been referred to nursing homes, no information was available at follow-up. The baseline demographic, cognitive and depressive characteristics of the dropouts were not significantly different from those of the other subjects.

Seventy-three subjects completed the study. AGECAT diagnosed 68 of them as organic cases (21 level O3, 44 level O4 and 3 level O5). From the remaining subjects 3 were organic subcases and 2 had no diagnosis at the organic cluster.

In table 1 the baseline characteristics are presented. Apart from a high age, the sample is characterized by a large proportion of women. Most subjects live alone. The median MMSE score of 19 reflects mild dementia. A total of 23 (32%) subjects died within the 12 month follow-up period. AGECAT diagnosed 14% of the survivors and 17% of the nonsurvivors as depressive cases and 20% of the survivors and 48% of the non-survivors as depressive subcases.

Table 1. Baseline characteristics of 73 elderly subjects with dementia

Characteristic	
Age (years)	
Median	87
(P25,P75)	(82,90)
Sex	
Male	N=9 (12%)
Female	N=64 (88%)
Mariatal status	
Married	N=3 (4%)
Unmarried	N=70 (96%)
Education (years)	
Median	6
(P25,P75)	(6,8)
MMSE score	
Median	19
(P25,P75)	(15,21)
Diagnosed diseases	
Median	2
(P25,P75)	(1,3)
AGECAT depression	
Case	N=11 (15%)
Subcase	N=21 (29%)
No depression	N=41 (56%)
Depressive symptoms	
Median	6
(P25,P75)	(3,11)
Mood symptoms	
Median	2
(P25,P75)	(0,4)
Motivation symptoms	
Median	1
(P25,P75)	(0,3)

Multivariate comparisons

Logistic regression models were used to study the effects of the baseline depression measures on the 12-month mortality. Potential confounders (age, sex, MMSE score and the number of diagnosed diseases) were included to adjust for their effects. The results are shown in Table 2. The effects of the potential confounders were insignificant in all models. Significant odds ratio's were found for the presence of a case or subcase of depression (OR 4.31 95% CI 1.38-13.46) and mood symptoms (OR 3.94 95% CI 1.31-11.82).
The effects of the interactions between the depression measures and dementia severity (product depression measure*MMSE-score) were insignificant (data not shown).

ble 2. Summary of final models: odds ratio's for non surviving.

	OR (95% CL)	OR (95% CL)	OR (95% CL)	OR (95% CL)	OR (95%CL)
Depression measure	1.27 (0.33, 4.90) Case	4.31 (1.38,13.46) Case+Subcase	1.86 (0.64, 5.37) Depressive symptoms	3.94 (1.31, 11.82) Mood symptoms	0.91 (0.32, 2.59) Motivation symptoms
Sex	1 95 0.35,10.80)	1 70 (0 28,10.28)	1.90 (0 34,10.60)	1.86 (0.32,10.80)	1 97 (0.36,10.91)
Age	0 76 (0.27,2.16)	0 48 (0 15, 1 55)	0 66 (0.23, 1.95)	0.59 (0.19, 1.82)	0.78 (0.27, 2 25)
Diagnosed diseases	1 62 (0.51,5.16)	1.30 (0 38, 4.39)	1.40 (0 43, 4.57)	1.19 (0.35, 4.06)	1 63 (0.51, 5.21)
MMSE	1 45 (0.51,4.10)	1.27 (0.42, 3.82)	1.46 (0 52, 4 14)	1.48 (0.50, 4.35)	1.42 (0.50, 4.01)

DISCUSSION

In the present study the effects of several measures of depression on mortality were investigated in a population of subjects with dementia. The considerable mortality and the high refusal rate of the sample reflect the high vulnerability of residents at homes for the elderly (Van Loveren-Huyben & Van der Bom 1983). The mean dementia severity was substantially lower than that in the study of Burns et al. (1991) (present sample: mean MMSE score 17.8 (sd 4.5); Burns *et al.*: mean MMSE score 8.0 (sd 6.7)).

The main conclusions are:
(1) the presence of a case or subcase of depression predicts short term mortality at the diagnostic level. At the symptom level the factor 'mood symptoms' is associated with 12 month mortality.
(2) there is no evidence that the effects of depression on mortality are influenced by the severity of dementia.

The combination of depressive subcaseness and depressive caseness was a better predictor of mortality in subjects with dementia than depressive caseness alone. In a community sample of subjects with and without dementia Jorm *et al.* (1991) drew a similar conclusion. Only after lowering the diagnostic threshold below case level they found a relationship between depression and mortality: not the diagnosis of DSM-III major depression but that of 'dysphoric mood' was associated with mortality.

In a number of studies (Macdonald *et al.* 1982, Ashby *et al.* 1991, Dewey *et al.* 1993, Skoog *et al.* 1996) symptoms indicating that life is not worth living have been found to be associated with mortality. The association between mortality and 'mood symptoms' (including the symptoms 'life not worth living' and 'wishes to be dead') in the present study seems to be in agreement. Although physical health appears to be a plausible confounder it was not identified as a mediator of the relationship between these depressive symptoms and mortality.

The absence of a significant relationship between the baseline severity of dementia and mortality contrasts with the results of earlier studies (Burns *et al.* 1991; Heyman *et al.* 1987; Knopman *et al.* 1988; Rosen & Zubenko 1991; Heyman *et al.* 1996). Probably the relatively small sample size and the short follow-up period in the present study account for this difference.

It is important to study the effects of interactions between depression measures and the severity of dementia because of the complex relationship between these variables. Forsell *et al.* (1993) showed that the symptomatology of depression changes with the severity of dementia. In addition, both depression and dementia have been shown to predict mortality (Davidson *et al.* 1988; Jorm *et al.* 1991; Henderson *et al.* 1997; Burns *et al.* 1991). The absence of significant interactions may indicate that the effects of

depression and the severity of dementia on mortality are largely independent.

In the present study significant associations were found between measures of depression and short term mortality in a population with milder dementia. These results are in agreement with those in subjects with severe dementia. However it is difficult to draw general conclusions as the sample was restricted to residents of homes for the aged who were characterized by a large proportion of females and a very high age.

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Chapter 6

The course of depression in elderly subjects with and without dementia

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ABSTRACT

Background
A persistent course of depression has been described in subjects with and without dementia. Up to the present it is unclear to what extent dementia affects the prognosis of depression.

Method
At baseline and at 6 and 12 months follow-up AGECAT depression diagnoses were made in 49 subjects with and 72 subjects without DSM-III-R dementia living in homes for the elderly.

Results
Adjusting for demographic characteristics and physical health, dementia was not associated with the severity of depression at follow up. The baseline depression severity and to a lesser extent somatic complaints predicted a bad prognosis of depression in the total sample.

Limitations
Because of the high vulnerability of the residents the results cannot be generalised to other populations of elderly subjects.

Conclusion
Depression is persistent in residents of homes for the elderly. Dementia does not affect its course.

INTRODUCTION

Although dementia and depression frequently cooccur (Wragg and Jeste, 1989, Janzing et al., 1993), little is known about the course of depression in subjects with dementia.
Two community based studies suggest a benign prognosis for depression in dementia. After a follow up of 12 months and 3 years respectively, both O'Connor et al. (1990) and Forsell et al. (1994) found remissions of depression in all their subjects with depression and dementia at baseline. Although unequivocal, the relevance of these results is limited because they are based on small groups of subjects and only the diagnosis of DSM-III-R major depressive episode was considered.

Indications for a chronic course of depression in dementia were found in outpatients with Alzheimer's disease. In twenty percent of the subjects with major or minor depression at baseline these diagnoses persisted for at least 6 months (Ballard et al., 1996). In the study of Starkstein et al. (1997) 58% of the subjects with major depression and 28% of the subjects with dysthymia at baseline were still depressed after 16 months.

Institutionalised elderly have been characterised by marked prevalences of depression and dementia (Mann et al., 1984, Chandler and Chandler, 1988, Morriss et al., 1990, Rovner et al., 1990). Also here, depression seems to have a chronic course. In only 23% of the residents with dementia living in homes for the elderly, depression had remitted after a follow up duration of 3.6 years (Ames et al., 1988).

So far, much of the evidence indicates that depression in dementia can be persistent. Up to the present it is unclear to what extent dementia influences the course of depression. To address this question subjects with and without dementia, including various stages of depression at baseline, were compared on their outcomes of syndromal and subsyndromal depression.

METHOD

Subjects

The study took place in 6 homes for the elderly in the region of Nijmegen, the Netherlands. Informed consent was obtained from the residents themselves or in the case of severe cognitive impairment from close relatives of the subjects. Subjects with and without dementia were selected using the following two step design:

Step 1: screening

All the residents were examined with the Mini Mental State Examination (MMSE; Folstein et al., 1975) and the Short Blessed Test (SBT; Katzman et al., 1983). Subjects with scores indicative of cognitive impairment (MMSE $\leq$ 24 and SBT >6) or normal cognitive function (MMSE$\geq$24 and SBT$\leq$6) proceeded in step 2.

Step 2: further diagnosis

The Clinical Assessment Battery (CAB) of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was administered (Morris et al., 1989). Based on the information obtained with this instrument, it was considered if subjects fulfilled the DSM-III-R criteria for dementia (American Psychiatric Association, 1987). In the present study, subjects with dementia had both DSM-III-R dementia and cognitive impairment according to the screening instruments. Subjects without dementia did not fulfil the DSM-III-R dementia criteria and had normal cognitive function at screening.

Criteria for exclusion were: inability to be tested (severe deafness, severe visual handicap, severe aphasia, too severe dementia), CVA with normal cognitive function, Parkinson's disease, choreatic disease, alcoholism, mental retardation, partner already included and missing data on depressive symptoms.

Diagnosis of depression

The participants underwent three full psychiatric assessments using the Geriatric Mental State (GMS; Copeland et al., 1976): at baseline and at 6 and 12 months after entrance. At each of these times the subjects were classified as 'not depressed', 'subcase of depression' or 'case of depression' according to AGECAT, the computerised diagnostic package of the GMS-AGECAT system (Copeland et al., 1988).

Statistical analysis

Mc-Nemar tests were carried out to examine longitudinal changes in depression prevalences within the cohorts. For comparisons of the baseline depression prevalences between the cohorts logistic regression analysis was used with adjustment for possible confounders.
Multiple regression analysis was carried out to identify predictors of the course of depression. For this analysis the AGECAT depression output was recoded as follows: no depression: score 0, subcase: score 1 and depressive case: score 2. The independent variables were included as z-scores in order to maximize the comparability of their effects.
In all the analyses the threshold for significance was $p<0.05$.

RESULTS

At baseline a total of 201 residents were eligible: 91 subjects with dementia and 110 without. During follow up 44 subjects refused participation. They were comparable regarding demographic characteristics, baseline dementia rates and depression syndrome diagnosis to the subjects who continued participation. A further 26 subjects died and 10 subjects moved to a nursing home during the follow-up period. The demographic characteristics and the depression diagnoses of these subjects were also comparable to those of the subjects who continued to participate. However, they had higher baseline rates of dementia (72.2% vs. 40.5%; $p<0.001$).

In the present study, the 12 month course of depression was studied in 121 subjects with complete follow up data: a cohort of 49 subjects with dementia and a cohort of 72 subjects without.
In table 1 the baseline characteristics of the participants are presented. Subjects with dementia were older (86.6 (sd=5.3) year vs. 82.6 (sd=6.5) year; $p<0.002$), had more physical illness or handicaps (51.0% vs. 26.4% $p<0.01$) but less somatic complaints (6.1% vs. 20.8% $p<0.05$) than subjects without dementia. The difference in MMSE scores (MMSE=18.2 sd=3.9 in subjects with dementia vs. MMSE=26.7 sd=1.7 in subjects without dementia) is due to the inclusion criteria. All further baseline characteristics were comparable for both cohorts.

Table 1. Baseline characteristics of subjects with and without dementia

	Subjects with dementia (n=49)	Subjects without dementia (n=72)
Age in years[a] (mean(sd))	86.6 (5.3)	82.6 (6.5)
Education in years (mean(sd))	7.0 (1.7)	7.1 (1.8)
Sex (%)		
Men	14.3	9.7
Women	85.7	90.3
Marital Status (%)		
Married	6.1	4.2
Widowed	83.7	79.2
Divorced	2.0	1.4
Unmarried	8.2	15.3
Use of anti-depressants (%)	6.1	5.6
Physical illness or handicap[a] (%)	51.0	26.4
Somatic complaints[a] (%)	6.1	20.8
MMSE[a] (mean(sd))	18.2 (3.9)	26.7 (1.7)

[a] $p<0.05$

In table 2 an overview is given of the course of depression in relation to the depression diagnosis at baseline. Adjusting for age, sex, physical illness or handicap and somatic complaints subjects with and without dementia had comparable baseline prevalences of depressive caseness (subjects with dementia 6/49 (12.2%), subjects without dementia 8/72 (11.1%) logistic regression analysis n.s.) and subcaseness of depression (subjects with dementia 10/49 (20.4%) subjects without dementia 28/72 (38.9%) logistic regression analysis n.s.). For both groups these prevalences remained stable during 12 month follow up (McNemar tests, data not shown).

The most severe diagnosis at follow up (at 6 and 12 months assessments) was used as the outcome measure of depression. In the majority of the subjects with depressive caseness at baseline this diagnosis occurred again during follow-up. Similarly, most of the subjects who were subcases of depression at baseline had episodes of depressive subcaseness at the 6 or 12 month measurement. The majority of the subjects without depression at baseline remained depression free during follow up. These findings refer to both cohorts.

Table 2. Baseline AGECAT depression diagnosis and depression diagnosis at follow up (assessments at 6 and 12 months)

	Depression diagnosis at follow up		
	6 months	12 months	most severe diagnosis at 6 & 12 months
Baseline diagnosis	case/ sub/ nd (%)	case/ sub/ nd (%)	case/ sub/ nd (%)
depressive case			
dementia (n=6)	50 / 33 / 17	67 / 17 / 17	100 / 0 / 0
no dementia (n=8)	37 / 50 / 12	12 / 62 / 25	50 / 37 / 12
depressive subcase			
dementia (n=10)	0 /100 / 0	30 / 40 / 30	30 / 70 / 0
no dementia (n=28)	21 / 64 / 14	11 / 71 / 18	28 / 68 / 4
no depression			
dementia (n=33)	0 / 9 / 91	0 / 18 / 82	0 / 18 / 82
no dementia (n=36)	6 / 25 / 69	8 / 22 / 69	11 / 28 / 61

case = depressive case
sub = depressive subcase
nd = no depression

Multiple regression analysis was used to study the influence of the baseline diagnosis on the outcome of depression. The most severe depression diagnosis at follow up served as the dependent variable. The results are presented in table 3. To adjust for possible confounders, the variables age, sex, physical illness or handicap and somatic complaints were entered in the regression model. From these variables only the presence of somatic complaints was significantly related to the outcome of depression. Subsequently, a strong positive effect was found for the baseline severity of depression. The diagnosis of dementia and the use of antidepressants were not significantly associated with the severity of depression at follow-up.

Table 3. Effects of baseline characteristics on the course of depression (most severe diagnosis at follow up); results from a multiple regression analysis

Baseline characteristic	Regression coefficient (95% CI)	P
Age	-0.01 (-0.12-0.10)	n.s.
Sex	0.03 (-0.08-0.14)	n.s.
Illness or handicap	0.03 (-0.08-0.14)	n.s.
Somatic complaints	0.11 (0.00-0.22)	<0.05
Depression	0.46 (0.35-0.57)	<0.0001
Dementia	-0.05 (-0.16-0.06)	n.s.
Antidepressants	0.02 (-0.09-0.13)	n.s.

DISCUSSION

In the present study the 12 month course of depression was observed in subjects with and without dementia living in homes for the elderly In contrast to earlier studies both syndromal and subsyndromal depression were assessed Subsyndromal depressive symptoms have been shown to be highly prevalent, especially in elderly samples (Copeland et al , 1992 , Judd et al , 1996, Ernst, 1997) They are associated with significant functional impairment and disability (Judd et al , 1994, Judd et al , 1996) and predict the occurrence of syndromal depression (Copeland et al , 1992 , Howarth et al , 1992) AGECAT provides a reliable and valid classification of depression into syndromal depression (caseness), subsyndromal depression (subcaseness) and no depression Depression rates in subjects with and without dementia can be easily compared because the diagnoses of depression and dementia are made independently in AGECAT, based on different symptom clusters (Copeland et al , 1988) Like in other diagnostic classifications, in AGECAT the diagnosis of depression has not been specifically validated in subjects with dementia

The baseline prevalences of depression were similar in the two cohorts Although different criteria were used, this is in agreement with observations in community and outpatients with dementia (O'Connor et al , 1990, Troisi et al , 1993, Forsell et al , 1993) The rates of comorbid AGECAT depressive subcases in the present study can not be compared with those of the final diagnoses reported from community studies (Copeland et al , 1992)
The main findings are
1 Both syndromal en subsyndromal depression were highly persistent in the residents
2 The course of depression was not affected by the presence of a diagnosis of dementia
3 The baseline diagnosis of depression and to a smaller extent somatic complaints were predictors of the severity of depression at follow up
4 Few residents used antidepressant medication Its use was not associated with the severity of depression at follow up

(1) The high persistence of depression is in agreement with earlier findings in residents of homes for the elderly with and without dementia (Ames et al , 1988) Also in large proportions of patients with and without dementia and elderly living in the community a chronic course of depression was found (Murphy 1983, Baldwin and Jolley 1986, Copeland et al , 1992, Ballard et al , 1996, Henderson et al , 1997, Starkstein et al , 1997)

(2) Because in most studies subjects with dementia have been excluded (Beekman et al , 1995), it is unclear to what extent dementia affects the course of depression The absence of a significant effect of dementia in our subjects seems to be in agreement with the results of Alexopoulos et al (1996) These authors found that the cognitive status of their subjects was unrelated to the outcome of geriatric depression O'Connor et al (1990) and Forsell et al (1994) observed more remissions of depression in subjects with than in subjects without dementia Their results can not be generalized

because they are based on very small groups of subjects. In contrast Magni et al. (1988) reported that subjects with symptoms indicating organic brain disease had a worse prognosis of depression than subjects without. In their study no operationalisation of organic brain disease is given so its relationship with cognitive impairment is not clear. Suggestions that the type of dementia plays a role are supported by Ballard et al. (1996). These authors showed that vascular dementia was associated with a more chronic course of depression.

(3) The severity of the baseline depression diagnosis was strongly associated with the 12 month depression outcome. This finding is in agreement with many earlier studies in different populations (Murphy 1983, Copeland et al., 1992; Ballard et al., 1996; Henderson et al., 1997; Starkstein et al., 1997).
Somatic complaints confounded the relationship between dementia and the course of depression. In contrast to the presence of a physical illness or handicap as observed by the investigator, their prevalence was higher in residents without dementia. In addition, somatic complaints predicted more severe depression at follow up. This is in agreement with earlier findings that especially subjective characteristics of physical health, are related to a bad prognosis of depression (Beekman, 1996).

(4) Little is known about the treatment of depression in dementia. In two clinical trials a clear placebo response was registered (Reifler et al., 1989, Roth et al., 1996). The effect of imipramine was comparable but the effect of moclobemide was superior to that of placebo. In the residents, like in community samples (Copeland et al., 1992, Forsell et al., 1994) antidepressants were infrequently used. This may contribute to the absence of a significant relationship between the use of antidepressant medication and the course of depression.

The present study describes the effects of baseline clinical characteristics, especially of dementia, on the course of depression. It is important to be cautious in generalizing the results: residents of homes for the elderly belong to the most vulnerable elderly living in society (Van Loveren-Huyben and Van der Bom, 1983). The relatively high drop out rate due to mortality, admission to a nursing home and refusal seems to be related to this vulnerability. Further studies, especially in community based populations, are needed to investigate the effects of dementia on the course of depression.

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Chapter 7

General Discussion

The aim of this study was to gain more insight into the relationship between depression and dementia in elderly subjects. Below some of the methodological aspects are critically reviewed and the main results are discussed.

METHODOLOGY

Subjects

The choice of residents at homes for the elderly as study subjects had a number of advantages. Up till now most studies on the relationship between depression and dementia were performed on samples of outpatients or clinical patients (see Chapter 4). This led to systematic bias in the findings, because of the high prevalences of severe dementia and depression. The bias is reduced in the present study as the subjects were characterized by milder stages of dementia and milder depression. Comparability between subjects with and without dementia was excellent because both groups originated from the same population of residents. This is an important methodological advantage over most of the earlier observational studies.

A limitation is that the results of this study cannot simply be generalised to elderly people in the general population. Residents at homes for the elderly can be regarded as the most vulnerable elderly living in society (Van Loveren-Huyben et al. 1983). This is supported by their demographic characteristics: their advanced age (83.5 years sd=6.5), the fact that most residents (87.1%) live alone, the low education level (7.0 years sd=2.1), the high prevalence of cognitive impairment (52.1% had an MMSE score of below 24 points) and the frequent use of medication (3.3 drugs sd=2.4) (Janzing et al. 1997).

Nonparticipation

From the total population of 601 residents, 194 (32.3%) residents refused to participate. This rate is in the same order as that reported in a number of population-based studies (Copeland et al, 1987, Skoog et al, 1993, Henderson et al, 1993). Data regarding the level of depression and cognitive status of these subjects could not be collected. So, the extent to which depression and dementia are over- or under-represented is unclear. In two recent studies, non-participation rates of 17.3% (only for the screening phase; Boersma et al. 1995) and 75% (van den Berg et al. 1995) were reported for residents at homes for the elderly.

Longitudinal drop-out

From the 201 residents included, 44 refused participation during follow-up. These subjects were comparable with those who completed the study with respect to demographic characteristics and baseline diagnoses of dementia and depression. A further 26 residents died and 10 moved to a nursing home during follow-up. As was expected (Knopmann et al. 1988, Jorm et al. 1991), the latter group had an increased rate of dementia at baseline. High drop-out rates were also observed in other longitudinal studies on psychopathology in the elderly (Copeland et al. 1992, Henderson et

al. 1997). In addition to the general vulnerability of these subjects, characteristics such as advanced age and a high prevalence of dementia are associated with dropping out.

Diagnosis of dementia

Dementia was diagnosed according to the criteria of DSM-III-R (American Psychiatric Association 1987). The diagnosis of "organic caseness" of GMS-AGECAT was not used because it is far more inclusive than DSM-III-R dementia (Copeland et al. 1990) so, it reduces comparability with other studies.
Almost all the subjects with dementia according to the DSM-III-R criteria were identified by AGECAT as organic cases. The CERAD protocol (Morris et al. 1989) helped in the standardized collection of data necessary to diagnose dementia according to the DSM-III-R criteria. Specification of the type of dementia was not possible in the residents. Several of the necessary investigations could not be carried out owing to the resident's low level of mobility.

Diagnosis of depression

The first advantage of a GMS-AGECAT diagnosis of depression is that it is relatively unaffected by the presence of organic disturbance: the diagnoses of depression and dementia are made separately on the basis of different symptoms (Copeland et al. 1988). Secondly, the diagnoses of depression (sub)syndromes according to AGECAT are more inclusive than the diagnosis of DSM-III-R major depressive episode (Copeland et al. 1990; Newman et al 1998). Although depressive symptoms are common in elderly subjects, the prevalence of major depressive episode decreases with age. Therefore the latter diagnosis has less relevance for the explanation of depressive symptomatology in populations of elderly subjects (Ernst 1997).
A disadvantage of GMS-AGECAT is that the algorithms of depression diagnoses have never been published. It has been recently shown that AGECAT depression diagnoses are mainly based on "dysphoric symptoms" that are comparable with our mood symptoms (Newman et al. 1998). The broad group of GMS-AGECAT depressive symptoms were used to study individual symptoms and to construct factors of depressive symptoms.

RESULTS

In Chapter 2 it was concluded that the application of concepts derived from "functional" psychiatric disorders in patients with dementia without any further consideration has resulted in great variations in prevalences. Especially the relationship between depression and dementia remains unclear. In the following sections we discuss the most important results from this thesis.

Mood and motivation symptoms (Chapters 3 & 4)

Principal Component Analyses of the depressive symptoms resulted in factors with a clear face validity. The symptoms of DSM-III-R major depressive episode were divided into factors of mood disturbance and motivation disturbance, which were identical to those found by Forsell et al. (1993). Mood and motivation symptoms were also the main factors of the depressive symptoms of GMS-AGECAT. The findings that motivation symptoms are more common in subjects with dementia and that their prevalences increase with the severity of dementia suggest that motivation symptoms are part of the dementia syndrome itself. In contrast, the prevalence of mood symptoms is comparable for subjects with and without dementia and is not related to the severity of dementia.
Interestingly, mood symptoms can also be distinguished from motivation symptoms in other neurological disorders. The disturbance of motivation seems to be associated with dysfunction of fronto-subcortical circuits (Cummings 1986; Marin 1997 Andersson et al. 1999).

Patients with dementia may earlier fulfil the criteria for DSM-III-R major depressive episode because of their increased rates of motivation symptoms. Owing to the low prevalence of major depressive episode in the residents (1.5%) this hypothesis could not be tested. In subjects with dementia, the higher levels of motivation symptoms did not result in higher prevalences of AGECAT depression or subdepression than in subjects without dementia. This can be explained by the fact that these AGECAT diagnoses are mainly based on "dysphoric" symptoms (Newman et al. 1998).

The relationship between symptoms of depression and those of other psychopathology, such as psychosis and behavioural disturbance was not a major subject in this thesis. It seems that the distinction between these types of psychopathology is less clear than is suggested in the literature (Chapter 2). For instance, it is has been shown that "behavioural disturbances" remit when depression is treated successfully (Lyketsos et al. 1999). The results in this thesis indicate that motivation disturbance, in many studies considered as a "disturbance of behaviour" is an important component in depressive symptomatology.

Depression and mortality in dementia (Chapter 5)

Twenty-three (32%) of 73 residents with mild dementia died within 12 months. Baseline mood disturbance and (sub)syndromal depression (which is also largely based on mood symptoms) were associated with short-term mortality. These findings show the predictive validity of the division into mood and motivation disturbance. It can be concluded that the life expectancy of patients with dementia, which is shorter than that of subjects without dementia (Davidson et al. 1988, Jorm et al. 1991), is further decreased when there are more mood symptoms. The effects of mood symptoms on mortality are not affected by the severity of dementia. The separate effects of dementia and measures of depression on mortality accord with other evidence in this thesis that mood symptoms do not belong to the dementia syndrome itself.
These findings are also in agreement with results showing that depressive symptoms predict mortality in subjects with and without dementia (Davidson et al. 1988; Jorm et al. 1991; Henderson et al. 1997 Burns et al. 1991).

A number of explanations are possible for the relationship between depression and mortality. Although the analyses were controlled for physical health as recorded by the general practitioner, it cannot be excluded that the mood symptoms are reactive to or a consequence of undiagnosed somatic disease. Other studies have shown that physical health problems are associated with depressive symptoms in elderly subjects (Beekman 1996; Ernst 1997).

Furthermore, the relationship between depressive symptoms and mortality could be mediated by a reduced immunological function which increases the risk of severe somatic disease (Herbert and Cohen 1993).
It is clear that the relationship between mood symptomatology and mortality in subjects with dementia requires further study. Investigations to the cause of mortality, detailed physical diagnosis and investigations of immunological function could be helpful.

The course of depression (Chapter 6)

It is remarkable how little is known about the influence of dementia on the prognosis of depression. This study showed that subjects with and without dementia had comparable courses of AGECAT syndromal and subsyndromal depression. As these AGECAT diagnoses are mainly based on mood symptomatology, this finding again supports the conclusion that mood symptomatology is relatively independent of dementia. In agreement with the findings from other studies (Murphy 1983, Copeland et al. 1992, Ballard et al. 1996, Henderson et al. 1997; Starkstein et al. 1997) depression is persistent in subjects with and without dementia. It is necessary to investigate the extent to which drug therapy and other interventions can help to reduce the rates of (sub)syndromal depression as few patients are treated for depression.
A further conclusion is that subsyndromal depression carries an increased risk of syndromal depression. This combined with its association with mortality further

underscores the importance of diagnosing and -if possible- treating subsyndromal depression in elderly subjects.

GENERAL CONCLUSION

In this thesis the division of depressive symptoms into mood disturbance and motivation disturbance forms a central theme. These two factors were convincingly demonstrated in a population of residents at homes for the elderly. Many results suggest that mood disturbance is relatively independent from dementia. In contrast, motivation disturbance seems to be part of the dementia syndrome itself. Further investigations on the associations of mood and motivation disturbance are indicated to gain more insight into the nature of depressive symptomatology in elderly subjects with and without dementia.

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SUMMARY

Chapter 1 is a general introduction on the relationship between depression and dementia.

Chapter 2 reviews the literature on the prevalence of depression, psychotic symptoms and behavioural disorders in patients with Dementia of the Alzheimer Type (DAT). There is a great diversity in the prevalences reported for these types of psychopathology. Compared to subjects without dementia, DAT-patients seem to have increased prevalences of psychotic symptoms and behavioural disorders but not of depression. Higher prevalences of behavioural disorders were reported in patients with more severe dementia. Findings regarding the relationship between prevalences of depression or psychotic symptoms and the stage of dementia are less consistent. There is a wide variation in the diagnostic methods applied and the study populations. No attention was paid to the overlapping symptoms of DAT and psychopathology. It is concluded that up till now, existing knowledge on the prevalence of psychopathology in DAT is very global.

In Chapter 3 the presence of DSM-III-R criteria for major depressive episode are investigated in subjects without dementia, subjects with mild dementia and subjects with severe dementia. The criteria could be divided into two factors:
A factor 'mood disturbance' and a factor 'motivation disturbance'. These factors are identical to those found by Forsell et al. (1993). In addition the factor 'motivation disturbance' increased with the severity of dementia. These results support the validity of the two-factor model of Forsell et al.. The motivation symptoms seem to have a specific relationship with dementia.

In Chapter 4, the prevalences of AGECAT-derived depression measures are studied in subjects with and without dementia. The two groups had similar prevalences of depressive syndromes, subsyndromes and depressive symptoms. The AGECAT depressive symptoms could also be divided into factors of mood and motivation disturbance. The prevalences of mood symptoms are comparable in the two groups, while motivation symptoms are more frequent in subjects with dementia. It is concluded that the nature of depressive symptomatology is affected by the presence of dementia but the prevalences of syndromal or subsyndromal depression are not.

Chapter 5 examines the effects of depression on mortality in subjects with milder dementia. During the 12-month follow up period there is a considerable mortality in this group (32%). The effects of the following AGECAT measures are studied: syndromal depression, subsyndromal or syndromal depression, total rates of depressive symptoms, motivation symptoms and mood symptoms. On the syndrome level, mortality is associated with the presence of syndromal or subsyndromal depression. In contrast to motivation symptoms and the total number of depressive symptoms, it was found that mood symptoms predicted mortality. There was no evidence of a synergism between depression and the severity of dementia on mortality.

In Chapter 6 it is investigated if dementia influences the course of AGECAT depression. Subjects with and without dementia were studied over a 12 month period.

It was found that the presence of dementia is not associated with the longitudinal course of syndromal or subsyndromal depression. In both subjects with and without dementia, the course of depression is persistent: most subjects who had depression at baseline had depression at at least one of the follow-up measurements. The severity of depression at baseline is the best predictor of its severity during the 12 months course. Independently of this effect, somatic complaints predicted depression at follow-up.

Chapter 7 is a general discussion of the study findings. Methodological aspects are commented on. It is obvious that residents at homes for the elderly are not representative for elderly in the general population because of their high vulnerability. The choice for the diagnostical instruments is motivated. The most important findings were: symptomatology of depression can be divided into mood and motivation symptoms. Motivation symptoms are more common in subjects with dementia. The presence of mood symptoms is a risk factor for mortality in subjects with mild dementia. Dementia on its own does not affect the course of AGECAT depression (sub)syndromes. These findings provide further support for the hypothesis that motivation disturbance is part of the dementia syndrome. It may reflect dysfunction of frontal-subcortical circuits.

SAMENVATTING

Hoofdstuk 1 is een algemene introductie over het verband tussen depressie en dementie.

Hoofdstuk 2 is een overzicht van de literatuur over het voorkomen van psychopathologie (depressie, psychose en gedragsstoornissen) bij Dementie van het Alzheimer Type (DAT). In de literatuur worden voor elk van deze vormen van psychopathologie sterk uiteenlopende prevalentiecijfers gerapporteerd. Vergelijkend onderzoek lijkt uit te wijzen dat het hebben van DAT wel het risico op psychotische verschijnselen en gedragsstoornissen vergroot, maar niet dat op depressie. Wanneer patiënten met verschillende stadia van DAT vergeleken worden, komen gedragsstoornissen vaker voor naarmate de dementie ernstiger is. Over de relatie tussen de ernst van dementie en het voorkomen van depressie en psychose bestaat geen duidelijkheid. De gebruikte diagnostische methoden en onderzochte populaties lopen sterk uiteen. Aan de overlap in symptomen tussen DAT en genoemde vormen van psychopathologie wordt geen aandacht besteed. Geconcludeerd wordt dat de kennis over de relatie tussen psychopathologie en DAT nog zeer globaal is.

In hoofdstuk 3 worden de criteria volgens DSM-III-R major depressieve episode bestudeerd in proefpersonen zonder dementie, proefpersonen met milde dementie en proefpersonen met ernstige dementie. De depressiesymptomen zijn onder te verdelen in twee factoren: een factor 'mood disturbance' en een factor 'motivation disturbance'. Deze factoren zijn identiek aan die van Forsell et al. (1993). Eveneens in overeenstemming is de bevinding dat 'motivation disturbance' toeneemt met de ernst van de dementie. Deze resultaten ondersteunen de validiteit van het twee factoren model van Forsell et al. De motivatiesymptomen lijken specifiek samen te hangen met dementie.

In hoofdstuk 4 worden de prevalenties van verschillende AGECAT depressieparameters bestudeerd bij proefpersonen met en zonder dementie. In beide groepen worden vergelijkbare prevalenties van depressiesyndromen, subsyndromen en totale hoeveelheid depressiesymptomen gevonden. Ook de AGECAT depressiesymptomen zijn onder te verdelen in factoren van stemmings- en motivatiesymptomatologie. De hoeveelheid stemmingssymptomen is in beide groepen vergelijkbaar. De motivatie gebonden symptomen komen vaker voor bij proefpersonen met dementie. Geconcludeerd wordt dat niet zozeer de prevalenties van (sub)depressies maar vooral de aard van de depressiesymptomatologie wordt beïnvloed door de aanwezigheid van dementie.

In hoofdstuk 5 wordt het effect van depressie op de mortaliteit bestudeerd bij patiënten met mildere dementie. Tijdens de 12 maands follow up periode is er sprake van een aanzienlijke mortaliteit (32%). De effecten van de volgende AGECAT depressieparameters werden bestudeerd: syndromale depressie, syndromale of subsyndromale depressie, totaal aantal depressiesymptomen, motivatiesymptomen

en stemmingssymptomen. Op syndroom niveau is mortaliteit geassocieerd met de aanwezigheid van syndromale of subsyndromale depressie. In tegenstelling tot motivatiesymptomen en totaal aantal depressiesymptomen is de factor stemmingssymptomen een voorspeller van mortaliteit. Er zijn geen effecten van interacties tussen depressie en ernst van de dementie op de mortaliteit.

In hoofdstuk 6 wordt nagegaan in hoeverre dementie het beloop van AGECAT depressie beïnvloedt. Hierbij worden proefpersonen met en zonder dementie gedurende een periode van 12 maanden bestudeerd. De aanwezigheid van dementie blijkt niet van invloed op het beloop van de syndromale en subsyndromale depressie. Voor zowel patiënten met als zonder dementie is het depressie beloop persistent: de meeste proefpersonen met depressie bij aanvang van de studie hebben dat ook op minimaal een van de follow up metingen. Depressie bij aanvang van de studie is de belangrijkste voorspeller van het beloop van depressie. Onafhankelijk daarvan voorspellen somatische klachten meer depressie at follow up.

Hoofstuk 7 is een algemene discussie van de resultaten. De methodologische aspecten van de studie worden besproken. Het is duidelijk dat de bewoners van verzorgingshuizen niet representatief zijn voor ouderen in de algemene bevolking. Het gaat om ouderen die gekenmerkt worden door een hoge mate van kwetsbaarheid. De keuze voor de onderzoeksinstrumenten wordt beargumenteerd. De belangrijkste bevindingen worden besproken: de depressiesymptomatologie is onder te verdelen in stemmings- en motivatie symptomen. Motivatie symptomen komen vaker voor bij patiënten met dementie. De aanwezigheid van stemmingssymptomen is een risicofactor voor mortaliteit bij patiënten met dementie. Dementie heeft op zichzelf geen effect op het beloop van AGECAT depressie(sub)syndromen. De bevindingen geven steun aan de hypothese dat de motivatiestoornis deel uitmaakt van het dementie syndroom. Ze lijkt samen te hangen met het disfunctioneren van frontaal-subcorticale circuits.

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 8 januari 1963 te Bloemendaal. Na het behalen van het Gymnasium diploma aan het Triniteitslyceum te Haarlem (1981), studeerde hij een jaar Psychologie aan de Rijksuniversiteit te Leiden. Vanaf 1982 studeerde hij Geneeskunde aan dezelfde universiteit. Het doctoraalexamen behaalde hij in 1987, het artsexamen in 1989. Vanaf 1990 werkte hij als Assistent in Opleiding (AIO) aan de in deze dissertatie beschreven studie. Van januari tot september 1994 was hij als AGNIO werkzaam op de afdeling Neurologie van het AZN (supervisoren: prof dr. O.R. van Eikema Hommes en dr. H.C. Schoonderwaldt). Vanaf september 1994 specialiseerde hij zich in de Psychiatrie. De basisopleiding volgde hij op het UMC St Radboud te Nijmegen (hoofdopleider: Prof. dr. F.A.M. Kortmann), de stage sociale psychiatrie op de afdeling Volwassenen van de Gelderse Roos te Arnhem (opleider. mw. Drs. A.M. van den Berg), de keuzestage klinische psychotherapie op de Venne te Apeldoorn (opleider Drs. J.N. Voorhoeve). Per 1 maart 1999 is hij als Psychiater/Universitair Docent werkzaam op de opnameafdeling van het instituut voor psychiatrie van UMC St Radboud te Nijmegen.

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STELLINGEN

1 Het onderscheiden van depressiesymptomen in stemmings- en motivatiegebonden symptomen is zinvol en van toepassing bij verschillende neurologische ziektebeelden.

2. Bij patiënten met milde dementie voorspelt de aanwezigheid van depressiesymptomen een tragere achteruitgang van cognitieve functies (J.G.E. Janzing et al. in voorbereiding)

3 We mogen blij zijn dat we somber kunnen worden (gebaseerd op Randolph M. Nesse, Archives of General Psychiatry 2000;57·14-20).

4 Een zinvolle dagbesteding leidt tot een afname van depressieve symptomen bij ouderen. Het verhogen van de pensioengerechtigde leeftijd heeft derhalve een gunstig effect op de geestelijke volksgezondheid.

5 Vroegtijdige systeeminterventies kunnen de opnameduur van patiënten op een PAAZ in belangrijke mate verkorten.

6 Kwaliteitsverbetering in de psychiatrie is niet zozeer afhankelijk van het verkrijgen van nieuwe wetenschappelijke inzichten maar van het toepassen van de reeds bestaande

7 De IQ-stijging die optreedt tijdens afbouw van benzodiazepines bij patiënten met benzodiazepineverslaving suggereert dat deze patienten na behandeling intelligenter overkomen

8 Stemmingsstoornis door benzodiazepinegebruik is een te weinig gestelde diagnose

9 Bij een aanzienlijk deel van de patiënten met een therapieresistente depressie aangemeld voor Electro Convulsieve Therapie (ECT) is er sprake van een organische stemmingsstoornis.

10. 'Promoveren' betekent dat je er in vele opzichten op vooruit gaat.

11 Omdat aandelenkoersen vaak zo los staan van de economische realiteit dient bij beleggers de diagnose 'gedeelde psychotische stoornis' te worden overwogen.

Stellingen behorend bij het proefschrift 'Depression in Dementia, A Longitudinal Study in Residents of Homes for the Elderly' van J.G.E. Janzing, Nijmegen, 6 juni 2000.