Agitation in Patients with Dementia –

Challenges in Diagnosis and Treatment

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A quiet storm
soft flakes reshaping each angle
of tree and field
How the lightest touch
of a stranger's glance changes me

TANKA from Carol Purington

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"The Lord is my shepherd; I shall not want."

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List of original papers included in this thesis

I Sommer OH, Aga O, Cvancarova M, Olsen IC, Selbæk G, Engedal K.2009. Effect of Oxcarbazepine in the treatment of agitation and aggression in severe dementia. Dement Geriatr Cogn Disord 27:155-163.

II Sommer OH, Kirkevold Ø, Cvancarova M, Engedal K.2010. Factor analysis of the Brief Agitation Rating Scale (BARS) in a large sample of Norwegian nursing-home patients. Dement Geriatr Cogn Disord 29:55-60.

III Sommer OH, Engedal K.2010. Reliability and validity of the Norwegian version of the Brief Agitation Rating Scale (BARS) in dementia. Aging & Mental Health, under review.

IV Selbæk G, Kirkevold Ø, Sommer OH, Engedal K.2008.The reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, Nursing-Home Version (NPI-NH). Int Psychogeriatr 20:375-382

Abstract

Background

Dementia is a serious health problem showing an increasing prevalence rate with increasing age. It is the main reason for institutionalizing elderly people. Disruptive and agitated behaviour affect 30 to 50% of all individuals with dementia at some point in the course of the illness. Such behaviour decreases the quality of life of patients and carers, puts heavy strains on relatives and professional carers and poses a diagnostic, therapeutic and economic challenge. There is a need for new psychopharmacological and non-psychopharmacological treatments, because the existing drugs have limited benefits and are associated with poor tolerance and serious side effects. Furthermore, there is a need for validated assessment tools to evaluate patients before therapy and during follow-up. Given the daily routine in nursing homes with many competing demands brief instruments are preferable.

Aims

The thesis had three aims:

1) To evaluate the effect of oxcarbazepine (OXC) in the treatment of severe agitation and aggression in patients residing in nursing homes with Alzheimer's disease or vascular dementia or a mixture of both.
2) To study the psychometric properties of the Norwegian version of the Brief Agitation Rating Scale (BARS) by performing a factor analysis on a large sample of Norwegian nursing-home patients and testing the reliability and validity on another sample.
3) To test the reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, Nursing-home Version (NPI-NH).

Methods

Ad 1) We conducted an eight-week, multicentre, randomised, double-blind, placebo-controlled trial carried out independently of the pharmaceutical industry, randomizing 103 patients in 35 nursing homes (NH) either to placebo or OXC. The change in agitation and aggression sub-scores on the NPI-NH was the primary outcome. The secondary outcomes were the change in the carers' total burden score measured by the NPI-NH and change in the BARS total score.

Ad 2) The BARS is a short form of the Cohen-Mansfield Agitation Inventory (CMAI) that measures agitation in dementia. For the study of the reliability and validity of the BARS we investigated the test-retest reliability and internal consistency of the BARS on 56 nursing-home patients, and the validity of the BARS on 138 patients. In the validity study, we compared the BARS scores with the NPI-NH sub-scale Agitation/Aggression (NPI-NH/AA) and the Cornell Scale for Depression in Dementia sub-scale Agitation (CSDD/A).

Data used to perform a factor analysis came from a study that investigated the use of restraints and surveillance in Norwegian nursing-homes, published by Øyvind Kirkevold et al. (2004). 1,870 nursing-home patients were included in the analyses.

Ad 3) The psychometric properties of the NPI-NH were tested by establishing inter-rater reliability using kappa statistics. Fifty patients were included and examined by a physician, who also rated the patients' behaviour using BEHAVE-AD and the Cornell scale. Concurrent validity of the NPI-NH and BEHAVE-AD was analysed.

Results

Ad 1) After eight weeks, no statistically significant differences were found between the two groups for all outcomes. The placebo group showed a 36.3% reduction in agitation and aggression score on the NPI-NH compared to 39.0% in the OXC group. A trend was observed in favour of the OXC group in the reduction of the score on the BARS ($p = 0.07$).

Ad 2) In the reliability study, the mean BARS score was 24.2 (SD 12.6), Cronbach's alpha was 0.76; the test-retest reliability showed a Spearman's rho of 0.64, and increased to 0.86 when we deleted the item 'complaining'. Mean score in the validation study was 19.7 (SD 11.5). The BARS score correlated with the NPI-NH/AA and the CSDD/A scores, Spearman's rho 0.55 and 0.52 respectively. These correlations changed when controlling for the Clinical Dementia Rating Scale (CDR) stages. The highest correlations between the BARS and the NPI-NH/AA and the BARS and the CSDD/A were found among patients with CDR score 2.

Using an eigenvalue of ≥1, the exploratory factor analysis of the BARS revealed clusters in three dimensions of agitation. The first factor was named 'physically aggressive behaviour', the second 'physically non-aggressive behaviour' and the third 'verbal agitation'. Cronbach's alpha was 0.70, 0.78 and 0.46 respectively. Linear regression analysis showed that less able functioning in the activities of daily living (ADL) was positively associated with physically aggressive behaviour and verbal agitation, whereas increased severity of dementia

and better ADL functioning were associated with physically non-aggressive behaviour. In addition, verbal agitation had a positive relationship with a higher number of drugs taken per day.

AD 3) Internal consistency of NPI-NH, as measured by Cronbach's alpha was above 0.8. Inter-rater reliability was, except for one item, between kappa 0.85 and 1.0 across assessors with different levels of health education. All correlations between the NPI-NH and the BEHAVE-AD items were significant, ranging from 0.38 to 0.72. The weakest correlations were between items assessing affective and anxiety symptoms.

Conclusions

We could not find any statistically significant difference between the OXC group and the placebo, but, interestingly, the outcomes for reduction of agitation measured with the NPI-NH and the BARS differed. The Norwegian version of the BARS is a reliable and valid instrument to measure agitation in dementia and it measures three dimensions of agitation: physically aggressive behaviour, physically non-aggressive behaviour and verbal agitation. The Norwegian version of the NPI-NH is a reliable and valid instrument for assessing the syndromes of behavioural and psychological symptoms in nursing-home residents, but it is not a specific instrument for the measurement of agitation.

Sammendrag (Norwegian summary)

Bakgrunn

Forekomst av demens øker med alderen. Demens er et alvorlig helseproblem og den hyppigste årsaken til innleggelse på sykehjem. Omtrent 30 til 50% av alle som får en demenssykdom utvikler en eller annen form av uro (agitasjon) i sitt sykdomsforløp. Dette bidrar til redusert livskvalitet hos pasientene, pårørende og helsepersonell som har omsorg for dem. Det kan bli til en stor belastning for pårørende og pleiepersonell og en diagnostisk, terapeutisk og økonomisk utfordring. Vi trenger psykofarmakologiske og ikke-farmakologiske behandlingsalternativer til de eksisterende medikamentene, fordi de har begrenset effekt, tåles dårlig og kan føre til alvorlige bivirkninger.

Det er behov for gyldige verktøy som måler agitasjon for å kunne bedre evaluere pasientene før behandling og følge dem opp under behandling, ikke bare i klinisk praksis men også i forskningssammenheng. De daglige rutinene på sykehjem med sine mange konkurrerende krav fører til at kortversjoner av slike instrumenter foretrekkes.

Formål

Avhandlingen har tre formål:

1) Evaluere effekten av okskarbazepin (OXC) i behandling av alvorlig agitasjon og aggresjon hos pasienter på sykehjem med Alzheimers sykdom eller vaskulær demens eller en blandingsform av begge.
2) Studere de psykometriske egenskapene av den norske versjonen av Brief Agitation Rating Scale (BARS): Vi testet påliteligheten/repeterbarheten (reliabiliteten) og gyldigheten (validiteten) i et utvalg av norske sykehjemspasienter og gjennomførte en faktoranalyse av BARS it et annet utvalg.
3) Teste reliabilteten og validiteten av den norske versjonen av Neuropsychiatric Inventory, Nursing-home Version (NPI-NH).

Metoder

Ad 1) Vi gjennomførte en dobbelblind, placebokontrollert multisenterstudie uavhengig av farmakologisk industri ved å randomisere 103 pasienter i 35 sykehjem enten til placebo eller OXC. Forandringen i agitasjons- og aggresjonsskårene på NPI-NH var det primære

endepunktet. De sekundære endepunktene var forandringen på pleiernes total belastning målt med NPI-NH og forandringen i sum skåren av BARS.

Ad 2) BARS er en kortversjon av Cohen-Mansfield Agitation Inventory (CMAI) som måler agitasjon ved demens. Vi undersøkte test-retest reliabiliteten og den indre konsistensen hos 56 sykehjemspasienter. Validitetsundersøkelsen utførte vi hos 138 pasienter. I validitetsundersøkelsen sammenliknet vi BARS skårene med NPI sub skala agitasjon/aggresjon og med Cornell Scale for Depression in Dementia: sub skala agitasjon.

Dataene som vi brukte for å gjennomføre en faktoranalyse kom fra en studie som undersøkte bruken av tvang og overvåkning i norske sykehjem og som ble publisert av Øyvind Kirkevold et al. (2004). 1,870 sykehjemspasienter ble inkludert i analysen.

Ad 3) De psykometriske egenskapene av NPI-NH ble testet. Vi undersøkte inter-rater reliabiliteten mellom fagpersoner med forskjellige nivåer av helseutdannelse. Til dette formålet brukte vi kappa-statistikk. Femti pasienter ble inkludert og undersøkt av en lege som også skåret pasientenes atferd med BEHAVE-AD- og depresjonen med Cornell-skalaen. NPI-NH ble validert mot BEHAVE-AD.

Resultater

Ad 1) Etter åtte uker fant vi ingen statistisk signifikant forskjell mellom placebo- og OXC-gruppen. Placebogruppen viste en 36.3% reduksjon av agitasjons- og aggresjonsskåren på NPI-NH sammenliknet med 39.0% i den OXC-gruppen. Man kunne observere en trend til fordel for OXC- gruppen ved reduksjon av BARS-totalskåret (p = 0.07).

Ad 2) I reliabilitetsstudien var den gjennomsnittlige BARS-skåren 24.2 (SD 12.6), Cronbach's alpha var 0.76. Test-retest reliabiliteten målt med Spearman's rho var 0.64, og økte til 0.86 når vi slettet symptomet "klaging". Gjennomsnittsskåren av BARS i validitetsstudien var 19.7 (SD 11.5). Spearman's rho mellom BARS og NPI-NH, subskåren agitasjon/aggresjon, og agitasjonsspørsmålet i Cornell-skalaen var henholdsvis 0.55 og 0.52. Disse korrelasjonsverdiene forandret seg når vi kontrollerte for demensgraden målt med kliniske demensvurderinsgskalaen (KDV). Høyest korrelasjonen fant vi mellom BARS og NPI-NH/AA og mellom BARS og CSDD/A hos pasienter med KDV-skåre 2.

I faktoranalysen av BARS fant vi at skalaen består av tre komponenter. Den første faktoren kalte vi fysisk aggressiv atferd, den andre fysisk ikke-aggressiv atferd og den tredje

verbal agitasjon. Cronbach's alpha var henholdsvis 0.70, 0.78 og 0.46. En lineær regresjonsanalyse viste at dårligere fungering i dagliglivets aktiviteter (ADL) var relatert til fysisk aggressiv atferd og verbal agitasjon, mens økt alvorlighetsgrad av demens og bedre ADL-funksjon var assosiert med fysisk ikke-aggressiv atferd. I tillegg fant vi en positiv sammenheng mellom verbal agitasjon og mer bruk av legemidler.

Ad 3) Cronbach's alpha, som mål for den interne konsistensen av NPI-NH var 0.8. Kappaverdiene var, med unntak for en variabel, mellom 0.85 og 1.0 når man sammenliknet evalueringen utført av personer med forskjellig helseutdanning. Korrelasjonene mellom leddene i NPI-NH og BEHAVE-AD var mellom 0.38 og 0.72. De svakeste korrelasjonene fant vi mellom symptomer på depresjon og angst.

Konklusjoner

Vi fant ingen statistisk signifikant forskjell mellom OXC- og placebogruppen, men interessant var det at resultatene målt med NPI-NH og BARS var så forskjellige. Den norske versjonen av BARS er reliabel og valid og måler tre dimensjoner av agitasjon: fysisk aggressiv atferd, fysisk ikke-aggressiv atferd og verbal agitasjon. NPI-NH er også reliabel og valid når man undersøker atferds- og psykologiske symptomer hos sykehjemspasienter, men er ikke et verktøy som spesifikt måler agitasjon.

Abbreviations & Definitions

AD	Alzheimer's Disease
ADL	Activities of Daily Living
BARS	Brief Agitation Rating Scale
BPSD	Behavioural and Psychological Symptoms in Dementia
CDR	Clinical Dementia Rating Scale
CMAI	Cohen-Mansfield Agitation Inventory
CSDD	Cornell Scale for Depression in Dementia
DLB	Dementia with Lewy Bodies
FTLD	Fronto-Temporal Lobe Dementia
ICD-10	International Classification of Diseases – 10
MCI	Mild Cognitive Impairment is a syndrome defined as a cognitive decline greater than that expected for an individual's age and education level, but which does not interfere notably with complex day-to-day activities.
MMSE	Mini Mental State Examination
NH	Nursing home
OBAD	Okskarbazepin i Behandling av Aggresjon og Uro ved Demens (Oxcarbazebine in the Treatment of Agitation and Aggression in Dementia)
NPI-NH	Neuropsychiatric Inventory – Nursing Home Version
PDD	Parkinson's Disease Dementia
QoC	Quality of Care
QoL	Quality of Life
RCT	Randomised Clinical Trial
Reliability	(Test-retest) is the extent to which a measurement made repeatedly in identical circumstances will yield concordant results. (Inter-rater) is the extent to which a measurement made by independent raters will yield concordant results.
RU	Regular Unit (Nursing home)
SCU	Special Care Unit (Nursing home)
VaD	Vascular Dementia
Validity	is the degree to which a study or scale appropriately answers the question being asked or appropriately measures what it is intended to measure.

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1. Introduction

Dementia is a devastating illness with an increasing prevalence, mainly because of the aging of the population [1-4]. Dementia has emerged as the most potent risk factor for institutionalisation in a 12-year community-based epidemiological study [5]. Besides the impact of dementia on the health and quality of life (QoL) of patients and their relatives and carers [6-11], which is a hidden cost, many countries are confronted with rising actual costs of dementia care [12].

Syndromes of behavioural and psychological symptoms are very common in dementia [13-17]. Agitation is highly prevalent in nursing-home patients [13 18 19], is highly disabling for the patient, is one of the most distressing aspects of dementia, and is one of the main causes of institutionalisation of elderly people [18 20-23]. Different scales for the assessment of psychological and behavioural symptoms have evolved, such as the Cohen-Mansfield Agitation Inventory (CMAI) [24], the Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale [25] and the Neuropsychiatric Inventory (NPI) [26] as the ones most used in research. The mentioned scales measure different aspects of agitation as reflected in the choice of items. This could also be seen in our study investigating the effect of oxcarbacepine (OXC), where NPI scores and BARS scores differed widely (see Paper I, figure 2a and 2b).

Agitation and other neuropsychiatric symptoms lead frequently to the use of psychotropic drugs and, in Norwegian nursing homes, especially antipsychotics [27-29]. Antipsychotics have only a modest benefit, and patients treated with such drugs run a definite risk of serious and even irreversible side-effects and higher mortality [30]. Therefore, treatment with antipsychotics is not an ideal solution for treating behavioural and psychological symptoms of dementia [31-34].

A review of pharmacological treatment of agitation and aggression concluded that no treatment may be preferable and the effect sizes have been modest at best [35]. Carbamazepine was effective in treating agitation and aggression in one study [36], whereas no effect was found in another study [37]. Studies investigating the efficacy of other anti-epileptic drugs, such as valproate and divalproex sodium, have reported conflicting and inconclusive results [38-42].

To find a better tolerated alternative to the existing psychopharmacological medications, we conducted a study to evaluate whether OXC is effective in the treatment of agitation and aggression in institutionalized patients with Alzheimer's disease or vascular dementia.

2. Dementia

2.1. Prevalence, incidence and survival

2.1.1. Prevalence

The study by Plassman et al. [4] stated that the prevalence rate of dementia in the USA increased with age, from 5.0% of those aged 71-79 years to 37.4% of those aged 90 and older. A meta-analysis of different prevalence studies in Europe came to the conclusion that the overall European prevalence for the five-year age groups from 60 to 94 years, were 1.0, 1.4, 4.1, 5.7, 13.0, 21.6 and 32.2%, respectively [43]. A study conducted in England and Wales (Table 2.1.1), the "MRC CFA Study" (1998), included 10,377 persons aged 65 and above, and one in Canada, "Canadian Study of Health and Aging" (1994), included 10,263 persons aged 65 and above. These large-scale studies reported prevalence data that are generalizable for England, Wales and Canada. Results from the British study are quite similar to the results of the Canadian study. The overall prevalence of dementia in persons 65 years and over was 6.6% in England and Wales. The figures for Canada are pooled to 8% for all individuals over age 65 and 35% of those older than age 85. Lobo et al. [44] undertook a collaborative study (EURODEM) of 11 population-based cohorts carried out in eight European countries and found that there were no important differences in the age-specific prevalence between the studies or between the countries.

Table 2.1.1. Results of the prevalence study from England and Wales (MRC CFA Study, 1998).

Prevalence of dementia by age and sex (%) (Pooled results from five centres of the Medical Research Council Cognitive Function and Ageing Study)		
Age-group	**Men (%)**	**Women (%)**
65-69	1.4	1.5
70-74	3.1	2.2
75-79	5.6	7.1
80-84	10.2	14.1
85+	19.6	27.5

Estimates of the prevalence of dementia in Norway are based on extrapolation from international studies [45-47] as well as results from a Norwegian study [48 49]. Table 2.1.2 presents the prevalence data for Norway (Oslo) compared with Rotterdam and the mean of the eight European countries that participated in the EURODEM study.

Table 2.1.2. Prevalence of dementia in Norway (Oslo) compared to Rotterdam and European countries (adapted from Engedal et al. 2004)

Age (years)	**Rotterdam (%)**	**EURODEM ♂ (%) ♀**		**Oslo (%)**
65-69	0.9	1.6	1.0	
70-74	2.1	2.9	3.1	
75-79	6.1	5.6	6.0	10.1
80-84	17.6	11.0	12.6	16.7
85-89	31.7	12.8	20.2	26.2
90+	40.7	22.1	30.8	28.3

2.1.2. Incidence

The incidence and risk for dementia were assessed in a large community-based prospective cohort study in Rotterdam with an average follow-up period of 2.1 years [47]. Overall, the incidence rate per 1,000 person-years was 7.7 for Alzheimer's disease and 1.5 for vascular dementia. The age-specific incidence rates were similar in men and women, continued to increase after the age of 84 years, and remained stable over time for both dementia and AD [50]. Incidence rates for dementia and AD increase across the 5-year age groups; AD rates rise from 2.8 per 1000 person-years (age group, 65-69 years) to 56.1 per 1000 person-years in the older than 90-year age group [51].

2.1.3. The number of patients with dementia worldwide in the years to come

Wimo et al. [52] estimated a considerable increase in the number of elderly patients with dementia worldwide from 25 million in the year 2000 to 63 million in 2030 (41 million in less developed regions) and to 114 million in 2050 (84 million in less developed regions). Ferri et al. [3] reported that 24.3 million people have dementia today, with 4.6 million new cases of dementia every year (one new case every 7 seconds). Wancata et al. [53] calculated the prevalence of dementia in Europe for the period 2000-2050. The number of dementia cases in the year 2000 was 7.1 million. Within the next 50 years, this number is expected to rise to about 16.2 million dementia sufferers. The number of new dementia cases per year is expected to increase from about 1.9 million in the year 2000 to about 4.1 million in the year 2050.

2.1.4. Survival

Xie et al. [54] used the same cohort from England and Wales, as already reported, to investigate the *median survival time*: "Estimated median survival time from onset of dementia to death was 4.1 years for men and 4.6 years for women. There was a difference of nearly seven years in survival between the younger old and the oldest people with dementia: 10.7 for ages 65-69; 5.4 for ages 70-79; 4.3 for ages 80-89, and 3.8 years for ages > or=90. Significant factors that predicted mortality in the presence of dementia during the follow-up included sex, age of onset, and disability."

The Cardiovascular Health (CHS) Cognition Study showed a more differentiated picture, making the distinction in survival time dependent on what kind of dementia the patients had. Adjusted accelerated life models estimated median survival time from the onset of dementia to death as 3.9 years for those with vascular dementia (VaD), 7.1 years for AD, 5.4 years for mixed dementia, and 11 years for matched controls with normal cognition [55]. Mild Cognitive Impairment (MCI), see chapter 2.4., in the CHS-Cognition Study had a prevalence rate of 22% among the participants aged 75 years or older [56].

2.2. Risk factors for dementia

2.2.1. Demographic risk factors

Old age is the most important risk factor for AD. A meta-analysis of incidence studies showed that both AD and dementia continue to increase with increasing age up to the age 98, although the rate of acceleration slows down [57]. However, it looks as though dementia is an inevitable disorder as a person gets older [58].

Whether or not *gender* is an independent risk factor has been discussed. One meta-analysis found women had a higher incidence of AD than men, but not a higher incidence of dementia in general [57]. Another study found that the risk of getting AD was not essentially higher for women than men [59].

Is e*thnicity* a risk factor? Jorm and Jolley [60] found in a meta-analysis that dementia has a higher incidence in Europe than in Far East. East Asia also tended to have a lower incidence of AD. Whether that is due to ethnicity, genetics or other factors, like the environment, differences in nutrition or socio-cultural aspects, is not clear.

2.2.2. Vascular risk factors

Among others, the Honolulu-Asia Aging Study (HAAS) [61-63] and a prospective study in Sweden [64] found good evidence that *hypertension* in middle-age increases the risk for AD 10 - 15 years later. A prospective, population-based study from Finland [65] showed that middle-aged people with raised systolic blood pressure or *high serum cholesterol* concentration had a significantly higher risk of Alzheimer's disease in later life, even after adjustment for age, body mass index, education, vascular events, smoking status and alcohol consumption, than those with normal systolic blood pressure (odds ratio 2.3) or serum cholesterol (odds ratio 2.1). Participants with both of these risk factors in midlife had a significantly higher risk of developing Alzheimer's disease than those with either of the risk factors alone (odds ratio 3.5). Diastolic blood pressure in midlife had no significant effect on the risk of Alzheimer's disease.

A systematic review and meta-analysis [66] found a significantly increased risk of Alzheimer's disease with current smoking and a likely but not significantly increased risk of vascular dementia, unspecified dementia and cognitive decline. Neither review found clear relationships with former smoking.

From the Framingham study [67], it could be concluded that the risk for *stroke* is equal to or greater than the lifetime risk (LTR) of AD. The LTR of AD at age 65 approximated 1 in 5 for women and 1 in 10 for men. Women had a higher risk because of their longer life expectancy. Schneider et al. [68] investigated the effect of sub-cortical infarcts on the development of dementia. After controlling for cortical infarcts and AD pathology, sub-cortical infarcts, present in 39 of 53 (73.6%) subjects with infarcts, increased the odds of dementia almost 4-fold and reduced cognitive function by more than a third of a unit. It may be hypothesised that there are two main pathways to AD [69]: in one, the vascular disease is an essential contributor, and in the other it is a multi-domain, but mainly genetic, pathway. In a general community-dwelling population, those with dementia most often have multiple brain pathologies, which greatly increases the odds of dementia. Knopman et al. [70] found in a fourteen-year longitudinal study that the vascular risk factors diabetes and hypertension, a history of stroke itself, and apolipoprotein E epsilon 4 (APOE ε4) genotype independently contribute to cognitive decline in late middle age and the early years of old age.

Hypercholesterolemia in midlife has been associated with an increased risk for dementia in cohort studies [65 71]. Midlife serum total cholesterol was associated with an

increased risk of AD and VaD [72]. Even moderately elevated cholesterol increased the risk of dementia.

Diabetes, especially type II (DM), has also been found to increase the risk for dementia in general and, more specifically, in AD [73]. Kopf and Frölich [74] reviewed 11 studies that investigated diabetes as a risk factor for AD. They concluded that DM is likely to increase the risk of Alzheimer's disease. The association of Alzheimer's disease and DM is more clear-cut, if mild cases of DM are included in the analysis. Also, biologically there is a connection between DM and AD through an enzyme called 'glycogen synthase kinase 3' (GSK-3) that mediates the addition of phosphate molecules to certain proteins (phosphorylation) and thus inactivates glycogen synthase. This enzyme is ubiquitous in all organisms and all body cells and is a factor in regulating insulin signalling. GSK-3 also plays a pivotal and central role in the pathogenesis of both sporadic and familial forms of AD. In the GSK-3 hypothesis of AD, GSK-3 is central in the (hyper)phosphorylation of the tau-protein and thus intervenes in the essential transport function of the microtubules, leading from the nerve body through the nerve axons to the synapses. Over-activity of GSK-3 accounts for memory impairment, tau hyper-phosphorylation, increased beta-amyloid production and local plaque-associated microglial-mediated inflammatory responses [75]. Interestingly, memory training and physical exercise decrease GSK-3 and, thereby, tau-phosphorylation.

Risk factors may be additive, for example, combining *obesity* with hypertension and high cholesterol led to an OR of 6.2 [76 77]. Luchsinger et al. [78] found that the risk of AD increased with the number of risk factors (diabetes + hypertension + heart disease + current smoking).

It has also been shown that higher *homocystein* levels contribute to faster cognitive decline [79-81].

In summary, Lutz Frölich presented an overview of the strength of association between risk factors and dementia as representative of the Working Group of the European Collaboration on Dementia (EuroCoDe, Alzheimer Europe) at the IPA 2009 in Montreal: OR=25 for age, OR=3-4 for genetic risk factors and OR=1.8-2.3 for cardiovascular risk factors or lifestyle risk factors, with strong, strong and moderate/insufficient evidence, respectively. Coley et al. [82] reviewed the epidemiological data and concluded that even if there are consistent findings from large observational studies regarding preventive or risk factors for dementia, few randomised controlled trials have been designed specifically to prove the protective effects of interventions based on such factors for the incidence of

dementia. Because of the multi-factorial origin of dementia, it appears that multi-domain interventions could be suitable for preventive interventions, but designing such trials remains very challenging for researchers. It is possible to estimate the risk relative to other individuals using variables derived from a population study and adding up to a midlife 'dementia risk score' [83], which identifies some excellent treatment targets for prevention, such as hypertension, obesity, hypercholesterolemia and lack of physical activity.

2.2.3. Head injuries

Head injuries may be a risk factor, but the studies are inconclusive. However, it is interesting to note that Mayeux et al. [84] found that head injuries are only a risk factor for AD in people with the APOE ε4 allele.

2.2.4. Genetic risk factors

Some key genes have been identified, which are causal in some early onset cases of AD, i.e., producing a higher amount of presenilin-1 (Chromosome 14), presenilin-2 (Chromosome e1), and amyloid precursor protein (Chromosome 21). The genetic influence of APOE-ε4 [85] is a known risk factor for AD [86]. Age-related memory decline in APOE-ε4 carriers diverges from that of non-carriers before the age of 60 years, despite ongoing normal clinical status [87 88]. A meta-analysis found age-adjusted odds ratios for AD of 2.6 for ε2/ε4 heterozygotes, 3.2 for ε3/ε4, and 14.9 for ε4/ε4 homozygotes [89]. However, these striking findings need to be put in context. Up to 50% of those who are homozygous for ε4 and who live beyond 90 do not develop AD and about two-thirds of those who develop AD have no ε4 allele [90].

The largest ever Alzheimer's genome-wide association study (GWAS) [91] involved 16,000 individuals, including 6,000 Alzheimer's patients. This study replicated the established association with the APOE locus and observed two loci not previously associated with the disease: the CLU (also known as APOJ) gene and the PICALM gene. These associations were replicated in stage 2 (2,023 cases and 2,340 controls), producing compelling evidence for association with Alzheimer's disease in the combined dataset. The results were compared to a similar French study of more than 7,000 individuals (2,032 with Alzheimer's disease and 5,328 controls), carried out at the National Institute of Health and Medical Research in Lille, France, by Philippe Amouyel and colleagues [92], which not only confirmed the two recently discovered genes but identified a third, CR1.

Furthermore, Down's syndrome is a well-established risk factor causing AD via amyloid precursor protein.

2.3. Protective factors

Different preventive or protective factor hypotheses are under scrutiny: genes [93], toxic hypothesis, psychosocial hypothesis, vascular hypothesis, oxidative stress hypothesis. Many different protective factors have been discovered.

A higher level of *work complexity* [94 95], *education and social relationships* [96 97] have been shown to be protective. The association between low education and dementia is probably not explained only by the unhealthy lifestyles of the less educated compared with higher educated persons. Higher educated persons may have a greater cognitive reserve that can postpone the clinical manifestation of dementia. With appropriate training and practice, adults over the age of 65 can significantly improve their memory, concentration, and problem-solving capacity, according to the findings of the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) clinical trial [98].

Mental, physical and social components of *leisure activities* equally contribute to decreasing the risk of dementia [99-101]. Rovio et al. [102] showed that leisure-time *physical activity* in middle-age, at least twice a week, was associated with a reduced risk of dementia and AD. They could also show that these associations were even more pronounced among the APOE-ε4 carriers and that regular physical activity, especially among genetically susceptible individuals, may reduce the risk or delay the onset of dementia and AD. The Framingham study [61 103] and new findings from the Finnish population-based CAIDE study [104 105], and some others showed that there may be possibilities of preventing AD and VaD, through intervention to reduce cardiovascular risk factors. Aerobic fitness and exercise are effective at preventing cortical decay and cognitive impairment in older adults [106]; altogether 16 studies have produced moderate to high evidence of this. A study of adults with subjective memory impairment with a 6-month programme of physical activity provided a modest improvement in cognition over an 18-month follow-up period [107]. A study published in 'Nature' showed a positive relationship between exercise and cognitive functioning [108]. Erickson et al. [109] used a region-of-interest analysis on magnetic resonance images and found a triple association such that higher fitness levels were associated with larger left and right hippocampi after controlling for age, sex, and years of education. Larger hippocampi and higher fitness levels were correlated with better spatial memory performance. Cognitive training [110], in particular reasoning training resulted in less functional decline in self-reported instrumental activities of daily living (ADL). Compared with the control group, cognitive training resulted in improved cognitive abilities five years after the initiation of the intervention.

Longitudinal observations of *dietary habits* could show that a high intake of unsaturated, unhydrogenated fats may be protective against AD, whereas an intake of saturated or trans-unsaturated (hydrogenated) fats may increase risk, especially among APOE-ε4 carriers [111-114]. Combining all the evidence related to *dietary interventions* to prevent dementia (poly-unsaturated fatty acids – PUFA – 6 studies; fish consumption, 4 studies; Mediterranean diet 1 study; moderate alcohol, 5 studies) resulted in insufficient evidence [115].

Personality traits, such as low neuroticism in combination with high extraversion are associated with the lowest dementia risk. However, among socially isolated individuals even low neuroticism alone seems to decrease dementia risk [116].

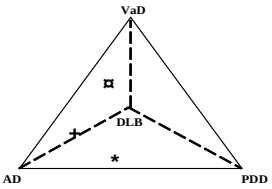
A 21-year follow up study showed that treatment of midlife vascular risk factors is effective in the prevention of AD in later life [65]. Haag et al. [117] evaluated prospectively the data from the Rotterdam Study and could show that treating hyperlipidemia with statins helps: compared with life-long non-use of cholesterol-lowering drugs, statin use was associated with a decreased risk of AD (HR 0.57), but non-statin cholesterol-lowering drug use was not (HR 1.05). HRs were equal for lipophilic (HR 0.54) and hydrophilic statins (HR 0.54). Haag et al. [118] investigated in the same cohort the association between the duration of antihypertensive use and the risk of dementia. They observed an 8% risk reduction per year of antihypertensive drug use for persons of under 76 years of age, whereas for persons over 75 years this was 4%. Equivalent estimates were observed for AD. No apparent differences were observed among different types of antihypertensive drugs. Finally, one can summarise that everything that works well in the prevention of coronary heart disease may be also effective in the prevention of dementia.

2.4. Different types and stages of dementia

Many of the prevalence studies report specific prevalence rates for different dementia disorders. The Rotterdam study [46], as an example, showed a prevalence of AD of 72%. The lowest rate of AD is 60% [119]. Next is vascular dementia (VaD) that shows a prevalence of 20-25%. The third and fourth most prevalent types of dementia are dementia with Lewy bodies (DLB) and Frontal / frontotemporal lobe dementia (FTLD), respectively. There are many patients who have elements of different dementias at the same time (mixed cases), and this is illustrated in Figure 2.4.1. Cerebrovascular disease is now believed to represent a continuum

of relevance for AD as well as for VaD [120-123]. Similarly, AD is frequently noted to be accompanied by pathological findings typical for DLB [124].

Figure 2.4.1. Different types of dementia, presenting in individual patients (**+,*, ¤**).



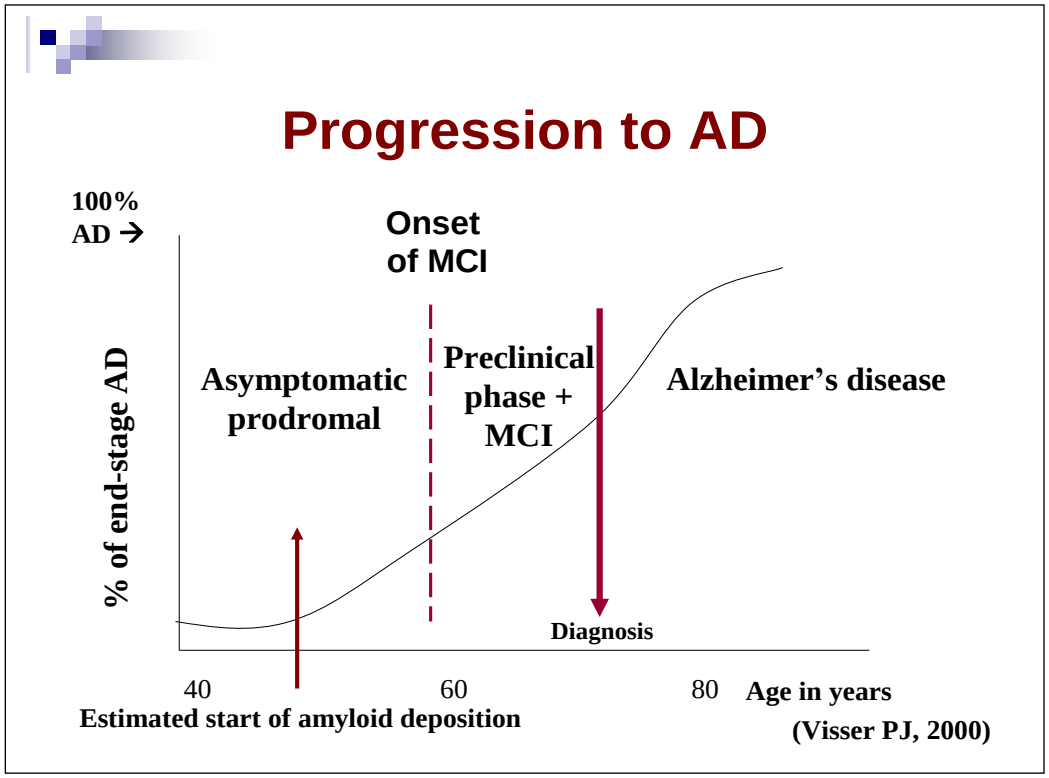
There are many *other types of dementia*, such as alcohol induced dementia, and different types of dementia in later stages of degenerative neurological diseases, such as Parkinson's disease, where 30-75% of patients are affected [125], Pick's disease, Huntington's disease and the late stages of infectious diseases, such as Creutzfeld-Jacob's disease, herpes, syphilis, AIDS, Borrelia, and some endocrinological diseases, such as phenylketonuria, and genetic diseases, such as Down's syndrome. Other causes may be brain tumours, normal-pressure hydrocephalus and traumatic lesions of the brain. This list is by no means complete; it shows only that there may be many different reasons for dementia, but 95% of all cases of dementia are AD, VaD, DLB, FTLD, and alcohol-related dementias.

Besides the different types of dementia, there is a consensus about *grading dementia* in mild, moderate and severe stages, dependent on the performance in the ADL. Long before a patient fulfils the criteria for a diagnosis of dementia, there is a preclinical phase or an asymptomatic prodromal. This may last as long as 20 years or more (Figure 2.4.2).

2.4.1. Preclinical AD and MCI

In recent years, there has been a strong focus on diagnosing the preclinical stages of AD. The preclinical phase is characterised by mild impairment in verbal memory, which probably reflects damage of the hippocampus, with later involvement of areas governing language, spatial orientation, attention, concentration, and psychomotor speed [126]. In one study, nuns who had poor linguistic abilities in their 20s had more senile plaques and neurofibrillary tangles in old age [127]. It is unclear whether these impairments reflect very early manifestations of the disease or risk factors for the disease [128]. Subjective cognitive impairment (SCI) or subjective memory impairment (SMI) and *mild cognitive impairment* (MCI) manifesting itself with different types of recognisable deficits, without any decline in functional abilities,

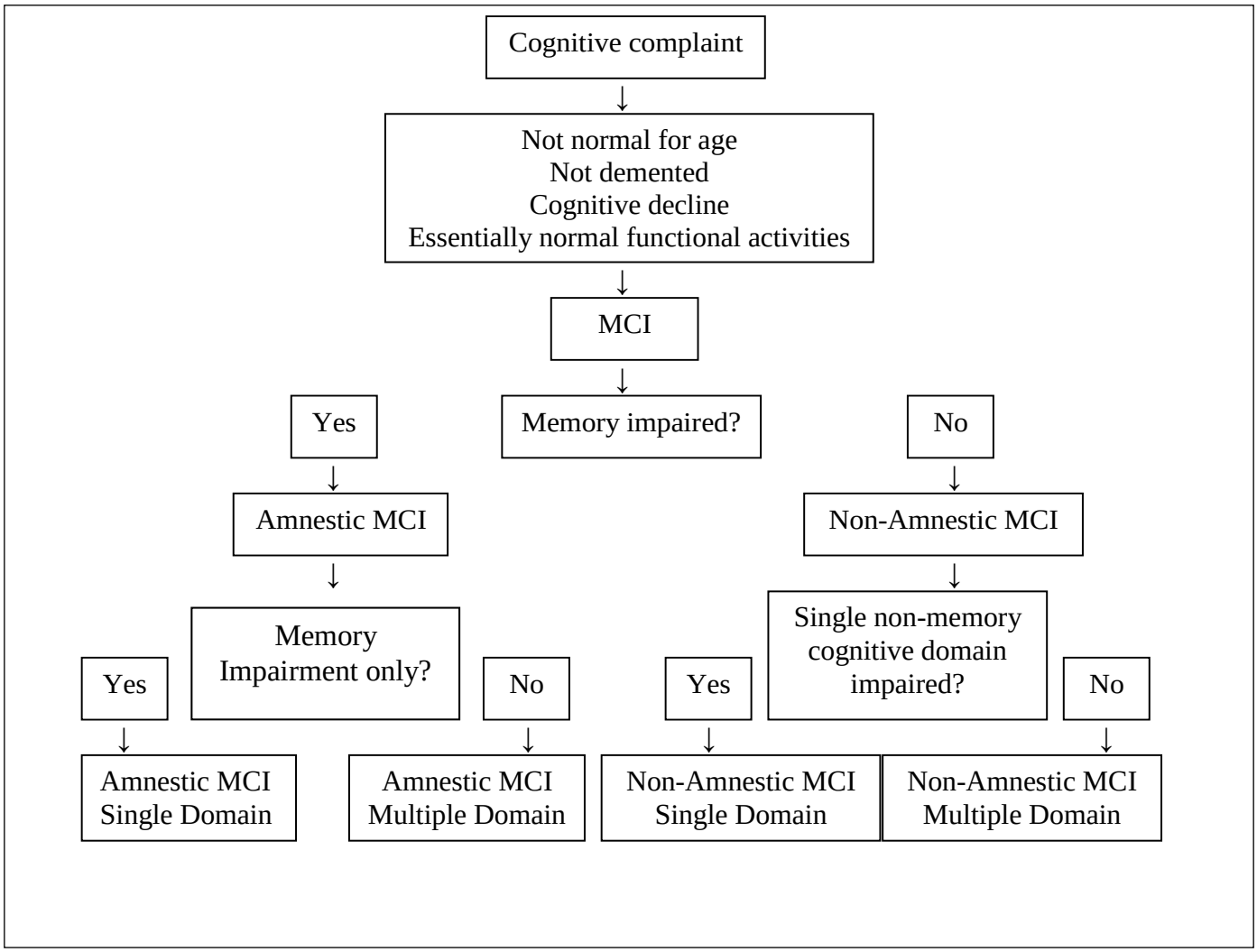
Figure 2.4.2. Progression to Alzheimer's disease (AD).



may constitute precursors of dementia. There are difficulties with terminology in this area. In collaboration with the International Psychogeriatric Association and the World Health Organization, a concept of "ageing associated cognitive decline" (AACD) was proposed [129], defined as being the normal course of cognitive decline in ageing. As a more specific pathological decline with recognizable degrees of objective cognitive impairment, Petersen and colleagues described MCI and focused on the amnestic (or memory) form of MCI as precursor mostly of AD [130 131], see Figure 2.4.3. It has become a generally accepted term (see definition in Abbreviations & Definitions). However, it is important to note that there are as yet no internationally agreed single sets of diagnostic criteria for MCI, though the broad criteria were recommended for use by an international consensus group [132]. The International Psychogeriatric Association's Expert Conference on Mild Cognitive Impairment summarized the research on MCI in a review, saying that the prevalence in population-based epidemiological studies ranges from 3% to 19% in adults older than 65 years. Some people with mild cognitive impairment seem to remain stable or return to normal over time, but more than half progress to dementia within 5 years. Mild cognitive impairment can thus be regarded as constituting a risk for dementia, and its identification could lead to secondary prevention by controlling risk factors such as systolic hypertension. The amnestic subtype of

mild cognitive impairment has a high risk of progression to Alzheimer's disease, and it could constitute a prodromal stage of this disorder.

Figure 2.4.3. Criteria for MCI (from Petersen, 2004).



Other definitions and subtypes of mild cognitive impairment need to be studied as potential prodromes of Alzheimer's disease and other types of dementia [133].

2.5. Diagnosing dementia

The term dementia describes a syndrome characterised by memory impairment, intellectual deterioration, decline in performance of the ADL, changes in personality and behavioural abnormalities. These symptoms have to be of such severity as to interfere with social

activities and occupational functioning. Distinct subtypes of dementia syndromes are identifiable from the etiologic factors, clinical presentation, and the pattern of impairment, the natural course of the dementia and laboratory or neuroimaging tools. The International Classification of Diseases (ICD-10) [134] Diagnostic Criteria for Research (DCR-10) [135] has represented one way of describing dementia (Table 2.5.1).

Table 2.5.1. Dementia ICD-10. Diagnostic criteria for research (DCR-10).1993. General criteria for dementia. Shortened version.

I Decline in cognitive function, objectively verified
- (1) Decline in memory, especially new information
- (2) Decline of at least one other cognitive function as judgment, planning, thinking, abstraction, calculation, orientation, language…
- *Mild:* Interferes with everyday activities; complicated daily tasks cannot be undertaken
- *Moderate:* Serious handicap to independent living, needs assistance from another person
- *Severe:* Continuous care necessary

II Awareness of the environment (i.e. absence of clouding of consciousness) is preserved. When there are superimposed episodes of delirium, the diagnosis of dementia should be deferred.

III Decline in emotional control or motivation, or a change in social behaviour manifest as at least one of the following:
- (1) emotional instability
- (2) irritability
- (3) apathy
- (4) coursing of social behaviour

IV The symptoms in criterion (I) should have been present for at least 6 months; if the period since the manifest onset is shorter, the diagnosis can be only tentative.

The primary requirement for diagnosis is evidence of a decline in both memory and thinking that is sufficient to impair the personal activities of daily living. The impairment of memory typically affects the registration, storage, and retrieval of new information, but previously learned and familiar material may also be lost, particularly in the later stages. The Mini Mental State Examination (MMSE) may be of some help in describing the different cognitive deficits and offers modest accuracy, and best value for ruling-out a diagnosis of dementia in community and primary care [136]. Dementia is more than problems with memory: there is also impairment of thinking and of reasoning capacity, a reduction in the flow of ideas, etc. The

processing of incoming information is impaired, in that the individual finds it increasingly difficult to attend to more than one stimulus at a time, such as taking part in a conversation with several persons, and shifting the focus of attention from one topic to another. If dementia is the sole diagnosis, evidence of clear consciousness is required. However, a double diagnosis of delirium superimposed upon dementia may be seen. The above symptoms and impairments should have been evident *for at least 6 months* to make a confident clinical diagnosis of dementia.

Differential diagnoses: A depressive disorder (F30-F39) has to be considered, which may exhibit many of the features of an early dementia, especially memory impairment, slower thinking, and lack of spontaneity; delirium (F05); mild or moderate mental retardation (F70-F71); states of subnormal cognitive functioning attributable to a severely impoverished social environment and limited education; iatrogenic mental disorders due to medication (F06).

Diagnosing dementia is no longer done only by testing and clinical examinations of the patient, as was originally recommended by the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease Related Disorders Association (NINCDS-ADRDA), ICD-10 (DCR-10) or the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) [137] criteria for AD, the prevailing diagnostic standards in research. Distinctive and reliable biomarkers of AD are now available through structural MRI [138] [139], molecular neuroimaging with PET, and cerebrospinal fluid analyses. Consequently, Dubois et al. suggested a revision of the research criteria for the diagnosis of Alzheimer's disease. These new criteria are centred on a clinical core of early and significant episodic memory impairment in addition to abnormal biomarkers like structural neuroimaging with MRI, molecular neuroimaging with PET, and cerebrospinal fluid analysis of beta amyloid or tau proteins [140]. However, much work lies ahead to find criteria that can be proven pathologically and will generally be accepted as clinically sound [141]. The dilemma can be exemplified, when comparing different diagnostic criteria for VaD [142] [143]. Wetterling's group [144] compared the criteria for the diagnosis of VaD in an unselected sample of 167 elderly patients with probable dementia using different criteria, and as a result they found poor concordance. Gold et al. [145] reported similar poor results comparing different diagnostic tools.

Bringing down the time from onset of the first symptoms until a diagnosis can be given, is still a challenge. Indeed, in Europe only about 45% of sufferers get a *diagnosis of dementia* [146]. Moreover, there is a lack of trained professionals to diagnose and manage the disease, a lack of human and financial resources to provide care and services for people with

AD (as well as their families) and a lack of infrastructure to deliver the required services. These difficulties are compounded by inadequate education of both the general public and physicians, which also has implications for the treatment recommendations given at the time when a dementia is diagnosed [147]. Waldemar et al. [148] reviewed and discussed existing *barriers to diagnosis and treatment* for patients with dementia in Europe as well as approaches to overcome these barriers. The barriers to care are manifold, being present at all levels in each society and every country in Europe. Multilevel and multifaceted strategies are needed to improve diagnosis and treatments for all patients with cognitive complaints. A multidisciplinary approach based on close collaboration between GPs and specialised memory clinics may be the ideal model for accurate early diagnosis and subsequently early pharmacological and psychosocial interventions. For all healthcare professionals, there should be specialised training in dementia and frequently updated practice guidelines to provide the framework for standards of care. Culture-sensitive strategies to promote public knowledge and destigmatise dementia are essential. Policy makers and authorities should be made aware of the benefits of early access to diagnosis and treatment. Green et al. [149] measured symptoms of anxiety, depression, and test-related distress 6 weeks, 6 months, and 1 year after disclosure or non-disclosure. The disclosure of APOE genotyping results to adult children of patients with Alzheimer's disease did not result in significant short-term psychological risks. Test-related distress was reduced among those who learned that they were APOE ε4-negative. Persons with high levels of emotional distress before undergoing genetic testing were more likely to have emotional difficulties after disclosure.

2.6. Quality of life in dementia

The WHO Quality of Life (QoL) working party defined the QoL as individuals' perception of their position in life in the context of the culture and value systems in which they live, in relations to their goals, expectations, standards and concerns. To define the QoL is a difficult task, especially in dementia care [150-154]. Research interest in the field of the QoL in dementia has been increasing over at least the past decade. A unifying theme is the influence that Lawton's model of the QoL in dementia had on conceptualization of the QoL [155]. Lawton identified four main dimensions that contribute to the QoL: (1) psychological well-being (e.g., positive and negative affect), (2) behavioural competence (e.g., cognitive and functional abilities), (3) the objective environment (e.g., carers and living situation), and (4) perceived QoL [156-159].

Whitehouse and Rabins [160] argued that the QoL of persons with dementia is not an isolated concept to be included as one of many measurements of the benefits of our care, but rather that it is the central goal of our professional activity.

Health-related quality of life (HR-QoL) *scales* are particularly important in older people as global outcome measures for interventions as shown in a systematic literature review and a meta-analysis of intervention effectiveness [161]. Improvement of the QoL in dementia should have a high priority in care, treatment and research, as has been stated in a position paper from the International Working Group on Harmonization of Dementia Drug Guidelines [162 163]. Addressing well-being has also been highlighted in a Norwegian study [164]. As in other diseases, so in dementia, QoL outcomes have not been prioritised in the past. In our OXC study, unfortunately, we did not use a scale measuring QoL outcomes either.

Needs that are not met lessen the QoL and may be associated with psychological problems, such as anxiety and depression. Worse orientation, greater physical dependency, pain, depression, and anxiolytic treatment are associated with a worse QoL [165]. Sensory or physical disability (including mobility problems and incontinence), mental health needs, and social needs, such as company and daytime activities, were often unmet [166]. A study[167] that assessed the QoL used as a proxy measure the Alzheimer's Disease Related Quality of Life (ADRQL) [168] and correlated it with the Neuropsychiatric Inventory (NPI) [169]. They found significant negative correlates with delusions, hallucinations, agitation or aggression, dysphoria or depression, anxiety, apathy, disinhibition, irritability, and aberrant motor behaviour. Agitation and aggression were the neuropsychiatric symptoms that best predicted a poor QoL, accounting for 19% of the variance.

People with dementia can experience a positive QoL throughout the disease, with about 50% experiencing no decrease in the QoL, although dementia's disabling course continues. The QoL can be improved in dementia. Interventions to treat neuropsychiatric symptoms, physical health problems and pain may serve to improve or slow the decline in the QoL for individuals with dementia. There is no evidence that psychopharmacotherapy improves the QoL, but some evidence that psychosocial interventions improve the QoL in AD. In a number of studies, the carer's QoL is improved by interventions like education *and* long-term emotional support.

3. Behavioural and psychological symptoms in dementia (BPSD)

3.1. Description

For some time, behavioural and psychological symptoms, including psychotic symptoms [170-173], have been known to be part of dementia. In Alois Alzheimer's classic case description of Auguste D, he noted that his patient believed "that people were out to murder her", "seems to have auditory hallucinations", "dragged objects here and there and hid them", and that "often she screams for many hours in a horrible voice." Therefore, Alzheimer identified delusions, hallucinations, activity disturbances, and aggression, as part of the clinical presentation. John Zeisel described it as the four 'A' of AD: agitation, aggression, anxiety and apathy.

The International Psychogeriatric Association (IPA) coined the non-cognitive symptoms in dementia as 'Behavioural and Psychological Symptoms in Dementia' (BPSD). BPSD constitute a major clinical component of AD and other dementia types [171]. They include delusions, hallucinations, activity disturbance (e.g., agitation and aggression), affective disturbances, anxieties, diurnal rhythm disturbances and apathy [169 174 175]. There is a growing interest in BPSD as they are responsible for a large share of the suffering of patients and carers, and they strongly determine the patients' and family carers' life situation, QoL and management [21 176 177]. Various studies have characterized these emotional changes in detail [25 178-191]. BPSD do not provide a diagnosis or a unitary concept, but a description of a multitude of symptoms that occur in persons with dementia, often clustered together in behavioural or/and psychological syndromes [192] (see Table 3.1.1). Some have presented these syndromes as three domains: psychosis/agitation, mood disorders and apathy. Specific behavioural disturbances in dementia may be associated with underlying disorders such as the presence of psychosis and depression [193]. In Kunik et al.'s study psychotic symptoms were associated with aggressive behavioural symptoms, and depressive symptoms were associated with constant requests for help, complaining, and negativism. Therefore, a search for underlying treatable psychiatric disorders should be considered when exploring the BPSD symptoms.

Lyketsos [194] summarised that BPSD are central features of dementia and an important treatment target. They should be assessed in future studies of emerging dementia therapies, using appropriate measures matched to the purpose of each study. Several significant issues remain regarding (1) the classification of these symptoms into syndromes,

Table 3.1.1. BPSD symptoms as listed by the International Psychogeriatric Association Task Force on BPSD, 1996 (adjusted).

Psychological or psychiatric symptoms assessed at patient/relative interview	**Behavioural symptoms assessed by behavioural observation or by patient/relative**
Anxiety	Aggression
Depressed mood	Screaming
Hallucinations	Restlessness
Delusions	Agitation
	Wandering
	Culturally inappropriate behaviour
	Sexual disinhibition
	Hoarding
	Cursing
	Shadowing

and (2) the development of better clinical measures for their quantification. Empirical characterization of clinically meaningful change in the BPSD by examining their relationship with the burden of dementia care, disability, the quality of life, carer distress, and resource utilization would be an important advance.

3.2. Scales measuring BPSD

3.2.1. Some methodological challenges related to scales

There are some methodological challenges common to all clinical scales: they are non-linear, have a floor and ceiling effect, they are biased by examiners' attitudes, perceptions and subject to unreliable recall. In addition, these clinical instruments have the disadvantage that they require quite a large number of participants when used as outcome measures in clinical trials to get enough power for the statistical analyses. Biomarkers, however, are not prone to so much subjective evaluation, and, used as endpoints in trials, do not require as many participants [195].

Appropriate and sensitive use of the instruments is critical for the delivery of improved quality of care. The use of tests in psychiatry has always been widespread in research, as they are the main method of measuring outcome in clinical trials. Tests are also increasingly common for screening and diagnostic purposes in clinical practice; for example, neuropsychological testing in the diagnosis of dementia [196]. Scales differ according to the source of information (e.g., carer versus patient), type of behaviour assessed (e.g., mood, agitation, or delusions), origin of the scale (i.e., imported from psychiatry, adapted from psychiatric scales, adapted from scales for neurologic conditions, or developed specifically

for dementia), and anticipated application of the tool (e.g., behavioural characterization, longitudinal follow-up, or differential diagnosis). Investigators have rarely articulated the theoretical framework on which their scales are based, and in most cases, theories were eschewed in favour of empirically based assessments of observed behaviour. Theoretical assumptions, however, can be inferred from the structure of the scales [197].

On principal, it is necessary to discuss the limitations of a tool. There is always a compromise between the bandwidth of a tool and its fidelity, a trade-off between depth vs breadth, between specificity and sensitivity. Important aspects are the informant interviewer interaction and the interpretation of the outcomes, the setting of the evaluation and the range and background of the health care professionals. Scores have to be seen in the context of the patients' education, social-cultural background, physical and mental health, sensory disabilities and last but not least the willingness to cooperate. No scale will be suitable for application with all individuals or in all contexts. Therefore, instruments have to be selected for specific purposes. There are so-called 'omnibus tools', global assessment scales, designed for example to screen many domains simultaneously. Another possible approach is to compile different scales into a comprehensive assessment battery.

The complexity and importance of behavioural and psychopathological phenomena in dementia require that they can be differentially assessed in the course of the disease and quantified for research purposes [198]. This holds particularly true for the measurement of therapeutic responses in drug efficacy studies. However, the lack of a clear definition and boundaries between entities automatically creates problems of measurement [199] (see also chapter 4.1).

Using rating scales in nursing-homes leads generally to special challenges: carers are not always present, the residents' behaviour challenges them in very different ways, an observation interval of two or more weeks may reduce the accuracy by more variance in individual recall. Assessment of the spectrum of different BPSD is necessary to improve the understanding of the individual patient's total picture. The assessment of BPSD is often complicated both by communication difficulties and by the complexity of the manifested behaviour.

In clinical settings and research, the following scales are those commonly used to assess the whole spectrum of the BPSD symptoms: The Neuropsychiatric Inventory (NPI) [169] or NPI-Nursing-home Version (NPI-NH) [200], the Behavioural Pathology in Alzheimer's Disease Scale (BEHAVE-AD) [25], along with the Behavioural Rating Scale for Dementia (BRSD) [201].

3.2.2. The Neuropsychiatric Inventory

The primary purpose of the measure is to provide a rapid assessment of a wide variety of behaviour encountered in dementia. The NPI is a fully structured interview in which all questions are provided and read verbatim. It is based on observations made by family or professional carers over the previous two weeks. A screening question is asked first, followed by sub-questions if the response to the screening questions suggests the presence of abnormalities involving that neuropsychiatric domain. Each of 12 items is rated by severity (1=mild, 2=moderate, 3=severe) and frequency (1=occasionally, 2=often, 3=frequently, 4=very frequently). The NPI also assesses the amount of carer distress engendered by each of the neuropsychiatric disorders. A total NPI score and a total carer distress score are calculated, in addition to the scores for the individual symptom domains. The frequency score and severity score get combined together by multiplication, consequently, the lowest score is 0 and the highest 12 for each item. The sum score for the whole scale ranges from 0 to 120 (NPI) and to 144 (NPI-NH) for the neuropsychiatric symptom items and from 0 to 50 (NPI) and to 60 (NPI-NH) for the carer burden. Three modified versions of the original 10-item NPI have been developed: the NPI-Nursing-Home version (NPI-NH) [200], the NPI-Questionnaire (NPI-Q) [202], a brief clinical questionnaire form of the NPI intended for use in routine clinical practice, and the Carer-Administered NPI (CGA-NPI) [203], in which carers complete the written form of the brief NPI-Q. The NPI-Q assesses the same 12 items as the NPI-NH, though only the severity and not the frequency of the symptoms, with scores ranging from 0 to 36. A carer distress score is also rated on a scale from 0-5 points ranging from 0 to 60. The CGA-NPI resembles the original NPI more closely than does the NPI-Q, with inclusion of both severity and frequency scales for each of the 12 items. Minor modifications were made to the NPI, such as excluding medical terms that may confuse carers. There is also good agreement between the CGA-NPI and the original NPI for prevalence (κ=.62), frequency (r=.69), severity (r=.64) and carer burden (r=.61) of anxiety.

The NPI is applied more and more frequently in clinical trial settings [204-213]. These quotations represent not a complete list, but an example of studies using the NPI. Having two different scores for severity and frequency for each domain potentially increases the utility of the NPI in drug efficacy studies.

After its introduction in 1994, the scale was translated into several languages and validated in various cultural settings [16 214-227]. The concurrent validity of the NPI was tested against relevant sub-scales of the BEHAVE-AD [25]. The correlations between the sub-scales of

the BEHAVE-AD and the sub-scales of the NPI were between 0.54 and 0.78 (frequency) and 0.47 and 0.80 (intensity). These studies suggest that the NPI is psychometrically sound, comprehensive and sensitive to change. We have evaluated the reliability and the validity of the Norwegian version of the NPI-NH in an unselected nursing-home sample.

There is an ongoing discussion that NPI-NH has shown a lower efficacy in intervention trials than other instruments. Also our study of oxcarbazepine's effect on agitation and aggression in severe dementia has shown a clear difference between the NPI-NH and the BARS results. Besides that which has already been mentioned, some argue that this discrepancy may be caused by registering a "lot of noise" (S.Gauthier, IPA 2009), because the NPI registers 12 variables with 6 to 8 items each. The difference between frequency and intensity of the sub-items is often not clearly understood and may be too complex.

3.2.3. Behavioural Pathology in Alzheimer's Disease Scale (BEHAVE-AD)

This scale was developed more than 20 years ago [25 228]. Its predecessor was the Symptoms of Psychosis in Alzheimer's Disease (SPAD) scale. The items were taken from a chart review which indicated that seven broad categories of BPSD are responsive to intervention with the antipsychotic medication thioridazine. Reisberg called these categories of BPSD the 'Psychosis of AD Syndrome' which contained the following domains: (1) Paranoid and delusional ideation; (2) Hallucinations; (3) Activity disturbances; (4) Aggressiveness; (5) Diurnal rhythm disturbances; (6) Affective disturbances, and (7) Anxieties and phobias. Reisberg et al. developed the BEHAVE-AD as a semi-structured interview to measure behaviour disturbances in patients with AD. An informant assesses these seven categories of symptoms on a 25-item scale, and rates each of these symptoms on a 4-point severity scale from 0 (not present) to 3 (most severe). The BEHAVE-AD rates the patient's behaviour occurring during the previous two weeks and a brief period of observing the patient. The second part of the BEHAVE-AD contains a global assessment of severity, the degree to which these symptoms are troubling to the carer and/or dangerous to the patient: from 0 (not at all) to 3 (severely troubling or intolerable to the carer or dangerous to the patient). The total possible score on the BEHAVE-AD ranges from 0 to 75. Adequate reliability and validity data have been reported [229]. BEHAVE-AD was moderately correlated to the BARS; Pearson's r was 0.44, 0.35 and 0.27 measured on day shift, evening and night shift, respectively [230]. Cummings et al. [169] tested the validity of the NPI by using the BEHAVE-AD sub-scales and compared them with the NPI sub-scales. They found correlation values (Spearman's rho) for

the frequency scores between 0.54 and 0.78, and for the severity between 0.47 and 0.80. A modified version of the BEHAVE-AD, the BEHAVE-AD-FW, includes a frequency component for each of the 25 symptoms assessed [231]. Subsequent studies supported Patterson's findings that the reliability of the BEHAVE-AD is excellent and similar to that of the most reliable cognitive dementia assessments [175 229 232]. A multicentre trial [233] has indicated that each of the BEHAVE-AD symptomatic categories responds statistically significantly to even minimal, non-specific psychological support; in response to the psychological effects associated with being in a trial and being on placebo treatment, total BEHAVE-AD decreased by 25% (the single categories decreased by 18% to 45%). The BEHAVE-AD has been found to be useful with outpatients and in NH settings, and appears particular useful for identifying behavioural disturbances in patients who are moderately to severely demented [234]. It appears to be appropriate for use in both outpatient and NH settings and has demonstrated sensitivity to change (i.e., significant improvement with active treatment in comparison to placebo) in both institutional and outpatient settings and in subjects with diverse dementia diagnoses [233 235]. Several studies have used the BEHAVE-AD as a kind of gold standard to validate other scales, as we did [227]. It may be a disadvantage that such important items as apathy and irritability are not included in the BEHAVE-AD. A reason may be that it was designed by empirical review of only 57 patients with AD with the main focus on psychosis.

3.2.4. Behavioural Rating Scale for Dementia (BRSD or CERAD-BRSD)

The BRSD was developed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). It was designed to assess behavioural symptoms in persons with dementia. The original version [201] has 48 items, and the revised version 46 items [236]. The CERAD-BRSD was developed based on existing instruments (BEHAVE-AD, the Columbia University Scale for Psychopathology in Alzheimer's Disease [237], the Cornell Scale for Depression in Dementia [238]) and clinical experience. The CERAD-BRSD is administered in an interview with the patient's primary carer, and rates the frequency of occurrence of items under code A on a scale of 0 (not occurred since illness began), 1 (1 to 2 days in past month), 2 (3 to 8 days in past month, up to twice a week), 3 (9 to 15 days in past month), and 4 (16 days or more in past month), 8 (occurred since illness began, but not in past month), 9 (unable to rate). Items with the code B are rated 0 (not occurred since illness began), 1 (Yes, has occurred in past month), 8 (Occurred since illness began, but not in past month), 9 (Unable to rate). If the frequency score is rated 1 to 4 then for 11 items severity is also rated. The CERAD-BRSD has

been demonstrated to have good inter-rater reliability. It consists of eight factors: depressive features, psychotic features, defective self-regulation, irritability/agitation, vegetative features, apathy, aggression, and affective instability [201]. The 46-item, revised version produced 6 factors/sub-scales [236] in mild to moderate dementia: depressive symptoms (7 items), psychotic symptoms (6 items), apathy (3 items), vegetative symptoms (4 items), irritability/aggression (5 items), and behavioural disturbances (5 items). The rating results in 6 sub-scores and two total scores for the psychopathological symptoms. One total score is weighted (0 to 4 for 26 items, 0 to 5 for 11 items, and 0 to 1 for 8 items) and is the sum of all individual item scores, except the one unspecific item (that comprises all other symptoms that are not part of the scale). This total score reflects the total psychopathological burden, based on the number of symptoms and the frequency of them. This total score may be 0 to 167. The other total score, "number of items rated 1 to 4" is the sum of items that have been registered as present during the past month, except the one unspecific item. The second total score ranges from 0 to 45.

Patterson et al. [239] examined, as part of the Alzheimer's Disease Cooperative Study (ADCS) Instrument Development Project, the CERAD-BRSD for its sensitivity to degree of cognitive impairment, its test-retest reliability, and its sensitivity to longitudinal change. The internal consistency, measured by Cronbach's alpha score, was 0.87. The Cronbach's alpha value for the sub-scales ranged from 0.48 (apathy) to 0.80 (psychotic symptoms). The inter-rater reliability (n=104) showed a kappa from 0.77 to 1.0, the vast majority being over 0.9. The test-retest reliability (one month) showed a Spearman's rho value ranging from 0.70 to 0.89. The convergent validity has been tested by Weiner et al. [240] by comparing the BRSD with the CMAI. Pearson's r was 0.76 when comparing the total scores of both scales.

Because the most frequent rating on the CERAD-BRSD is "16 or more times in the past month", it does not distinguish between behaviour that occurs very frequently (several times a day) and those that occur once every 1 to 2 days. This may limit its usefulness in detecting subtle changes of treatment effects. Weiner et al. [240] tested the sensitivity for change during a period of 12 months and could not show any significant change. These results have been confirmed by Patterson et al. [239].

3.2.5. Other scales

There are some other scales like the non-cognitive sub-scale of the Alzheimer's Disease Assessment Scale (ADAS-noncog) [241] and the Comprehensive Psychopathological Rating Scale (CPRS) [242] for patients with a dementia of the Alzheimer's type and multi-infarct dementia.

Supplementary to the scales which measure the whole spectrum of the BPSD, there are more specific scales that explore single symptoms or syndromes like the Cornell Scale for Depression in Dementia (CSDD), the Cohen-Mansfield Agitation Inventory (CMAI), the Brief Agitation Rating Scales (BARS), to mention only a few. This issue will be revisited more specifically in connection with the assessment of agitation.

3.3. Prevalence of BPSD

3.3.1. BPSD in MCI

Hwang et al. [243] compared the neuropsychiatric features of the *amnestic-type MCI* with those of mild AD patients and normal controls. The Neuropsychiatric Inventory (NPI) was used for this purpose. They found significant differences in apathy, dysphoria, irritability, anxiety, agitation, and aberrant motor behaviour between the MCI and control groups. Delusions were less common in MCI compared with mild AD.

3.3.2. BPSD in AD vs VaD

Fuh et al. [244] explored the neuropsychiatric manifestations in patients with AD, cortical and subcortical VaD, and mixed cortical and subcortical VaD. There were few differences between the patients with AD, subcortical VaD and cortical VaD. The most consistent difference was the high sleep disturbance scores in those with cortical VaD.

3.3.3. BPSD in FTD vs AD

Liu et al. [245] took volumetric measurements of the frontal, anterior temporal, ventromedial frontal cortical (VMFC), and amygdala regions of the brain in patients with FTD and normal control subjects, as well as patients with AD. Both the temporal and frontal variants of the FTD showed significant increases in rates of elation, disinhibition, and aberrant motor behaviour compared with AD. The frontal variant of FTD (fvFTD) group also showed more anxiety, apathy, and eating disorders, and the temporal variant of FTD (tvFTD) showed a higher prevalence of sleep disturbances than AD. The only behaviour that differed significantly between fvFTD and tvFTD were apathy, greater in fvFTD, and sleep disorders more frequent in tvFTD. Mendez et al. [246] found in analyses of SPECT results in FTD patients that early temporal involvement is associated with frivolous behaviour and right temporal involvement is associated with emotional disturbances. In contrast, those with right frontal disease may present with alterations in non-verbal behaviour.

3.3.4. BPSD in out-patients with dementia

Mega et al. [23] compared consecutive outpatients with AD with normal age-matched control subjects and reported the prevalence of all forms of BPSD together of 88% in AD patients. All 10 items of aberrant behaviour of the NPI-scale were significantly increased in the AD patients compared with normal subjects. The most common item was apathy, which was exhibited by 72% of patients, followed by agitation (60%), anxiety (48%), irritability (42%), dysphoria and aberrant motor behaviour (both 38%), disinhibition (36%), delusions (22%), and hallucinations (10%). Piccininni et al. [17], Ritchie [247] and Holtzer et al. [248] found similar prevalence data in ambulatory care settings.

3.3.5. BPSD in nursing homes

In NH BPSD are frequent [13 14 249-254]. Approximately 80% of the patients in Norwegian nursing homes have dementia and 84% of these exhibit at least one behavioural or psychological symptom. Table 3.3.1 lists all the BPSD with a prevalence of nearly 75% in the whole nursing-home population, included those who do not have dementia.

Table 3.3.1. Frequency of psychiatric and behavioural symptoms at different levels of severity among nursing-home patients (n=1,163), Selbæk 2007.

Psychiatric and behavioural symptoms	**N[a]**	**Any symptoms (%)[b]**	**Clinically significant Symptom (≥4) (%)[b]**	**Serious symptom (≥9) (%)[b]**
Delusions	1,112	31.1	20.7	8.8
Hallucinations	1,127	21.6	12.2	3.9
Depression	1,140	40.8	21.4	5.9
Anxiety	1,148	29.4	20.5	6.4
Euphoria	1,155	8.4	5.5	1.0
Aggression/agitation	**1,156**	**34.9**	**22.8**	**6.7**
Apathy	1,150	33.0	25.7	7.3
Disinhibition	1,146	30.1	19.5	6.1
Irritability	1,159	43.2	26.5	5.6
Aberrant motor behaviour	1,147	20.0	17.6	7.2
Any NPI-symptom	**1,162**	**73.8**	**65.2**	**29.2**

[a]Number of patients with complete data.
[b]Percentage of patients with complete data (prevalence of the various symptoms and clusters of symptoms).

Irrespective of the severity of the AD, many studies have shown that apathy is the most frequent symptom, followed by depression, anxiety and agitation. In the pre-dementia phase of the disease, apathy and depression are the earliest neuropsychiatric symptoms [255]. In the dementia stage, numerous symptoms are present in over 80% of patients, as emphasised by various European studies [192]. The co-occurrence of symptoms is frequent and can,

according to Savva et al. [256], be explained by clustering of symptoms. By the use of a factor analysis of the NPI a four-factor solution was found, corresponding to psychosis/apathy, depression/anxiety, irritability/persecution and wandering/sleep problems.

Psychosis occurred more frequently with declining cognition. Anxiety and depression were more common in younger individuals and in those with poor self-reported health. Aalten et al. [257] analysed NPI-factors from cross-sectional data of 2,354 patients with AD from 12 centres from the European Alzheimer's Disease Consortium. In Aalten et al.'s analyses the sub-syndrome apathy was the most common, occurring in almost 65% of the patients. The factors hyperactivity/agitation and affective symptoms were present in all sub-analyses, but the presence of the factors apathy and psychosis was dependent on use of cholinesterase inhibitors and the severity of dementia, respectively [258]. Data from the Cache County Study [259], a population-based phenomenological study, showed that the spectrum of neuropsychiatric symptoms in AD can be empirically classified into three groups: an affective syndrome, a psychotic syndrome and other neuropsychiatric disturbance. A syndromic grouping may be useful for understanding the aetiology and, consequently, to improve treatment and care.

3.3.6. The course of BPSD

Steinberg et al. [260] examined the longitudinal course of BPSD in the *community*. He estimated a point and 5-year period prevalence of neuropsychiatric symptoms in an incident sample of 408 dementia participants from the Cache County Study. The NPI was used to assess symptoms at baseline and at 1.5 years, 3.0 years, 4.1 years, and 5.3 years. Point prevalence, period prevalence and mean symptom severity at each time point were estimated. Point prevalence for delusions was 18% at baseline and 34 to 38% during the last three visits; hallucinations, 10% at baseline and 19 to 24% subsequently; agitation / aggression fluctuated between 13% and 24%; depression 29% at baseline and 41 to 47% subsequently; apathy increased from 20% at baseline to 51% at 5.3 years; elation never rose above 1%; anxiety 14% at baseline and 24 to 32% subsequently; disinhibition fluctuated between 2% and 15%; irritability between 17% and 27%; aberrant motor behaviour gradually increased from 7% at baseline to 29% at 5.3 years. Point prevalence for any symptom was 56% at baseline and 76 to 87% subsequently. Five-year period prevalence was greatest for depression (77%), apathy (71%), and anxiety (62%); lowest for elation (6%), and disinhibition (31%). 97% experienced at least one symptom. Symptom severity was consistently highest for apathy. Steinberg et

al.'s results gave converging evidence that syndromal definitions may more accurately capture neuropsychiatric co-morbidity in dementia.

Selbaek et al. [261] (see Table 3.3.1) found in their study of a large Norwegian *nursing home* sample similar results: clinically significant BPSDs (defined as NPI item scores ≥4) were exhibited by 84% of patients with dementia at the baseline or follow-up interviews. Overall persistence of symptoms was 79%. Individual symptoms, such as depression (58%), delusions (56%), and agitation/aggression (47%) had resolved at a high rate. Ryu et al. [262] investigated a smaller sample. In all 93.8% had BPSD at baseline; 75.0% had at least one clinically significant symptom, 80.4% of whom had persistent significant symptoms at 6-month follow-up. BPSD were highly persistent overall, there was no significant change in mean BPSD score for any symptom over 6 months, but many individuals became better or worse; 61.2% of those with at least one significant baseline symptom in any domain improved.

3.3.7. Predictors of BPSD

Zuidema et al. [253] examined predictors of neuropsychiatric symptoms in a large sample of nursing-home residents. For grading of the stage of dementia they used the Global Detoriation Scale for Assessment of Primary Degenerative Dementia (GDS): stage 1 to 4 cognitive decline without dementia, stage 5= mild stage of dementia, stage 6=moderate stage of dementia, stage 7=severe stage of dementia. While physically aggressive behaviour was more common in patients with very severe cognitive deterioration GDS stage 7, disinhibition, irritability, physically non-aggressive and verbally agitated behaviour were more common in patients in GDS stage 5 or 6. Physically aggressive behaviour was more common in men, whereas female patients demonstrated more verbally agitated behaviour. With respect to other neuropsychiatric symptoms, delusions and depression were also more common in patients in GDS stage 5 and 6, while the prevalence of anxiety and apathy further increased in severely demented patients, GDS stage 7. Apathy was more prevalent in male patients, while depression and anxiety were more common in females.

3.3.8. Recurrence rate of BPSD

Recurrence rates of neuropsychiatric symptoms during a 1-year period were 85% for depression, 93% for agitation, and 95% for psychosis [184].

3.4. Impact of dementia and BPSD

3.4.1. Patients

Neuropsychiatric symptoms have been found to be predictive for several outcomes like the course of the disease [248 263], institutionalisation [18 177 263-266], costs of dementia care [12], use of psychotropic drugs [261 267], increased risk of mortality, decreased QoL for patients and carers [6 176 268], and higher rates of carer and staff burnout. Hurt et al. [6] found that BPSD symptoms relating to a lower quality of life differed between patient and carer ratings: depression and irritability were found to predict lower carer ratings of quality of life, whilst delusions and apathy indicated lower patient ratings. Agitated behaviour such as wandering and physical aggression are a leading cause of transfer from assisted living to NHs [269 270].

3.4.2. Family and carers

Dementia and BPSD impose enormous burdens on the patients' families [10 271-273]. Carers are generally the spouses or the children of the patients. There is a transition from having a reciprocal relationship to one of being a carer. Family members and other carers experience psychological distress, physical ill health, social isolation and financial hardship [235 273-275]. The ability of carers to provide emotional support is reduced if they are distressed emotionally or overwhelmed by competing demands. BPSD complicate the course of the disease and increase the stress on the carers. A newly performed review [276] to identify the predictors of nursing-home admission (NHA) identified 782 relevant studies; 80 were selected for review based upon eligibility criteria. The most consistent predictors of NHA of persons with dementia included severity of cognitive impairment, Alzheimer disease diagnosis, dependencies in the activities of daily living, behavioural symptoms, and depression. Carers who indicated greater emotional stress, a desire to institutionalize the care recipient, and feelings of being "trapped" in care responsibilities were more likely to admit persons with dementia to nursing homes. Levels of depression and exhaustion are higher than in non-carers of similar age in the general population. Predictors of carer stress, related to the patient, are BPSD, lack of knowledge about dementia and its care on the part of the carer, immature coping mechanisms like avoidance and denial [275], previous poor psychological or physical health and a poor relationship between the patient and his relatives. Carers were found to be poor at identifying the antecedents and consequences of BPSD.

Support of carers should be adjusted to their needs. These may differ depending on the stage of dementia. The Relative Stress Scale (RSS) may be useful in identifying these needs and in facilitating individualised intervention. In multiple regression analysis, total NPI as a measure of BPSD, the carer being a wife and the hours spent caring per week, contributed to the explanation of total RSS with a quite high explanatory power of 48% [277]. Kaufer et al. [278] developed a scale corresponding to the NPI, the Neuropsychiatric Inventory Carer Distress Scale (NPI-D). They concluded that NPI-D ratings for 9 of 10 NPI symptom domains correlated most strongly with either NPI symptom severity or total (frequency x severity) scores. Agitation, dysphoria, irritability, delusions, and apathy were the symptoms most often reported to be severely distressing to carers. There is increasing evidence that the features of neuropsychiatric symptoms may be influenced by carers' characteristics. Sink et al. [279] found that, after adjusting for patient characteristics, carers who were younger, less educated, more depressed, more burdened, or spent more hours per week giving care, reported more BPSD in care recipients, independent of patient characteristics, including dementia severity.

Interventions on behalf of the carer showed diverging results. Studies including family carers of patients with dementia have shown that psycho-educative programmes and long-term emotional support reduce distress and postpone institutionalisation [280-282]. These studies underline the importance of long- term, individually tailored, interventions to help the carers cope with the many challenges they face.

3.4.3. Staff

The term 'staff' describes professional and paraprofessional health-care personnel in a variety of settings [e.g. day care, assisted living, nursing home (NH) with regular care units (RU) and special care units (SCU)]. Nursing homes have been described as a complex adaptive system [283]. This system theory may open up new insights, lead to new management approaches, and result in a more efficient and better quality of care. This again will have positive effects on the patients' QoL and the severity and frequency of their symptoms.

Distress caused by BPSD, experienced by staff carers, is similar to that faced by family carers [9], often arising from disrupted interaction with and responses to residents and their family members.

There is a growing movement toward less restrictive care settings, such as assisted living facilities [284], not least because care costs are 21 to 30% lower (in the USA) than in skilled nursing facilities [285].

An increasing number of profoundly cognitively impaired and more physically disabled patients are nowadays referred to NHs [13 286 287], which has potential cost and policy implications. In Norwegian NHs more than 80% of the patients have dementia. In Selbæk et al.'s [13] study in Norwegian NHs, only 3 per cent had no sign of cognitive decline. One out of three had a severe stage of dementia, 72% of the patients with dementia had clinically significant psychiatric and behavioural symptoms (NPI-NH item score ≥4), 40% had symptoms of psychosis, and from the total NH population 41% had symptoms of depression and 23% clinically significant aggression or agitation. An elderly person in a Norwegian NH has on average six diagnoses that need treatment. Consequently, NHs nowadays have acquired many new tasks like specialised medical treatment and individualised psychosocial interventions, and can no longer be seen as just a residence for the elderly. On one hand, these changes create a need for providing higher standards of qualified care services in NHs; on the other hand, the staff are not prepared to meet the increasing needs. Contrary to the big challenges caused by BPSD and physical co-morbidities in NHs, over 40% of the staff in Norwegian NHs have no formal health education. Not being educated well enough for the challenges arising in their daily work, staff in NHs experience higher stress, probably reflected in higher percentages of sick leave (11% in the years 2004 – 2008, Statistics Norway, 2009. http://www.ssb.no/pleie/tab-2009-07-02-09.html) as one easy-to-measure consequence. There are not enough physicians working in Norwegian NHs. Taking into consideration all these facts, the time spent for individual contact with the patients is limited by the daily routine in nursing-homes, which presents many competing demands. Cohen-Mansfield et al. [180] could show that time spent together with the patients contributed to reducing agitation in NHs.

The consequences of distress may also be experienced when aspects of the nursing-home environment, often caused by financial gaps and educational deficits, fail to meet the expectations of staff carers. Staff members report that they are frequently burdened by the repetitious, sometimes frightening and unpredictable behavioural problems, such as aggression and agitation displayed by the residents, without the ability to correct or change them. This kind of behaviour can lead to frustration, guilt, and emotional and physical exhaustion, and may result in feelings of failure and inadequacy or being overwhelmed by care and responsibilities on part of staff members. Antisocial behaviour of the residents may cause embarrassment and resentment for staff members as well as family carers.

In addition, attempts by family members to continue to participate in caring are often discouraged by staff members. This perspective can result in family-staff role conflicts [288 289].

However, systematic implementation of family involvement in institutional care settings can yield positive outcomes for the job satisfaction of the formal carers [290 291]. In Norway, a study [292] showed that most of the patients in NHs get good basic care and that acceptable quality of care (QoC) had a strongly negative association with such patient characteristics as low function in mental capacity, low function in activities of daily living and aggressive behaviour. In most of the measured areas of QoC, ward characteristics, such as type of ward, size of ward and staffing ratio, do have an influence on QoC.

There is little research documenting the work situation of the enrolled nurses and nursing assistants who make up the majority of carers for older people today. Edvardsson et al. [293] showed that in settings where staff reported high job strain, the prevalence of behavioural symptoms was significantly higher than in settings where staff reported low job strain. Furthermore, settings characterized by staff having a more positive caring climate had significantly less prevalence of escape, restless and wandering behaviour compared to settings having a less positive caring climate. The attitudes that staff members bring with them and the procedures that they use in interacting with the residents are crucial factors in achieving positive relationships with the residents and creating an environment that imparts trust and a feeling of safety on the residents' part. In another study, Edvardsson et al. [294] pointed out predictors of job strain perceived by staff members: perceived caring climate of the unit, staff education level, the chance to discuss difficulties and ethics at work and the age of the staff. These predictors had a statistically significant association with job strain. Focus on training and administrative interventions can produce desired staff outcomes [280 295-299].

There has been a trend in long-term care in the last decades to move from a traditional medical model towards a holistic approach. New models of care address more and more individual needs of the aging population [300 301].

3.4.4. Finances

Hemels et al. [302] reported the clinical and economic factors in the treatment of BPSD and could show that BPSD was remarkably costly, because it involves more health-care professionals and early institutionalisation. As the costs for institutional long-term care rise, the public and private health service providers are more and more determined to find solutions for the increasing challenges. Therefore, they promote research into the QoC [303], also into NHs. One example of that is an international collaboration to create standards of care and the measurement of outcomes. It started with creating the Residents Assessing Instrument (RAI). Today it is a collaborative network of researchers (www.InterRAI.org) in over 30 countries

committed to improving health care for persons who are elderly, frail, or disabled. Their goal is to promote evidence-based clinical practice and policy decisions through the collection and interpretation of high quality data about the characteristics and outcomes of people served across a variety of health and social service settings. As Harriet Finne-Soveri (personal communication) has stated, there are five nuts to crack: (1) Who is the client in a NH? (2) Who has the right to define "expensive"? (3) What is 'quality' when the patient has dementia, several incurable diseases, multiple medication, persistent symptoms, unknown distance to death? (4) How do we measure quality? (5) What is the influence of structure and process on outcomes? The term 'structure' includes architecture, furniture, aids, instruments, staffing, not only the number of staff but also their qualifications. The 'process' of care means data gathering, examinations, diagnostics, care procedures, and service procedures, such as leadership and management.

Briefly, the challenges of financing the costs of dementia care, with focus on the situation in Norway, will be described here. Since 1994, the Husbanken and other governmental incentives [Handlingsplan for eldreomsorgen (St.meld. nr.50 (1996-1997)] have supported the counties in building assisted-living homes for the elderly, so as to get a more differentiated and at the same time cheaper care system. These apartments are rented by the residents; care services are provided as individually needed by the counties' mobile home-care teams. Between 1996 and 2003, the number of this type of care facilities has increased four times to 23,000. At the same time, the places in NHs were reduced, as has already been mentioned. In 2003, about 40,800 persons over 49 years were long-term residents in care facilities.

The future population structure may contribute to an explosive need for care services. In 2060, the number of persons over 65 years old in Norway will be more than double those of today – from 617,000 in 2009 to 1.5 millions in 2060. The percentage of those aged 80 years or more will increase from 4.6 to 9.1 per cent – from 219,000 to 635,000 (Statistics Norway, 2009, http://www.ssb.no/emner/02/03/folkfram/). This implies that the number of persons with physical illnesses and dementia who will need a place in NHs will increase and, consequently, the health-care expenses will rise. Consumers prefer assisted living to NHs, and state agencies interested in controlling the escalating costs of long-term care also favour assisted living. Table 3.5.1 gives an overview of what kind of care services the counties in Norway provided in 2008 (provisional numbers):

Table 3.5.1. Care service recipients and type of services provided in Norway in 2008 (not final numbers).

		Percentage					
Age	**No. of recipients**	**Only practical assistance**	**Only home services**	**Practical assistance & Home services**	**Other services**	**Short term care in NH**	**Long term care in NH**
Total	260.604	18	24	23	20	3	13
0-17	14.990	3	7	0	83	7	1
18-49	44.285	20	41	16	21	1	1
50-66	31.660	20	34	25	16	1	4
67-79	45.355	20	25	23	16	3	12
80-89	91.163	19	19	26	15	3	18
≥90	33.149	12	12	30	10	4	32

Use of formal services and the associated costs of caring for people with dementia will not only be driven by increasing numbers of people 85 years of age and older, but also by general economic inflation and the annual increases in health costs exceeding the inflation rate in industrialised countries. We also may face a decrease of informal (unpaid) carers who provide the vast majority of long-term care to disabled people today [304-309], because the number of adults in single-person housholds is rising steadily and more couples have no children. The most rapid growth in persons living alone for all age groups occurs in the oldest-old age group, creating an increased need for long-term assistance [310 311]. Formal service use and costs also may increase because of changes in the employment structure of the economy, such as the increasing number of women in paid employment [312]. In a study of the future need for long-term care (LTC) in the UK the calculation [313] was as follows: Expenditure on LTC services for older people with cognitive impairment is projected to rise from 0.60% of Gross Domestic Product (GDP) (£5.4 billion) in 2002 to 0.96% of GDP (£16.7 billion) in 2031, assuming no other changes. Varying the assumptions, the projection for 2031 ranges from 0.83% to 1.11% of GDP. These figures do not include the opportunity costs of informal care.

Estimates of both the direct and indirect costs of care for individuals with AD in the United States vary from a high of US$67.3 billion (1991 dollars) to a low of US$52 billion (1990 dollars) [314]. Wimo et al. [315] calculated the costs for dementia care for Sweden and estimated the increase in the number of patients from 1991 to 2025 and the respective costs from Swedish Crowns (SEK) 74 billion to SEK 110 billion. The costs for dementia care in Norway today are calculated to be over 18 billion Norwegian crowns and will increase in the future as in Sweden, if essential progress in the prevention of dementia does not occur [316].

Jonsson et al. [317] found that costs of care in patients with AD are high and related to the severity of the dementia as well as the presence of behavioural disturbances.

4. Agitation in dementia

4.1. Description

Agitation is a common neuropsychiatric phenomenon of dementia. The term 'agitation' encompasses a wide variety of behaviour: restlessness, wandering, cursing, screaming, repetitive motor activities, irritability, hostility, resistance and aggression…

Historically, prior to the research of Jiska Cohen-Mansfield, the literature did not specify a definition for agitation in dementia. Cohen-Mansfield and Billig [176] searched all the literature available at that time and as a result of that defined agitation as "inappropriate verbal, vocal or motor activity that is not explained by needs or confusion per se." Jiska Cohen-Mansfield has spearheaded this field and found in an observational study that agitated behaviour (in particular 'strange noises', 'requests for attention', 'repetitious mannerisms', 'picking at things', 'strange movements', and 'pacing') were manifested at very high frequencies [318]. They created the Cohen-Mansfield Agitation Inventory (CMAI) on a NH patient sample [21 24 176 319]. The original factor analyses by Cohen-Mansfield et al. [24] and Finkel et al. [320] yielded three syndromes of agitation labelled as aggressive behaviour (items: hitting, kicking, pushing, tearing things, cursing/verbal aggression, grabbing, biting and spitting), physically non-aggressive behaviour (pacing, disrobing, wandering and repetitious mannerisms), and verbally agitated behaviour (complaining, negativism, repetitious sentences and screaming). Later on, Cohen-Mansfield described the factor structure of agitation as measured by the CMAI in outpatients as comprising four sub-types and conceptualised agitation along two axes: aggressive-nonaggressive and physical-verbal [321 322]. In 1989, Taft [323] described two components of agitation: 1) excessive motor or vocal activity and 2) the inappropriateness of the behaviour.

Agitation can also be grouped into disruptive but non-aggressive physical and verbal behaviour (e.g., pacing, handling things repeatedly, restlessness, or repeated requests for attention), socially inappropriate behaviour (such as undressing or urinating in public), or verbal or physical aggression. Some authors have operationalised all behavioural symptoms in dementia as agitation [324]. The conceptual difficulty arises because the term 'agitation' can include many different kinds of behaviour, but according to Cohen-Mansfield's definition, the

behaviour must be inappropriate and not clearly the sole outcome of cognitive impairment or better explained by some other condition, such as delirium. For example, repetitive screaming due to obvious pain would not be considered a manifestation of agitated behaviour but would be seen as an appropriate means of communicating the need for pain relief [325]. Because agitated behaviour is context-dependent and a given behaviour may be classified as agitated for one individual and not another, the objective measurement of such behaviour is difficult [20]. There is still considerable confusion in the psychiatric community as to how aggression and agitation are to be specifically defined and best distinguished [326].

The four-fold typology of Jiska Cohen-Mansfield is, however, not universally accepted, and other typologies have been suggested. One such typology is based on a factor analysis performed by Devanand et al. [327], who found factors such as disinhibition, apathy or indifference, catastrophic reactions, sundowning, and denial. One reason for these disparate findings is the use of different assessment instruments that encompass different domains.

There are also classification systems for subtypes of agitation, such as aggressive behaviour focusing on the following dimensions: 1) the nature of the behaviour, such as physical aggression, verbal aggression, or sexual aggression [328]; 2) the target of the behaviour (i.e., disturbing or endangering the self or others) [329]; 3) the degree of disruption (i.e., disturbing versus endangering) [330]; or 4) the environmental conditions under which the behaviour occurs (e.g., night time or during intimate care) [331].

Factor analytic studies of aggressive behaviour revealed three factors that are thought to describe aggression among the demented elderly; these are: verbal aggression, physical aggression and antisocial behaviour [332]. For a pragmatic therapeutic approach, Lesser et al. [333] suggested dividing agitation into three subtypes: spontaneous (episodic, no obvious precipitant, frequently accompanied by disorientation and sometimes hallucinations), reactive (preceded by an identifiable precipitant), and disinhibited (chronic and unrelenting, with no clear periodicity or trigger).

Nonetheless, there is still a debate going on as to whether agitation and aggression in dementia are unitary concepts or not, and which aspects of agitation we should focus on when designing intervention trials so as to maximise outcome effects. In two out of eight factor analyses of the CMAI, Zuidema et al. [19] and Rabinowitz et al. [334], found the 3-factor solution of physical aggression, physically non-aggressive behaviour and verbally agitated behaviour. Zuidema's conclusion was that "the robustness of these findings across different care settings suggests that agitated behaviour have a common basis." Also our factor analysis of the BARS, a short version of the CMAI, confirms the existence of these three factors; we labelled them

physically aggressive, physically non-aggressive and verbally agitated behaviour. However, this may only reflect the basic assumptions of agitation incorporated into the CMAI and the BARS, by that looking through the same spectacles, while blinded to other aspects of the agitation spectrum.

Lastly, Poole et al. [335] reviewed 80 articles and found 47 types of behaviour classified as agitation. This shows that problem behaviour is a complex phenomenon affected by an interaction of the type of degenerative brain diseases, the grade of cognitive impairment, physical health, mental health, past habits and personality, unmet needs and environmental factors [336]. Caused by the many-faceted aetiology, agitation is individually shaped and difficult to define. The lack of a precise definition and the complexity of the problem may lead to research difficulties in terms of defining research questions and relevant outcome measures.

4.2. Scales measuring agitation

The core of all assessment in dementia care is careful enquiry and attentive listening, and there is no substitute for a clinical interview by a trained doctor, nurse, psychologist, occupational therapist or social worker. However, having acknowledged this, there is a special and important role for the use of formal scales in dementia assessment. Although this has to be balanced by a clinical and 'holistic' approach, the provision of a number allows measurement of change and ready comparison of the patient to others and to a population norm. Furthermore, measurements can encourage full and more objective assessment of, for example, behaviour problems in dementia rather than relying on the carers' complaints.

Assessment and management of agitation is challenging and confronts carers and doctors with tasks that are sometimes frustrating and overwhelming [337 338].

Many instruments have been devised to measure aggressive and agitated behaviour in different patient populations and in a variety of settings, but up to now no single scale has emerged as the 'gold standard'. Some are global scales, such as the NPI and the BEHAVE-AD, measuring the whole spectrum of psychological and behavioural problems in dementia as described in chapter 3.2, others measure single domains like agitation and aggression, e.g., the CMAI and the BARS.

4.2.1. The Cohen-Mansfield Agitation Inventory (CMAI)

The CMAI provides extensive coverage of an undifferentiated agitation domain in dementia. It was developed using the following definition of agitation: "agitation is defined as

inappropriate verbal, vocal or motor activity that is not explained by apparent needs or confusion *per se*" [176]. The CMAI is a 29 to 36 item observational instrument, completed by nursing staff, measures agitation in nursing-home residents on a 7-point Lickert-type scale per item according to frequency of occurrence during the preceding 2 weeks (1=never; 7=several times an hour). This scale yields three factors physically aggressive behaviour, physically non-aggressive behaviour and verbally agitated behaviour. The CMAI has good internal consistency, inter-rater reliability and concurrent validity [19 319 320 334 339-346]. There is also a CMAI Short Form (CMAI-SF) [20 322] that has been used in some trials [347-349]. It reflects the three factors of the original CMAI and includes 14 types of aggressive behaviour that carers may rate on a 5-point frequency scale. The items are based on the factor structure of the original inventory.

The factor structure of the CMAI enables clinicians and researchers to avoid global scores and obtain sub-scale scores. It is thereby possible to relate different behavioural symptoms to medical, cognitive, and demographic variables in order to understand and manage them better.

Weiner et al. [240] made a longitudinal comparison of two carer-administered assessment tools, the CMAI and the CERAD-BRSD, among community-dwelling patients with AD with baseline and 12-month follow-up data. Among the AD subjects, the correlation between total CMAI at baseline and 1 month re-administration was 0.83. In the same subjects, stratified into 5 groups by MMSE scores, the correlations between BRSD baseline and 1-month scores ranged from 0.70 to 0.89. There was high correlation between total scores of both instruments at baseline and 12 months. In addition, all CMAI sub-scales, except 'verbally aggressive', correlated significantly with total BRSD score at both time points. At baseline BRSD sub-scales for irritability/aggression, behavioural dysregulation and psychotic symptoms and at 12 months, irritability/aggression and behavioural dysregulation correlated with total CMAI scores. Neither scale changed significantly over 1 year, but there was wide individual variation. CMAI and BRSD scores correlated with 1-year change in the FAST, but not with MMSE or CDR (which weight cognition heavily), suggesting that behavioural disturbance may be more strongly related to ability to manage the activities of daily living (executive function) than to other aspects of cognition. The CMAI and the CERAD-BRSD appear to be interchangeable as measures of agitation, with the CMAI possibly more useful for patients who lack language and the CERAD-BRSD more sensitive to apathy and depression.

4.2.2. Scale for Aggressive Behaviour in the Elderly (RAGE)

The Scale for Aggressive Behaviour in the Elderly (RAGE) [332] measures the quantity and severity of aggressive behaviour, and gives a score on a four-point scale (0 to 3) for each of the 21 items and a total score. The RAGE scale was derived using the following definition of aggressive behaviour: "Aggressive behaviour is an overt act, involving the delivery of noxious stimuli to (but not necessarily aimed at) another organism, object or self, which is clearly not accidental". This scale was developed for use by nursing staff on psychogeriatric inpatients with dementia, but it has since then also been used in nursing homes for all patients. It has excellent reliability and validity [331 350-352]. The scale has three components: verbal aggression, physical aggression and antisocial behaviour.

4.2.3. Pittsburgh Agitation Scale (PAS)

The Pittsburgh Agitation Scale (PAS) [353] is a brief screening instrument for agitation in dementia; however, unlike the CMAI and the BARS, it measures the severity but not the frequency of agitation. The PAS is based on the following definition of agitation: "Agitation is vocal or motor behaviour that is either disruptive, unsafe, or interferes with the delivery of care in a particular environment." The PAS is designed as an observational instrument for use in NH or in psychogeriatric wards. The scale takes only one minute to administer and is rated by direct observation by clinical staff over a period of 1 to 8 hours (one shift) or also one week. It is very flexible because the observer himself or herself may choose the period that should be rated. The quantification of the severity of the disruptive behaviour is provided within four general behaviour groups (items): aberrant vocalization, motor agitation, aggression and resisting care, on a scale ranging from 0 to 4. The score reflects the most severe behaviour within each behaviour group. The maximum total score is 16, which indicates very severe agitation problems. Therefore, an improvement in PAS score, as in other scales, may represent an improvement in particularly severe behaviour, but other symptom domains of agitation may still exist. Inter-rater reliability exceeded 0.80. Validity was assessed by comparing the PAS score with the number of clinical interventions required. The PAS has been used in clinical trials [354].

4.2.4. Staff Observation Aggression Scale (SOAS) and revised version (SOAS-R)

This scale is designed as an observational instrument [355] for monitoring the nature and severity of aggressive incidents in a psychiatric ward. By filling in a form of this scale at

every incident of aggression, it may also be used to monitor the frequency of aggression. The SOAS severity scoring system was refined on the basis of the staff severity estimates. The revised scoring method and other refinements in the contents of the instrument led to the construction of the SOAS-R. The validity of the SOAS-R was tested by comparing a visual analogue scale (VAS), on which the staff member marked the severity of the aggression on a continuous 100-mm scale ranging from "not severe at all" (at the 0-end of the VAS) to "extremely severe" (at the 100-end of the VAS). The SOAS-R seems to be a promising tool for monitoring a wide range of (self-) destructive acts in psychiatric wards [356]. The SOAS-R scale is built up of five columns: (1) Provocation (0 to 2 points), (2) Means used by the patient (0 to 3 points), (3) Target of aggression (0 to 4 points), (4) Consequence(s) for the victim(s) (0 to 3 points), (5) Measure(s) to stop aggression (0 to 2 points). The total severity score of the SOAS-R can vary from 0 (least severe form of aggression, mostly verbal aggression) to 22 (most severe form of aggression). Nijman et al. [357] reviewed the correlations between the SOAS and SOAS-R and found that the SOAS-R severity scores were more closely related to clinical judgements of aggression severity than the original ones (SOAS). The correlation of the original SOAS total scores between observers was 0.87 and the kappa was 0.61, indicating fair to good agreement [358]. Furthermore, the scale is quick to complete and there is no need for staff to be trained to use it. In their review of papers on violence among psychiatric patients, Shah et al. [359] described the SOAS as an instrument "of particular interest . . . with evidence of good reliability and validity" (p.307). As a result of another study investigating the RAGE and the SOAS, Shah et al. [360] recommended a "run in" period of at least 4 weeks in intervention studies using the SOAS to reduce contamination by spontaneous decline. The RAGE and all its sub-items did not spontaneously decline, but the total number of aggressive incidents on the SOAS, the SOAS total score, and the sub-item scores, spontaneously declined after week 4 and became stable by week five. The SOAS focuses exclusively on aggression and is not constructed especially to validate patients with dementia.

4.2.5. Ryden Aggression Scale (RAS)

This scale was designed to assess agitation in patients with dementia who live in the community with family carers [328]. It is based on the modified Lanza's aggression model [361] where aggressive behaviour is defined as: "hostile action directed towards other persons or objects or towards the self." The RAS was created by reviewing the literature and taking the consensus of five registered nurses on the different items. It is a 25-item scale that rates the

frequency of occurrence of aggressive behaviour from 0 (less than once a year) to 5 (one or more times daily) and is composed of three sub-scales: 'physically aggressive behaviour' (PAB, 16 items), 'verbal aggressive behaviour' (VAB, 4 items), and 'sexually aggressive behaviour' (SAB, 5 items). It is designed as a questionnaire to be completed by carers about their dementia patient. The RAS was used in a pilot study by Ryden [328] where he investigated a sample of 183 patients with dementia living at home. It showed good internal consistency (Cronbach's alpha: RAS=0.88; PAB=0.84; VAB=0.90; SAB=0.74) and test-retest reliability (Pearson's r=0.86). The validity data are not as good.

4.3. Brief Agitation Rating Scale (BARS)

Finkel et al. [230] developed the BARS to allow nurses and other carers in a nursing-home to assess the level of agitation in a patient rapidly. It was developed as a subset of the Cohen-Mansfield Agitation Inventory (CMAI) after the CMAI was administered to 232 NH residents by interviewers who had been trained by a psychiatrist. The BARS was developed in a three-stage process. First, correlations of individual items against the total score were rated, with those having a high correlation selected for possible inclusion. Secondly, inter-rater reliability was assessed. Thirdly, items were selected to be representative of the original CMAI factor structure. The BARS captures the following ten agitation items on a 7-point scale from 1 (=never) to 7 (=several times an hour) looking back over the last two weeks.

Items included in the BARS:

(1) hitting	(2) grabbing	(3) pushing
(4) pacing or aimless wandering	(5) repetitious mannerisms	(6) restlessness
(7) screaming	(8) repetitive sentences or questions	
(9) making strange noises	(10) complaining	

In the light of the desire to keep the rating scale even simpler and easy to do by busy clinicians, some have streamlined the scoring system and reduced the point range from 0 (=never) to 3 (=often or continuous), reporting agitation during only one week.

This scale's performance data, as reported by Finkel et al. [230], are listed in the following: the Cronbach alpha for the 3 daily shifts ranged from 0.74 to 0.82. The intra-class correlation between rater pairs was 0.73. The scores correlated well with a CMAI done on the same patient group. Shah et al. [362] compared three scales that measure agitation in dementia: the CMAI, the RAGE and the BARS. They found that the internal consistency, measured by

Cronbach's alpha, was greater than 0.8 on all three scales. The test-retest and inter-rater reliability correlations were 0.75 or greater for all three scales, but the BARS showed some weaker results.

4.3.1. Studies using BARS as outcome measure

Although the BARS has been used in studies in Norway [27 210 363 364] and other countries [40 276 365-369], no study, besides that on the developing sample, has been carried out to explore the factor structure. The aim of our study was to examine the extent to which the BARS is a homogeneous scale, measuring shared underlying constructs, and whether the dimensions Finkel et al. [230] found, would be revealed in an exploratory factor analysis on a large Norwegian sample. The BARS has been recommended for use in the "Agitation Decision-Making Framework" for nurses and care staff, developed by Dr.John Bidewell at the University of Western Sydney, Australia.

4.4. Prevalence and correlates of agitation

Already in the early 1980s, Rabins et al. [7] described the prevalence of catastrophic reactions and physical violence as very high, 87% and 47% respectively, and 75% of the carers reported this as the most serious problem they face in patients with dementia. Burns et al. [179] found that out of a sample of 178 patients with AD, aggression was observed in 20%, wandering in 19%, binge-eating in 10%, hyperorality in 6%, urinary incontinence in 48%, and sexual disinhibition in 7%. Behavioural abnormalities were greater in those with more severe dementia. Temporal lobe atrophy correlated with aggression. Later research confirmed that behavioural symptoms, such as aggression, agitation and psychosis, are common in moderate to severe stages of dementia [16 23 339 370 371].

McShane et al. [372] investigated over a four-year follow-up, whether individuals who experience psychiatric symptoms early in dementia are more prone to develop behavioural problems later in the illness. They found that physical aggression was predicted by a sad appearance. Motor hyperactivity was predicted by ideas of persecution. These associations were robust, remaining significant over 2, 3 and 4 years of follow-up time and were independent of cognitive function, age, sex and duration of the illness. They concluded that there may be two distinct longitudinal syndromes of non-cognitive symptoms in dementia and that important aberrant behaviour in late dementia may share pathophysiological mechanisms with psychiatric symptoms in early dementia. A study examining the longitudinal course of

Table 4.3.1 Comparison of BARS with other scales measuring agitation in dementia.

Scale	Setting	Observat. period (days)	Informant	No of items	Factors*	Agitation types assessed									Other domains assessed				Staff burden	Freq. Sev.	
						A	V	G	D	R	I	C	U	M	PS	AN	DE	O		F	S
CMAI	NH CI	14	Nurs. staff Carer	29	A,M,V	Y	Y	Y	Y	Y	N	Y	N	Y	N	N	N	Y	N	Y	N
NPI-NH	NH	14	Nurs. staff Carer	12		Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
BEHAVE-AD	Out NH AD	14	Carer	25+1	PSx2, DE, AN,A,VE,M	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	Y
CERAD - BRSD	Out NH CI	30 modifiable	Nurs. staff Carer	48, 46	A,DE, PS,U, I,VE, AP, EL	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
RAGE	In NH CI	3	Nurs. Staff	21	V,A,AB	Y	Y	Y	Y	N	Y	Y	Y	N	N	N	N	Y	N	Y	Y
PAS	In CI	1-8 hrs unto 7 days	Nurs. Staff	4		Y	Y	N	Y	Y	N	Y	Y	Y	N	N	N	N	N	N	Y
RYDEN	Out CI	365	Family carers	25	A,V,SB	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N
OAS	In	One incident	Nurs. Staff	4	V, A (3 forms)	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	Y
SOAS	In	One incident	Nurs. Staff	5 Columns		Y	Y	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y
BARS	NH CI	14	Nurs. Staff	10	A,M,V	Y	Y	Y	N	Y	N	Y	N	Y	N	N	N	Y	N	Y	N

*Factors are listed in order of their explanatory contribution

A=Aggression (physical)
AB=Antisocial behaviour
AD=Alzheimer's disease
AN= Anxiety
AP=Apathy
C=Complaining (critical)
CI=Cognitively impaired patients
D=Demanding
DE= Depression
EL= Emotional instability
F=Frequency
G= General restlessness
I=Irritability
In=Inpatient (hospital ward)
M=Motor agitation
NH=Nursing home
N=No
O=Other domains assessed
Out= Outpatient
PS= Psychosis
R=Repetitive (motor and verbal)
S=Severity
SB=Sexually aggressive behaviour
U=Uncooperative (resisting care)
V=Verbal agitation (aggression)
VE=Vegetative functions (sleep…)
Y=Yes

agitation in NHs was performed by Burgio et al. [286]. This study used information from both staff ratings and direct observation of agitation. The design they used was longitudinal hierarchical linear modelling (with assessments every six months) to capture the dynamic nature of behaviour change as a function of the individual resident's characteristics and the progress of time. The severely cognitively impaired residents displayed more agitation than the moderately impaired group at baseline. Longitudinal analysis found a significant linear and quadratic trend only with the profoundly impaired residents. These residents showed slightly less agitation up to 12 months, with agitation increasing significantly from 12 to 18 months.

Aarsland et al. could show that about a quarter of the variance in aggression could be attributed to psychosis [373]. Gilley et al. [374] examined the relationship between psychotic symptoms and subsequent physically aggressive behaviour in outpatients with AD. The presence of delusions significantly predicted the presence and frequency of physical aggression. Of participants with high rates of physical aggression (> 1 episode/month), 80% had delusions. This effect was robust, even after controlling for the effects of other clinical variables. By contrast, hallucinations did not reliably predict episodes of physical aggression.

Almost 50% of dementia patients in NHs exhibit some form of agitation at any point in time. Agitation, particularly wandering and physical aggression, appears to be more common in NH populations, but agitation often poses a much more serious management problem for carers who live with a demented person at home. Agitation is perceived by the carers as more distressing than cognitive decline. After incontinence, agitation is the second most cited reason for NH placement. If carers could be provided with better ways of dealing with agitation, the benefits for them and for the health care system could be substantial.

The objective of Jiska Cohen-Mansfield's study in 2008 [375] was to *examine the relationship between type, frequency, and level of disruptiveness* of physically aggressive agitated behaviour, physically non-aggressive agitated behaviour, verbally aggressive agitated behaviour, and verbally non-aggressive agitated behaviour in persons with dementia. The highest overall frequencies were reported for verbal non-aggressive behaviour and the highest average disruptiveness was correlated to verbal aggression. Frequency and disruptiveness of behaviour were highly correlated. When controlling for frequency of a certain type of behaviour, physically aggressive behaviour was the most disruptive across two nursing staff shifts. In understanding the impact of agitated behaviour, it is important to take into account both the type of behaviour and its frequency.

Engelborghs et al. [376] studied the *profiles of neuropsychiatric symptoms in several degenerative dementias*. In AD and mixed AD and VaD, activity disturbances and aggressiveness occurred in more than 80% of the patients. In FTD patients, with a prevalence of 70%, apathy was very common whereas delusions and hallucinations were rare. Frequently used behavioural assessment scales like the BEHAVE-AD systematically underestimated BPSD in FTD, whereas Rosen et al. [377] proposed a short version of the Neary criteria [378], a neuropathological validated set of five clinical features, which displayed high sensitivity for frontal lobe symptoms. Hallucinations discriminated DLB patients from other dementias. A high prevalence of disinhibition (65%) in DLB pointed to frontal lobe involvement. They concluded that behavioural assessment may help in differentiation between different forms of dementia and stressed the need for the development of new and more sensitive behavioural assessment scales. By means of the Middelheim Frontality Score (MFS), frontal lobe involvement was frequently observed in DLB. As 70% of FTD patients displayed apathy, prevalence was higher compared to the other disease groups, meanwhile indicating that apathy is frequently observed in dementia, irrespective of its aetiology.

4.5. Prevention of agitation and aggression

There are some general principles that should be mentioned as means to prevent agitation and aggression in dementia: Analyse situations triggering agitation or aggression; try to find the patient's unmet needs and what he/she wants to communicate; relieve discomfort and pain; adjust care to the patient and not the patient to care; individualise the therapeutic approach to the single patient and to the stage of the dementia disease; make indoor architecture and outdoor spaces safe and easy to understand; contribute to helping the patient to understand the situation. Know the patient's life history and his/her likes and dislikes; think proactively – registering the moments the patient enjoys and introducing more of them, like relaxation with aroma-therapy, footbath, music therapy, massage, touch, walking, dancing, and good meals. Facilitate a good day-night rhythm by day light or light therapy and exercise, and a calm and warm place to sleep.

4.6. Aetiology of aggression and agitation in dementia

Agitation is related to severity of dementia [379] and to specific types of associated psychopathology implicating frontal lobe dysfunction [371]. With respect to the aetiology of aggression in demented patients, different approaches have been suggested. Raskind [326] described the interaction of three factors, which lead to aggression in this population:

(1) From a neurobiological perspective, greater neuronal loss [380] leads presumably to neurobiological dysregulation, e.g., cholinergic deficits [381], altered adrenergic function [382 383], and γ-aminobutyric acid disturbances in the substantia nigra, that may lower the threshold for the expression of aggression. (2) Cognitive impairment in patients with dementia increases the aggressive potential due to misperceptions, poor insight or disinhibition. 3) Factors like an unfamiliar environment might lead to an exacerbation of aggressive symptoms. In this respect, climate, noise level and general level of stimulation have to be balanced. Lehninger et al. [384] described the aetiology of agitation in dementia with the 'Seven I's', illustrating what diagnosis and therapy should focus on: **I**atrogenic (anticholinergics, sedatives, etc.), **I**nfection (urinary tract infection, pneumonia…), **I**llness (acute and chronic with exacerbation), **I**njury (hip fracture, subdural hematoma, pain…), **I**mpaction (fecal), **I**nconsistency in the environment (changes, different approaches…), **I**s the patient depressed?

Depending on which approach is chosen, many different models have been developed which try to explain agitation and aggression in dementia.

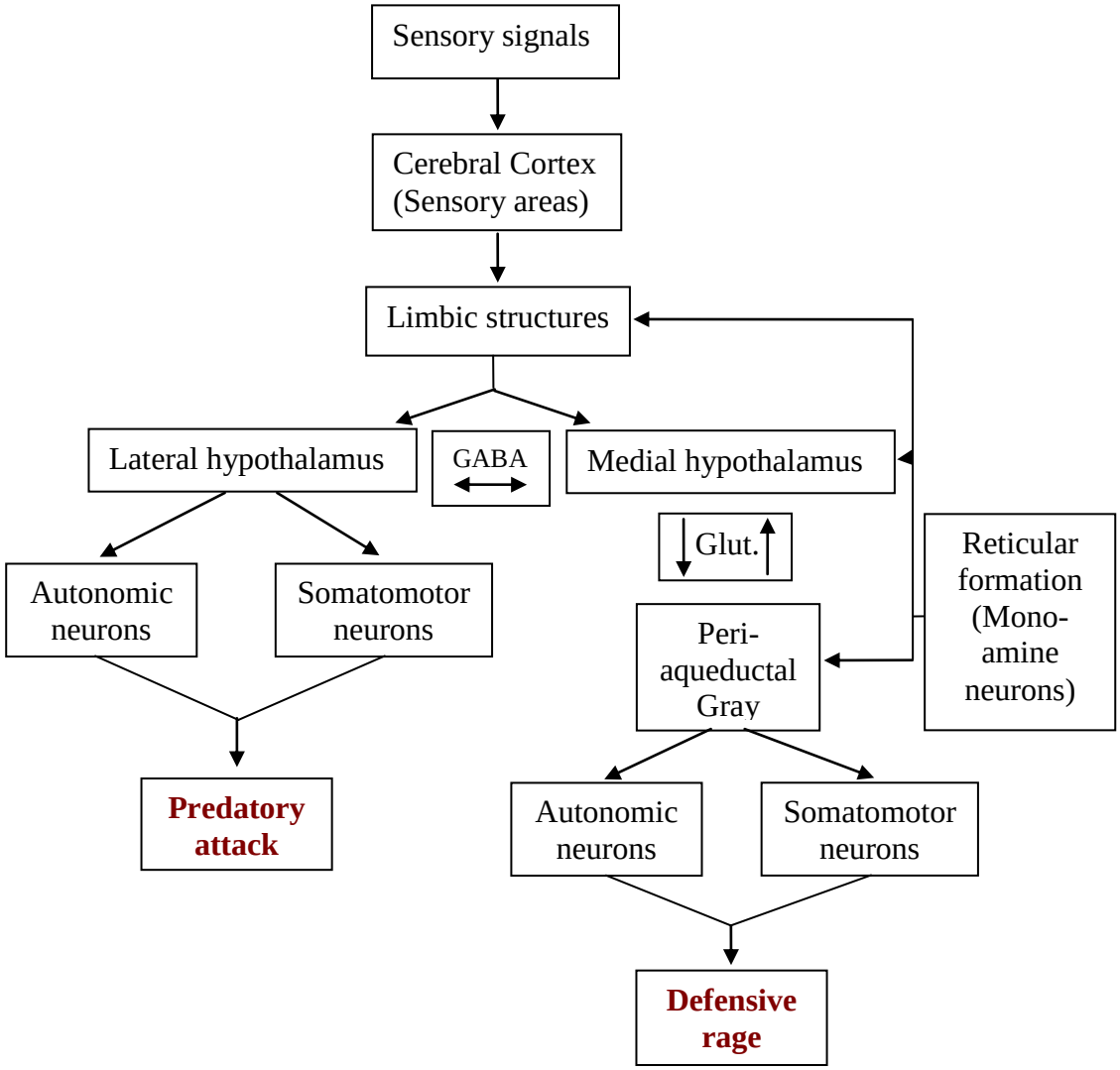
4.6.1. Biological substrates

4.6.1.1. Neurobiology or direct impact of dementia disease

Psychological condition, progressive cognitive and functional losses in dementia influence the nature of BPSD. Lindenmayer [385] stated that, generally, agents that reduce dopaminergic or noradrenergic tone or increase serotonergic or GABAergic tone will attenuate agitation, often irrespective of aetiology.

The findings of Siegel et al. [386] will be presented in summary form. The various types of aggression may be reduced to two categories — *defensive rage* (affective defence), a reactive kind of aggression, and *predatory attack* or the proactive form of aggression. This approach helps explain the behavioural properties of aggression as well as the underlying neural substrates and mechanisms of aggression, both in animals and humans. Defensive rage behaviour is activated by a threatening stimulus that is real or perceived and is associated with marked sympathetic output. This yields impulsivity with minimal cortical involvement. Predatory attack behaviour in both animals and humans is generally planned, taking minutes, hours, days, weeks, months, or even years to produce action. In degenerative brain diseases aggression is mostly of a defensive nature and often driven by psychotic elements in perception [373].

Figure 4.6.1. Brain structures involved in aggression, based on: Siegel and Victoroff (2009).



The limbic structures and the hypothalamus are involved in the control of aggression and rage in humans (Figure 4.6.1). The data is based upon studies involving neurological disorders in patients [387]. These include behavioural correlates of temporal lobe epilepsy, sclerosis of the temporal lobe, tumours of the temporal lobe, other regions of the limbic system, and the hypothalamus. The limbic system powerfully modulates functions of the hypothalamus. Accordingly, damage or disruption of a limbic structure significantly disrupts the regulatory mechanisms modulating aggressive behaviour, resulting in loss of control over these functions.

Gamma-amino butyric acid – A (GABA-A) receptors in the medial and lateral hypothalamus suppress defensive rage and predatory attack behaviour, respectively. GABA-A receptors in the medial hypothalamus are activated by GABA neurons projecting from the lateral hypothalamus, and likewise, GABA neurons arising in the medial hypothalamus activate these receptors in the lateral hypothalamus. There are striking similarities between the characteristics of defensive rage in animals and in humans. Defensive rage is associated with sudden, significant increases in sympathetic activation. The response is quite impulsive and clearly lacks cortical involvement (as shown from animal studies). This response remains intact in spite of ablation of the forebrain. In humans, many studies have reported a link between brain damage to the frontal cortex and increased aggressive behaviour [388]. These findings are consistent with reports that individuals who rank highly on measures of reactive aggression show lower-than-average
baseline activity in the frontal cortex [389 390]. Defensive rage behaviour contains the following basic features: it is activated by a threatening stimulus (which may include self-generated emotions); it is associated with marked sympathetic output; it is impulsive; it does
not require cortical involvement for its expression; and the attack response may be directed at a variety of targets present within the visual field.

4.6.1.2. Neurobiological studies in dementia

Sharp et al. [383] studied the [3H]prazosin binding to alpha1-AdR in post-mortem brain tissue obtained from 24 patients with Alzheimer disease (AD) and 25 comparison cases. They found that aggressive behaviour was significantly correlated with the alpha1-adrenoceptor number in patients with AD. Furthermore, patients receiving ongoing antipsychotics had significantly higher density for [3H]prazosin than those who were not. They concluded that upregulation of alpha1-AdR is associated with aggressive behaviour and chronic treatment with antipsychotic medication. Aggression may also be facilitated by a dysbalance resulting from adrenergic system overactivity during a loss of serotonergic function.

Lai et al. [391] investigated the state of 5-HT(1A) receptors in the postmortem neocortex of 33 AD patients prospectively assessed for cognition and behavioural symptoms, together with 20 matched controls. 5-HT(1A) receptor binding affinity and density were unchanged in the overall AD group compared with the controls. Within the AD group, 5-HT(1A) receptor density in the temporal cortex inversely correlated with aggression and the severity of dementia. The 5-HT(1A) receptor density remained the best predictor for aggression, while temporal cortical neurofibrillary tangle grading was the best predictor for the severity of

dementia. This suggests that 5-HT(1A) receptor alteration is directly related to aggression in AD, while the severity of dementia is more strongly related to the neurodegenerative process.

Garcia-Alloza [392] assessed the cholinergic and serotonergic functions in post-mortem frontal and temporal cortex from 22 AD patients who had been prospectively assessed with the Mini-Mental State examination (MMSE) for cognitive impairment and a scale measuring BPSD. Not only cholinergic deficits, but also the cholinacetyltransferase/serotonin ratios, were significantly correlated with the final MMSE score both in the frontal and the temporal cortex. In addition, decreases in cholinergic function were correlated with the aggressive behaviour factor, supporting a dual role for the cholinergic system in cognitive and non-cognitive disturbances associated to AD. The serotonergic system showed a significant correlation with overactivity and psychosis. An imbalance between cholinergic-serotonergic systems may be responsible for the cognitive impairment associated with AD.

Garcia-Alloza et al. [393] found in addition to cholinergic deficits, significant decreases in GABA content, with no changes in glutamate content, in the frontal and the temporal cortex. Both GABA levels and the glutamate/GABA ratio showed significant correlations with depression in AD. In the temporal cortex, higher densities of GABA(A)/benzodiazepine receptors also correlated with more severe depression. Consequently, it has been suggested that in a situation of cholinergic deficit, such as AD, an imbalance between the excitatory glutamatergic tone and inhibitory GABAergic tone may be responsible for non-cognitive behavioural disturbances.

Tekin et al. [394] identified 31 patients with a diagnosis of definite AD, on whom an autopsy had been carried out. Behavioural changes had been assessed with the NPI. Brain sections were collected from bilateral orbitofrontal and left anterior cingulate, superior temporal, inferior parietal, occipital, and hippocampal cortices for quantification of neurofibrillary tangles (NFTs) and diffuse neuritic plaques. The results suggest that agitation and aberrant motor behaviour are correlates of greater NFT pathology in the orbitofrontal cortex in AD, whereas increasing apathy may relate to greater NFT burden in the anterior cingulate.

Using Positron Emission Tomography (*PET*) examinations Sultzer et al. [395] established relationships between non-cognitive symptoms and metabolic activity. They found that non-cognitive symptoms had regionally specific representations, with significant correlations between the agitation/disinhibition factor score and metabolism of the frontal and temporal lobes, between psychosis factor score and metabolism in the frontal lobe, and between anxiety/depression factor score and metabolism of the parietal lobe. These results

confirmed that psychiatric symptoms are fundamental expressions of the cortical dysfunction of AD.

Hirono et al. [396] studied the relation between regional brain perfusion and aggressive behaviour, using a Single Photon Emission Computed Tomography (*SPECT*) scan, in two groups of 10 patients with dementia with and without aggression, that were comparable for demographic factors, severity of cognitive impairments, and other behavioural symptoms as measured by the NPI. Patients who showed aggression revealed significant hypoperfusion in the left anterior temporal cortex; additional, bilateral dorsofrontal and right parietal cortex were also found to be significantly hypoperfused.

4.6.1.3. Clinical neurobiological correlates

Senanarong et al.s' study [371] is one of the largest and most comprehensive assessments of agitation reported. There was no difference in agitation sub-scale scores between patients with dementia of various aetiologies. The data suggest that agitation in AD is a frontal lobe syndrome. Frontal lobe dysfunction may predispose AD patients to agitation by exaggerating behavioural responses to many types of coexisting psychopathology or environmental provocations.

Herrmann et al. [397] examined in their review the role of norepinephrine (NE) on BPSD, including depression, aggression, agitation and psychosis. A number of lines of evidence suggest that NE dysfunction leading to BPSD may result from increased NE activity and/or hypersensitive adrenoreceptors compensating for loss of NE neurons with the progression of AD.

In a case control study Sukonick et al. [398] wanted to investigate the importance of the dysfunction of serotonin neurotransmission for aggressive behaviour in AD. Homozygosity for the long variant (*L) of an identified bi-allelic polymorphism of the serotonin transporter promoter region (5-HTTPR) is associated with increased expression of the transporter protein and increased speed of response to serotonin reuptake inhibitor treatment. Fifty-eight inpatients on a hospital geriatric psychiatry ward with AD and a history of aggressive behaviour and 79 never-aggressive patients with AD with comparable severity of cognitive impairment were studied. The *L/*L genotype was significantly associated with aggression in patients with AD.

Risperidone may be cited as an example of the clinical relevance of the 5-HT-system. Risperidone antagonises serotonin type 2 (5-HT2) and dopamine type 2 (D2) receptors. In many trials, risperidone has been investigated in use as therapy against aggression and

agitation in dementia. By decreasing serotonergic activity, reactive aggression in humans increases. That may be a reason for the modest efficacy of the drug against agitation in dementia.

At a clinical level, aggression has been shown to correlate very highly with psychosis [373]. The presence of delusions is the best clinical indicator for the occurrence of aggressive features [374 399].

4.6.2. Psychological and environmental factors

Many different concepts and models have been discussed as possible explanations of the psychological aetiology of agitation and aggression in dementia. The available literature suggests that the various types of agitated behaviour have different meanings. Most seem to be associated with discomfort, which may include physical pain, external restraint, or feelings of depression or of loneliness. In contrast, some of the types of behaviour, especially in the physically non-aggressive category, may be adaptive and not an indication of discomfort. On the basis of these interpretations of the reasons for disruptive behaviour, several approaches for treatment follow logically.

Focusing on discomfort that the patient is not able to communicate verbally, Pelletier and Landreville [400] performed hierarchical linear multiple regression analyses controlling for the patients' characteristics (sex, severity of dementia, and disability). They could show that discomfort explains a significant share of the variance in overall agitation, non-aggressive physical behaviour and verbally agitated behaviour. No significant relationship was observed between discomfort and aggressive behaviour, but the power to detect this specific relationship was low.

Burgio et al.'s work [286] included a small number of NH residents. The purpose was to examine aspects of [401] model of need-driven dementia-compromised behaviour. In this model, the authors hypothesized that background factors (e.g., age, gender, motor ability) combined with proximal factors (e.g., physical and social environment) determine the display of agitation. The model suggests that as the residents' cognitive and functional behaviour declines, residents become more vulnerable to ''environmental stress'' and more likely to display agitation because of their inability to meet their own needs. The profoundly cognitively impaired residents displayed more agitation than the moderately impaired group. In a longitudinal analysis they found a significant linear and quadratic trend only with the profoundly impaired residents. These residents showed slight reductions in agitation up to 12 months, with agitation increasing significantly from 12 to 18 months.

Schreiner et al. [342] studied agitated behaviour in elderly NH residents with dementia in Japan. From staff reports, it appeared that most physically aggressive behaviour occurred in relation to personal care. Other research has shown that dependency in personal care is related to aggressive behaviour [402] [403] which probably relates to overall decline in cognitive functioning.

One of the most prominent models is that which explains agitation and aggression in dementia as an attempt to communicate unmet needs, a similar model to that of need-driven theory. In dementia, the patient has a decreased ability to meet his own needs because of his decreased ability to communicate his needs combined with his decreased ability to provide for himself (e.g., unable to use prior coping mechanisms). In addition, there are environmental limitations, because of a lack of understanding about what the patient wants to communicate or because the environment cannot provide his physical or psychosocial needs, e.g. the patient is residing in the wrong level of care. The behaviour may be a means of fulfilling needs, communicating needs or an outcome of frustration and other negative affects interacting with decreased inhibition. On the one hand, physical illnesses - including pain [404], inactivity, loneliness, insufficient staffing levels, cold or hunger at night - the reasons may be many that lead to problem behaviour caused by the environment or by the environment not meeting the patient's needs. On the other hand, structured activities, music, social interactions (creating the good moments of the day), and relaxing activities like a foot bath, aroma therapy, massage, touch, pets (visits with a dog) [405], family videotapes, walking in a garden and so on may be associated with decreased agitation. It should not be forgotten that agitation may also be related to sensory deprivation [406].

From a psychodynamic point of view, Hagberg [407] suggested that the organisation of the personality is affected, resulting in a reduction in ego resources, regressive behaviour, use of more primitive defence mechanisms to stave off painful emotions, and reactivation in conscious awareness of previously unconscious material. It may also be interesting to look to this issue from another perspective, the predictors of aggressive behaviour. Cognitive impairment and the poor quality of a relationship were the main predictors of physically aggressive behaviour. Verbally aggressive behaviour was predicted mainly by depressed mood, poor quality of relationships, and poor physical health. These results validated and expanded prior cross-sectional research on the correlates of aggression in other populations. Cohen-Mansfield and Werner [408] analysed in the same population the longitudinal predictors of physically and verbally non-aggressive inappropriate behaviour in 200 community-dwelling elderly persons attending senior day care-centres. Models based on ratings obtained

from staff members and family carers were compared. Multiple factors contributed simultaneously to the prediction of non-aggressive behaviour. Similar to previous cross-sectional results, physically non-aggressive behaviour was predicted mainly by good health and cognitive impairment. In addition, depression emerged consistently as a predictor of physically non-aggressive behaviour in all models. Verbally non-aggressive behaviour was predicted by a depressed mood and pain, confirming previous suggestions that these types of behaviour are related to discomfort. The relationship of these types of behaviour with cognitive functioning was relatively weak.

Summarising, it can be said that the most common unmet needs in verbally agitated patients are fears, pain, loneliness and depression, in physically non-aggressive behaviour the most common needs that are unmet are those for activity and stimulation, and in physically aggressive behaviour the need to evade discomfort, frustration after fruitless attempts to communicate needs, and need for more personal space, especially in psychosis [409]. It is worth just mentioning that sheltered parks or gardens may have a positive effect on patients who pace or wander.

4.7. Diagnostic challenges of BPSD

Multi-morbidity [410]: advanced age, female gender, and education finishing at a lower level have been independently associated with a more than 50% increased risk for multi-morbidity. Multi-morbidity is the most common clinical description of the elderly and may be increased by unhealthy behaviour. In addition, neuropsychiatric symptoms, especially agitation, are linked to inadequate medical assessment and management of NH residents' other health conditions [20 411]. In this way, agitation has the potential to be life threatening and reduces the quality of care the patient receives.

4.7.1. Delirium

Besides depression and dementia, the third of the three "Ds" in old age psychiatry is delirium. It is a condition characterised by an acute onset and fluctuation in consciousness, memory, perception, behaviour and orientation (American Psychiatric Association 2000). In the context of our research, we have had to differentiate between agitation caused by dementia and a state of confusion like delirium. It occurs in hyperactive, hypoactive and mixed forms. The hyperactive and mixed form may present like agitation in dementia.

Delirium affects up to 42% of older hospital inpatients [412], many with pre-existing dementia [413]. The occurrence of delirium is associated with many poor outcomes, including

increased cognitive impairment and functional disability [414], increased length of hospital stay [415 416], and rates of institutionalisation [414 416]; it is a marker of a higher risk of getting dementia and earlier death. In one study, it was reported that the incidence of dementia was 5.6% per year over 3 years for those without delirium and 18.1% per year for those with delirium [417]. It could be shown that many symptoms of delirium persist over a long period and they often do not resolve at all:

> "Only five patients (4%) experienced resolution of all new symptoms of delirium before hospital discharge, and only 20.8% and 17.7%, respectively, had resolution of all new symptoms by 3 and 6 months after hospital discharge. These data suggest that delirium is a common disorder that may be substantially less transient than currently believed and that incomplete manifestations of the syndrome may be frequent." [418]

A large meta-analysis showed that the combined proportions with persistent delirium (PerD) at discharge from hospital, 1, 3 and 6 months were 44.7%, 32.8%, 25.6%, and 21%, respectively. The outcomes (mortality rate, nursing-home placement, function, cognition) of patients with PerD were consistently worse than the outcomes of patients who had recovered from delirium [419]. Cole et al. also showed that even sub-syndromal delirium has bad outcomes [420].

In clinical praxis, it may be quite a challenge to differentiate delirium from dementia with psychotic features. Often both conditions are present in the same individual, because physical illness in a patient with dementia may easily cause delirium. In addition, there are types of dementia, such as LBD, that characteristically show elements of delirium as fluctuating cognition with pronounced variations in attention and alertness. Further, other disorders like depression and acute psychosis may pose difficulties in differentiating the symptoms and finding the right diagnosis [421]. A good medical history is the best tool in the performance of this task, including information collected from relatives and carers who have known the patient well over a long period of time. In our research project we asked a specialist in old age psychiatry or geriatric medicine to use the ICD-10 criteria (WHO 1992) for dementia and delirium as an approach to the differential diagnosis. The diagnosis of delirium is likely, if the medical history showed a rapid onset of clouding of consciousness and disturbance of cognition and behaviour, in contrast to the dementia criterion of a slow decline in memory and other cognitive abilities, which has been present for at least six months.

4.7.2. Comorbid psychiatric disorders

Patients with AD have a three-fold higher risk of exhibiting psychopathology than controls, with *depressive disorders* being by far the most frequent type of comorbid psychiatric disorder (see chapter 3.3). In fact, depressive episodes are known to precede the 'onset' of clinical AD. Multiple studies have demonstrated an increased history of depression in patients who go on to develop dementia, compared with those who do not [422]. Data from a case-register study of almost 23,000 patients with an affective disorder suggested that increasing severity, expressed as the number of major depressive episodes leading to an inpatient admission, increased the risk of developing dementia [423]. On average, the rate of dementia tended to increase 13% with every episode leading to admission for patients with depressive disorder, and 6% with every episode leading to admission for patients with bipolar disorder, when adjusted for differences in age and sex. The presence of depression in individuals with MCI is predictive of a higher likelihood of developing AD; after three years 85% of the depressed patients had developed AD, in comparison with 32% of the non-depressed subjects.

While several studies failed to find any association between insight into AD and depression [424], others have found the opposite [425 426].

The potential pathogenetic mechanisms leading to the development of depression in dementia include psychosocial factors, prior psychiatric history, level of education, genetic risks, and biological changes associated with the process of dementia per se. These biological changes include inflammatory processes, abnormalities of monoaminergic transmission, and neuroanatomical pathology, like the presence of white matter hyperintensivities and hypometabolism in frontal lobes that has been associated with depression in dementia [427 428]. Depression and AD may share common pathogenic mechanisms that would explain the higher prevalence of depression in AD patients. These include structural and functional abnormalities of common neuroanatomical regions, specifically atrophy of mesial temporal and mesial frontal structures, like the hippocampus [429 430].

Depression in AD very often differs symptomatically from primary depressive disorders. Its early recognition and treatment are important, as persistent depression may have a very negative impact on the QoL of patients and families, and may accelerate cognitive detoriation, or the need to transfer the patient to a NH. This is exemplified in a prospective study [431] with AD patients, who were evaluated annually. The presence of depression was, in addition to the cognitive impairment level, physical aggression and hallucinations, one of four predominant predictors of institutionalisation.

Depression in AD may mimic major and minor depression seen in primary depressive disorders. Depression in dementia is more likely to have an atypical presentation. The patients are often unable to express symptoms of depressed mood (e.g., feelings of sadness or hopelessness, or suicidal ideation), as these require relatively unimpaired higher cognitive functions, the ability to recall recent events, and to think in the abstract. Furthermore, patients with AD are likely to exhibit a variety of physical and neurovegetative symptoms that are directly related to the underlying medical and neurological disorder, such as apathy, fatigue, disturbances of sleep and appetite, mood swings and crying attacks, all of which may also be present in non-depressed AD patients [432]. In addition, often those symptoms that are elicited may not be present 'most of the day, nearly every day' as required by the criteria of dysthymia or major depression.

Apathy is a particularly problematic symptom, as it may occur in depressed and non-depressed AD patients. For example, in the Cache County Study, apathy was identified in almost one-third of AD patients; 40% of these patients were found to suffer from depression [179]. Some of the other differences in depression between individuals with and without dementia include the presence of more 'motivation' symptoms and fewer 'mood' symptoms among people with dementia, despite a similar severity of depressive symptoms [433] [434]. Additionally, several studies have suggested that depressed patients with AD are more likely to exhibit psychotic, as well as aggressive, symptoms [435-437]. Research studies fairly consistently report higher frequencies of depression in dementia with Lewy bodies, e.g. Ballard [438] and Klatka [439], and Parkinson's disease dementia (PDD) [440] than in AD.

There is some evidence that depression is one factor leading to aggression [441]. The goal of Lyketsos et al.'s study was to determine the frequency of physically aggressive behaviour in community-residing patients with dementia and its relationship to depression. They found that aggressive behaviour was closely associated with moderate to severe depression, male gender, and greater impairment in the performance of the activities of daily living, even after adjustment for delusions, hallucinations, sleep disturbance, and the severity of cognitive impairment. After adjustment for depression, gender, and impairment in performing the activities of daily living, there was no association between physically aggressive behaviour and the presence of either delusions or hallucinations. Lyketsos et al. [442] stated that depressive features are associated with agitation and psychosis and may mediate the relationship between other forms of psychopathology and aggressive behaviour. Such a mediating role might explain contradictory findings of prior studies. Another study [373] has assessed the relationship between depression and physically aggressive behaviour, and it

showed no association between the two. However, the investigators in that study used a less systematic quantification of depressive symptoms and a broader definition of aggression. Furthermore, the number of subjects was much smaller.

The heterogeneity of depressive symptoms in AD may often preclude the recognition of depression. To overcome this problem, the National Institute of Mental Health has developed provisional diagnostic criteria for depression in AD [443 444].

Anxiety, as an important and often overlooked part of BPSD, should be mentioned as a differential diagnostic challenge. Until recently, little attention has been paid to anxiety symptoms in dementia [445]. However, anxiety is common in this population with a prevalence rate ranging from 5% to 21%, and associated with poor outcome and quality of life [446-448]. The prevalence of anxiety symptoms ranges from 8% to 71% [259 449]. The rate of anxiety disorders and symptoms in dementia varies dramatically from study to study, suggesting that there is a lack of consensus about how to define and conceptualize anxiety in this population. Several issues complicate this question, including the distinction between symptoms of anxiety and symptoms of dementia, the overlap between anxiety, depression, and agitation, and what constitutes the best source of information. Using revised diagnostic criteria for anxiety disorders in dementia, as has been proposed by Starkstein et al. [450], is a promising approach. Such an approach, however, should be based on consensus guidelines from experts in the field in addition to empirical data, as exemplified by the provisional diagnostic criteria for depression in AD [444].

People with dementia must deal with significant changes - from threats to their physical and financial independence to loss of spouses and friends, home and the freedom to make their own decisions - at a time when they are often least equipped to deal with them. A state of anxious tension and frustration is built up caused by the feeling of losing control over life, losing orientation in time, by chaotic impressions, being exposed to stress and not able to use former coping strategies anymore, being dependent on unknown others, losing intimacy and privacy.

Anxiety disorders have been underestimated for several reasons. For example, older patients, and especially dementia patients, are less likely to report psychiatric symptoms and more likely to emphasize their physical complaints. There are only a few such studies, and some major epidemiological studies have excluded general anxiety disorders (GAD), one of the most prevalent anxiety disorders in older adults. However, an anxiety disorder should be considered in any patient with depressive symptoms or with physical symptoms that are not

explained by a physical problem, such as chest pain, palpitations, shortness of breath, diarrhoea or sleep problems, or behavioural disturbances like agitation or aggression, wandering and shouting. Though some question the "capacity" for anxiety in those with limited cognition, the same question has not been raised about children, who also have an underdeveloped nervous system.

> "What may be operating in both cases…are right-brain phenomena, such as the role of intuition, sensing, interpreting or misinterpreting something that seems not right… There are many examples in the case of anxiety where the diagnosis does not rely on what patients say, but rather on what they display. Overlooking the potential role of anxiety as clinically significant in AD is to overlook important intervention opportunities." (Cohen, 1998) [451]

Anxiety in AD is a frequent comorbid condition of major depression. GAD was present in 26% with major depression and in 5% without depression [450]. The authors validated a set of diagnostic criteria for anxiety in dementia. These criteria include restlessness, irritability, muscle tension, fears, and respiratory symptoms in the context of excessive anxiety and worry.

Another important question regarding anxiety symptoms in dementia is whether they should be considered as a separate clinical entity or as part of a broader syndrome. Some authors have suggested that there is a strong overlap between anxiety and agitation [452], and that perhaps agitation may be a symptom of generalized anxiety [453]. To determine whether anxiety is distinct from other neuropsychiatric symptoms in dementia, Seignourel et al. [454] reviewed six factor analyses pertaining to this question. Four studies used orthogonal rotations, constraining factors to be uncorrelated, which may result in the appearance of unreliable factors [455]. The other two studies used oblique rotations. Regarding the overlap between anxiety and agitation, two studies [456] [457] found anxiety and agitation to load on the same factor, while three others [458-460], including the two studies that used oblique rotations [459] [460], found them to load on separate factors. Moreover, one study that explicitly examined the relationship between anxiety and agitation found only a modest correlation, suggesting that the two constructs are not equivalent [461]. Thus, the existing evidence provides more support for the distinctiveness of anxiety and agitation than for their equivalence.

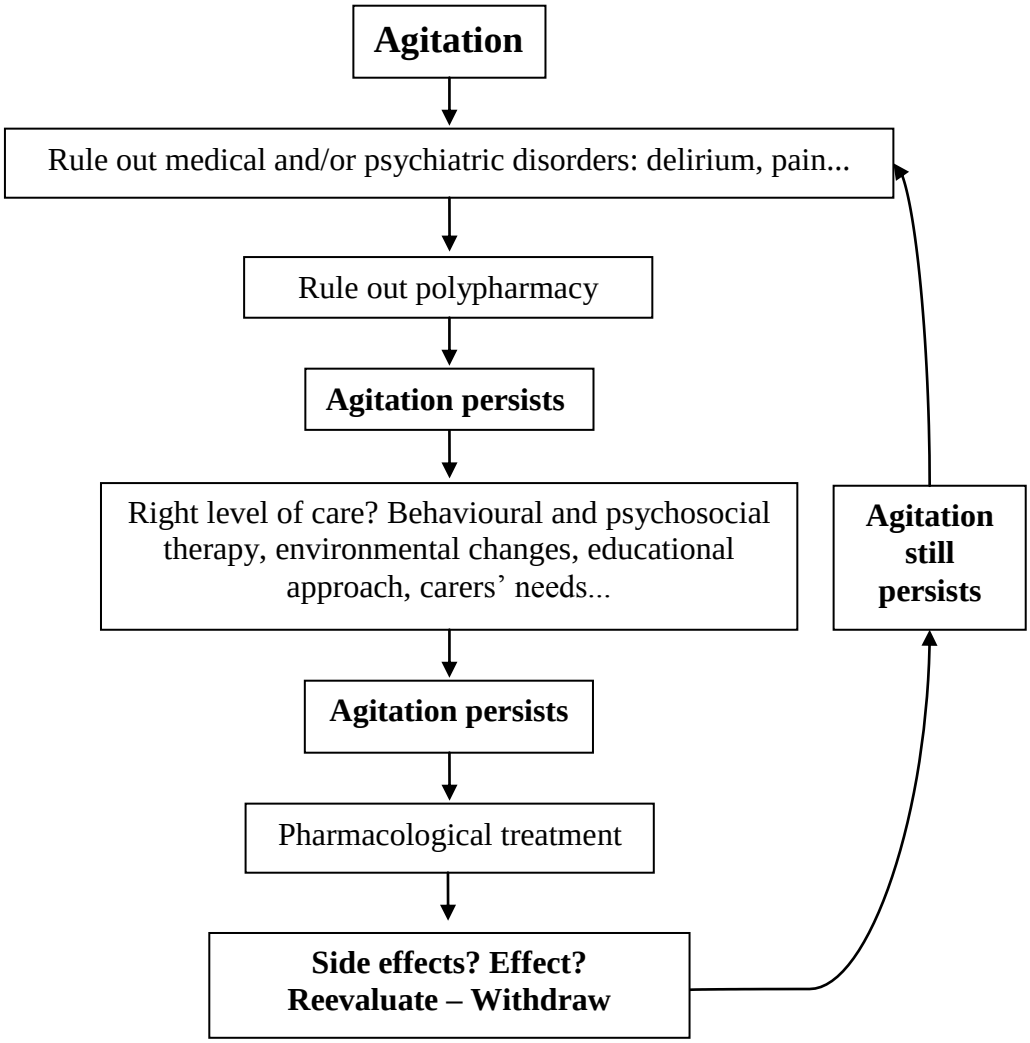
Aggressive and non-aggressive agitation occur in about 20% of people with AD in contact with clinical services [179] or living in the community [462] and 40% to 60% of people in care facilities [463]. A review of 55 studies, showed that *psychosis* was reported in 41% of patients with Alzheimer's disease, including delusions in 36% and hallucinations in 18% [464].

Aggressive behaviour was more frequent among patients with hallucinations than among those without. About a quarter of the variance in aggression could be attributed to psychosis [373]. Psychotic phenomena in dementia do not have the same quality as those that occur in primary psychotic disorders such as schizophrenia. It is sometimes difficult to distinguish between true delusions and the overvalued ideas in someone with cognitive impairment. Often, delusions of patients with AD are of a paranoid nature and simple, probably because of cognitive impairment that precludes the elaboration of complex ideas. Hallucinations are slightly less common than delusions, and when they occur, they are usually visual. They may be striking and complex and lead to reactions, as for example a patient leaves the TV on so as not to disturb the others, whom she sees sitting there watching a programme. Visual hallucinations are a key symptom of DLB and PDD [438 465]. The frequency of psychosis and agitation is similar in patients with VaD to people with AD, but delusions and visual hallucinations are significantly more frequent in DLB [438] and PDD [440]. Psychotic symptoms are probably associated with the severity of the illness [182], and seem to occur more often in women than in men [466]. Several studies report an association between delusions and the upregulation of muscarinic M1 or M2 receptors in DLB [467 468] and AD [469]. Teaktong et al. summarised their results as follows: Impaired consciousness was significantly associated with increased M4 binding and delusions were significantly associated with increased M2 binding. Increased M2 and M4 receptor binding in DLB was also associated with visual hallucinations. Upregulation of M2 and M4 muscarinic receptors in the cingulate and adjacent cortex may thus contribute to the development of psychosis in DLB. Psychosis in general appears to increase in frequency with greater burden of neurofibrillary tangles [470]. In DLB there is a well-established relationship between visual hallucinations and reduced cholinergic function [467 471], but the relationship is less clear in the context of AD [381].

4.8. Non-pharmacological therapy of agitation

The treatment of agitation ideally entails identification and alteration of underlying causes as physical, environmental, social, and psychiatric factors [472]. Most researchers and clinicians who treat agitated patients with dementia believe that behavioural and psychosocial treatment should be the primary approach [473]. However, patients with aggressive agitated behaviour (either event or non-event related) may not respond to the behavioural treatment approach and will require the additional use of pharmacological agents. In 1996, Mintzer [474] proposed a clinical decision tree that is still helpful. We have adjusted it (Figure 4.8.1). Salzman et al. [475] supported this procedure.

Figure 4.8.1. Clinical decision tree for the treatment of agitated patients with dementia, adjusted (Source: Mintzer, 1996).

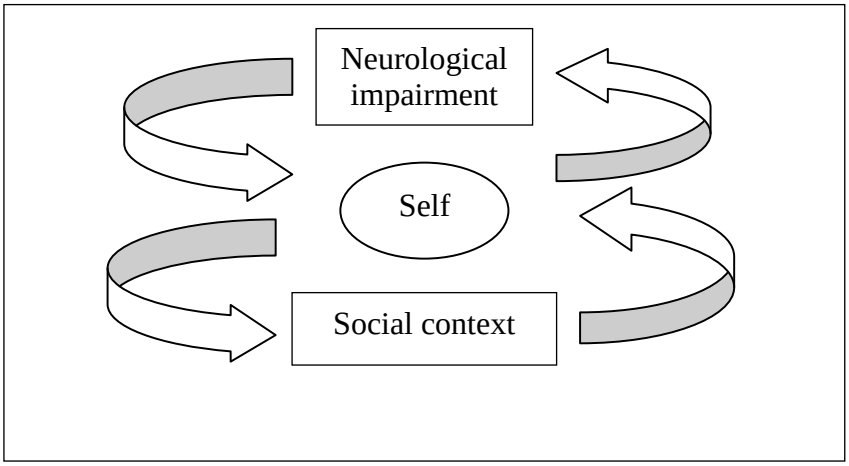


Before looking at the different treatment options, it is useful to discuss the term 'efficacy', briefly. 'Efficacy' in our context may mean that an intervention reduces the severity of agitation or number of symptoms, or improves the function in ADL and cognition; it may also mean that the therapy reduces the carer burden, or has a positive impact on the prevention of detoriation of cognition. Consequently, prevention of disability or reduction of the speed of decline may count as a positive outcome. Some newer studies have other efficacy outcomes, like the period of time the drug was taken as an indication, e.g., of how well patients tolerate the drug or if the treatment helps.

4.8.1. Behavioural and psychosocial interventions

The 'standard paradigm' for understanding dementia has been a medical or disease model. However, a number of findings indicate that causal mechanisms are far from straightforward, and a broader focus is needed [476]. A more complete explanation requires consideration of psychosocial factors. An 'alternative paradigm' to the pure biological view has been most clearly articulated by Kitwood [477] [478] [479] - a pioneer in the field of person-centred dementia care. He proposed a dialectical model of dementia, which is summarised in Figure 4.8.2. The term 'dialectical' reflects the emphasis on interactions between variables operating at the biological and psychosocial levels.

Figure 4.8.2. Dialectical model of dementia (based on Kitwood, 1997).



Kitwood suggested that the manifestation and progression of AD in any individual are influenced by the interplay of neurological impairment, physical health and sensory acuity, personality, biographical experiences, and social psychology, in terms of environment, communication and interaction. Consequently, a therapeutic approach to agitation, and other behavioural disturbances in dementia, has to take into consideration each of these facets as a possible treatment approach. The brain has considerable potential for change (plasticity), some of which is retained in dementia. It was conceptualised that psychological experiences may affect the structure of the brain just as the brain structure may affect experience. This has clear implications for the provision of care, indicating a requirement for care that meets people's psychological needs and affirms personhood, sense of self and social value. These may have a positive impact on the QoL. Kitwood believed that a benign social psychology

coupled with an enriched environment might facilitate some regeneration or at least the maintenance of function for a period. While a malignant social environment might contribute to greater disability and speed up a decline (see Figure 4.8.2).

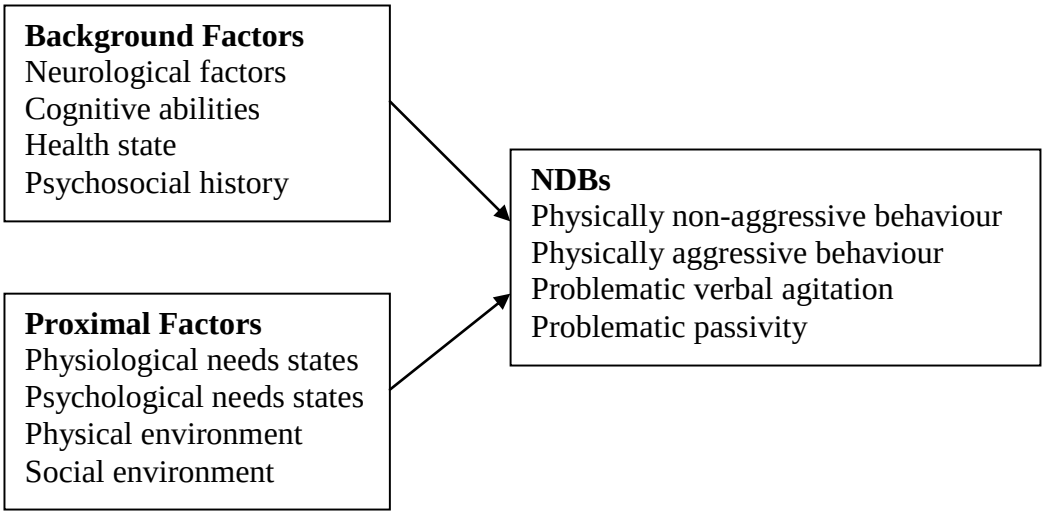
There is some evidence that supports this theory: Karlsson et al. [480] reported in an experimental study that environmental factors influenced biochemical markers of transmitter activity. Widerlov et al. [481] observed improvements in intellectual and motor functioning induced by integrity-promoting care and that somatostatin concentrations in cerebrospinal fluid were significantly elevated in an experimental group, but not in a control group. Conceptualising dementia within a bio-psycho-social framework encourages us to consider each of these levels and the interactions between them, in order to maximise well-being. Kitwood's dialectical model is consistent with this approach. Tom Kitwood developed innovative research projects and training courses, challenging the "old culture of care". His aim was to understand, as far as possible, what care is like from the standpoint of the person with dementia. One of his major innovations was Dementia Care Mapping (DCM), an observational method for evaluating the quality of care in formal settings. Kitwood described the DCM tool as based on "a serious attempt to take the standpoint of the person with dementia, using a combination of empathy and observational skill." The reasons for using DCM in practice can be listed as follows: driving forwards person-centred care through a developmental evaluation, assessing difficult situations with residents or at particular times of the day, staff training, to demonstrate the QoC, research and evaluation of interventions.

Kitwood was always interested and involved in research with the aim of following it through to practice. His book 'Dementia Reconsidered: The Person Comes First' (1997) brought together all his work, developments and discoveries. His philosophy is based on "person-centred care" (PCC), quite simply summarised as "treat others in the way you yourself would like to be treated".

Edvardsson et al. [482] emphasised that PCC generally includes the recognition that the personality of the person with AD is increasingly concealed rather than lost, includes the tailoring of the person's care and their environment to their needs, offers shared decision-making, interprets behaviour from the point of view of the patient, and prioritises the relationship as much as the care tasks.

The Need-Driven Dementia-Compromised (NDB) Behaviour Model (see Figure 4.8.3.) [401] has a similar approach to that of Kitwood.

Figure 4.8.3. The Need-Driven Dementia-Compromised (NDB) Behaviour Model (Algase et al., 1996).



Seemingly simple adjustments in care routines and approaches can make a significant difference to the experience of people with dementia [483]. They suggested interventions that can help providers understand the "behavioural symptoms" of dementia, which are often considered a way of communicating unmet needs. By focusing on the person rather than on the disease, nurses promote comfort and functional autonomy in older adults whose cognitive impairments have progressed and yet who are very much alive and deserving of respectful, dignified care.

Brooker [484] developed the concept of PCC further to what she called VIPS, an acronym for the four key elements of PCC. 'V' stands for 'values people' with dementia and those who care for them, 'I' for 'treat people as individuals' – individualised care recognises the uniqueness of the person, 'P' for 'perspective of service users' – the experience of the person with dementia is the starting point, and 'S' for 'supportive social psychology' – relationships are paramount.

Chenoweth et al. [485] conducted a cluster-randomised trial, the 'Caring for Aged Dementia Care Resident Study (CADRES)' of PCC and DCM compared with the standard system of care in dementia. The primary outcome was agitation measured with the CMAI. The CMAI score was lower in sites providing DCM and PCC compared with the standard system of care. At 4 and 8 months, agitation had increased in the control group but decreased

in residents under the experimental care approaches. The CMAI proved to be more sensitive than the NPI-NH in detecting improvement in behaviour. The authors concluded that care that addresses residents' total human needs may mitigate cognitive and functional deterioration, supporting the need for individually tailored behavioural intervention. Ballard and Aarsland [486] commented on the study, saying that CADRES is of major importance in showing the value of DCM as an effective approach to reducing agitation in care-home residents with dementia.

Marte Meo supervision (MMS) is another method intended to support communication and interactions between the carer and a person with dementia. It was developed by the pedagogue Maria Aarts during the 1980s using videotape to help with diagnosis and treatment of the child-parent interaction. Later on, this method was also applied in dementia care. It uses short video recordings of an interaction, followed by staff training. It has not been possible to find a scientific article published either in an international journal, a meta-analysis or a Cochrane Review that evaluates this method in dementia care.

A Cochrane Review [487] evaluated music therapy as a therapy for behavioural, social, cognitive and emotional problems. Five studies were included. The methodological quality of the included studies was too poor to draw any useful conclusions. However, the evidence available suggests that music therapy may be beneficial in treating or managing dementia symptoms (Table 4.8.1). Linda Gerdner was one of the first to apply systematically individualised music as therapy for agitation in dementia [488] [489]. A statistically significant reduction in agitation was found during the presentation of music. Staff and family interviews provided convergent validity of these findings. Music also promoted meaningful interaction between the resident and others. Gerdner [489] suggested that music may help residents to shift focus from meaningless and confusing stimuli to the sort of stimuli a person with dementia is able to interpret [490]. Hicks-Moore [491] found that relaxing music during mealtimes reduced agitated behaviour. At the end of the 4-week study, overall reductions in the cumulative incidence of total agitated behaviour were observed. Reductions in absolute numbers of agitated behaviour were achieved during the weeks with music. Clark et al. [492] investigated the response of aggressive behaviour to individualised music during bath time. While the music was playing, 12 out of 15 identified aggressive behaviour types decreased. Decreases were significant for the total number of observed types of behaviour and especially for the hitting type of behaviour. While the music was playing, carers frequently reported an improved state of mood and a general increase in cooperation with the bathing task.

Garland et al. [493] compared simulated family presence with preferred music as treatment of agitated behaviour in NH residents with dementia. Simulated presence and preferred music both proved to be effective in reducing incidents of physically agitated behaviour. Simulated presence, but not music, resulted in significantly reduced incidents of verbally agitated behaviour. The placebo tape proved more effective than expected. Participants' responses to simulated presence and music varied widely. Incidents of agitated behaviour fell by one-half or more in many cases. However, other residents became more agitated.

Physical activity programmes have been evaluated and published in a Cochrane Review by Forbes et al. [494]. Four trials met the inclusion criteria, but only two were included in the analyses. The result of this review suggests that there is insufficient evidence of the effectiveness of physical activity programmes in managing or improving cognition, function, behaviour, depression, and mortality in people with dementia. Few trials have examined these important outcomes. In addition, family carer outcomes and use of health care services were not reported in any of the trials included (Table 4.8.1).

Validation therapy – A Cochrane Review [495], found no statistically significant differences between validation and social contact or between validation and standard therapy. There was no assessment of carers. There is insufficient evidence from randomised trials (Table 4.8.1).

Hand massage and therapeutic touch were effective in producing a relaxation response in persons with dementia who had a history of agitated behaviour; they did not, however, decrease agitation behaviour. Hand massage was more effective in producing relaxation than was therapeutic touch [496].

Li-Chan Lin et al. [497] explored the effectiveness of acupressure and Montessori-based activities in institutionalized residents with dementia in a cross-over trial. They compared the treatment with the potentially calming presence of a visitor who acted as a control. All participants underwent all three treatments in three different sequences. Acupressure daily (6 days weekly) for 4 weeks significantly decreased overall agitated behaviour, especially in the CMAI subcategories of physically non-aggressive and physically aggressive behaviour. Montessori-based activities significantly reduced aggressive behaviour and physically non-aggressive behaviour. Neither approach decreased verbally agitated behaviour. Nursing assistants noted that it was easier to assist residents with eating, toileting, bathing, grooming, sleeping, walking, and various other activities after the acupressure or Montessori-based activities.

A Cochrane review [498] (reviewed April 2008), described the effect of a method called Snoezelen, which is a multi-sensory stimulation programme. Four trials were included [499-502]. They examined the short-term, and/or longer-term values of Snoezelen on the behaviour of people with dementia. Meta-analyses could not be performed because of the limited number of trials and different study methods used. Overall, there is no evidence showing the efficacy of Snoezelen for dementia (Table 4.8.1).

Livingston et al. reviewed the literature [503] of psychological approaches in the management of neuropsychiatric symptoms of dementia (Table 4.8.1). They concluded:

> "Only behaviour management therapies, specific types of carer and residential care staff education, and possibly cognitive stimulation appear to have lasting effectiveness for the management of dementia-associated neuropsychiatric symptoms. Lack of evidence regarding other therapies is not evidence of lack of efficacy. Conclusions are limited because of the paucity of high-quality research (only nine level-1 studies were identified). More high-quality investigation is needed."

Table 4.8.1. Evidence for Psychological Therapies (Livingston 2005, Am J Psychiatry)

Treatment	**RCT**	**Cochrane Review**	**Number of participants**	**Evidence**
Reality Orientation	6	Spector 2002	?	withdrawn
Validation	3	Neal & Barton Wright 2003	116	Insufficient evidence
Reminiscence	4	Woods 2005	144	Promising indications
Multi sensory - Snoezelen	2	Chung & Lai 2002	260	No evidence
Light therapy	5	Forbes 2009	?	Insufficient evidence
Physical activity programs	2	Forbes 2008	145	Insufficient evidence
Music therapy	5	Vink 2004	125 (?)	Promissing, but no conclusion

References: [487 494 495 498 504 505]

Kverno et al. [506] performed another systematic literature review focusing on treatment of neuropsychiatric symptoms in persons with advanced dementia. Out of 215 only 21 specifically focused on treatments for individuals with moderately severe to very severe dementia. These 21 studies provided moderate to high quality evidence for the use of sensory-focused strategies, including aroma therapy, music preferred by the patient or live music, and multi-sensory stimulation. Interventions appear to work best when they are tailored to balance individual arousal patterns.

O'Connor et al. [507] performed a further systematic review of 12 selected experimental studies to evaluate the effectiveness of psychosocial treatments in reducing psychological symptoms in dementia (e.g. anxiety, depression, irritability and social withdrawal). They concluded:

> "Some psychosocial interventions appear to have specific therapeutic properties, over and above those due to the benefits of participating in a clinical trial. Their effects were generally modest with an unknown duration of action. This limited efficacy suggests that treatments will work best in specific, time-limited situations, tailored to individuals' requirements. There is no preferred method to rate psychological symptoms."

4.8.2. Environmental changes

Evidence that carer and environmental precipitating factors are of importance for BPSD is scattered [508] [509]. Testad et al. conducted [510] a comparative survey comparing environmental influences on agitation and the use of psychotropics in NH residents in three European countries: Norway, Austria and England. They found differences in agitation and antipsychotic drug use which are likely to be related to structural and cultural differences in nursing homes between these three countries. The findings suggest that structural changes can improve the quality of care and the quality of life for nursing-home residents.

Zuidema et al. [511] reported that the prevalence of neuropsychiatric symptoms differed between SCUs, also after correcting for patient factors. Patient-related factors explained 7 to 21% of the total variance of neuropsychiatric symptoms. When the staff spent more time on care activities, patients' level of apathy decreased. He further described a substantial variation of prevalence rates between SCUs. This finding in combination with the clustering of symptoms within SCUs is strong evidence that environmental factors contribute to neuropsychiatric symptoms in dementia.

4.8.3. Educational approaches

Boustani et al. [347] studied the characteristics associated with behavioural symptoms related to dementia in long-term care residents. The prevalence of BPSD was associated with staff training and residents' cognition, mood, mobility, and psychotropic use. They concluded that attention to staff training and depression management might improve BPSD.

Graff et al. [512] provided a 10-session occupational therapy programme over five weeks. The patients were trained to use aids to compensate for cognitive decline. The family carers learned how to cope better with challenging behaviour in patients. The intervention improved patients' daily functioning and reduced the burden on the carers, despite the patients' limited learning ability. Effects were still present at 12 weeks, which justifies implementation of this intervention. Graff et al. [513] concluded in another article that community occupational therapy should be advocated both for dementia patients and their carers, because it improves their mood, the quality of life, and health status and the carers' sense of control over life. Effects were still present at the follow-up interview. In addition, Graff et al. showed [514] that community occupational therapy intervention for patients with dementia and their carers is cost effective.

Spijker et al. [515] have developed the Systematic Care Program for Dementia (SCPD). They found an urgent need for cost-effective support programmes, including education, that may prevent informal carers of people with dementia from becoming overburdened, which might result in a delay or decrease in patient institutionalisation. Spijker et al. reported the aim and design of an ongoing multi-centre, cluster randomised, controlled trial.

The Tailored Activity Program (TAP) [516] is a home-based occupational therapy intervention. In a randomised trial, this intervention showed that it could reduce behavioural symptoms and the burden on carers. TAP involves 8 sessions over a period of 4 months. Preserved capabilities, the previous roles, habits, and interests of individuals with dementia are identified. Thereafter, activities customized to individual profiles are developed; and the families are trained in the use of the relevant activities. Carers reported great confidence in using these activities, being less upset with behavioural symptoms (86%), enhanced skills (93%) and personal control (95%). Therapists observed enhanced engagement (100%) and pleasure (98%) in individuals with dementia during the sessions.

Shah and De [517] studied the effect of an educational intervention programme with the aim of reducing aggressive behaviour directed towards nursing staff. The efficacy was prospectively evaluated over an 18-week period. The programme was administered during the

middle 6-week period. Aggressive behaviour was measured using the RAGE and SOAS scales. Aggressive behaviour measured with both scales was reduced after the educational intervention.

Testad et al. [364] investigated the effect of staff training on the use of constraints in a single-blind controlled trial. The content of the educational programme focused on the decision-making process in the use of restraint and alternatives to restraint. The intervention consisted of a full day seminar, followed by a one-hour session of guidance per month over six months. The primary outcome measures were number of restraints per patient in the nursing-homes in one week and agitation was measured with the Brief Agitation Rating Scale (BARS). After the intervention period, the number of restraints had declined by 54% in the treatment group, and increased by 18% in the control group.

Fossey et al. [518] delivered training and support intervention to nursing-home staff over 10 months, focusing on alternatives to drugs for the management of agitated behaviour in dementia (FITS trial). At 12 months the proportion of residents taking antipsychotics in the intervention homes (23.0%) was significantly lower than that in the control homes (42.1%). No significant differences were found in the levels of agitated or disruptive behaviour between intervention and control homes. The overall QoL was not improved, but individual QoL may have been improved. These results showed that educational intervention and support are an effective alternative to antipsychotics.

Cohen-Mansfield et al. [519] explored the effect of staff education on how to enable engagement in persons with dementia. Significant, positive correlations were found between higher cognitive functioning and longer engagement duration, more attention, a more positive attitude and a lower refusal rate. There was a positive and significant correlation between the co-morbidity index and engagement duration, and between the number of medications and attention. All functional status variables yielded significance in a positive direction. Participants with poor hearing had a higher refusal rate. Cognitive status was the most consistent and potent predictor of engagement in this population.

Ballard et al. [520] conducted a study to examine the effect of a psychiatric liaison service in care homes. The main outcomes were changes in NPI, reduction of use of antipsychotics and GP visits. There was a significant reduction in the use of antipsychotics in the facilities receiving the liaison service, but not amongst those receiving standard clinical support. There were also significantly less GP contacts for residents in the facilities receiving the liaison service, and a three-fold reduction in psychiatric in-patient bed usage (bed days per person 0.6 vs. 1.5). Residents in care facilities receiving the liaison service experienced

significantly less deterioration in expressive language skills, but there were no significant differences in BPSD or wellbeing.

Kuske et al. published a review on NH staff training [521]. A total of 21 studies were identified, mostly published in the United States. Most were of poor methodological quality. Although nearly all reported positive effects, their results must be interpreted cautiously due to methodological weaknesses. Vasse et al. [522] performed a systematic review for the use of communication strategies in residential and nursing-homes. The aim of this review was to study the effects of non-pharmacological interventions in residential and nursing-homes on (1) communication between residents with dementia and care staff, and (2) the neuropsychiatric symptoms of residents with dementia. Interventions around daily care activities had positive effects on communication outcomes. Effects of both types of interventions on neuropsychiatric symptoms were divergent.

Levy-Storms [523] reviewed critically the contemporary experimental research and found that the following therapeutic communication techniques can be taught and can benefit staff and older adults' quality of life: verbal and non-verbal communication behaviour including open-ended questions, positive statements, eye contact, affective touch, and smiling. Nursing aides need not only more training in therapeutic communication, but also ongoing, dedicated supervision in psychosocial aspects of care.

Non-pharmacological interventions offer the potential for safer alternatives to pharmacotherapy and, therefore, should always be the first approach. Ballard et al. [486] reviewed the increasing evidence in support of psychological interventions or alternative therapies (such as aromatherapy) as a first-line management strategy for agitation, as well as the potential pharmacological alternatives to atypical antipsychotics - preliminary evidence for memantine, carbamazepine, and citalopram is encouraging. That leads on to the next chapter.

4.9. Studies on psychopharmacological treatment of agitation

4.9.1. Antipsychotic agents

Antipsychotics are widely used as the first-line pharmacological approach to treat the neuropsychiatric symptoms of dementia. Efficacy has been examined in eight randomised, double-blind, placebo-controlled trials with typical antipsychotics and 18 double-blind, placebo-controlled trials with atypical antipsychotics. The atypical antipsychotic risperidone

was recommended in view of its modest efficacy and relative safety until FDA warnings were issued in 2005 and 2008 and meta-analytic studies showed no significant difference to placebo. The U.S. Food and Drug Administration's (FDA) warnings on the cardiac, metabolic, cerebrovascular, and mortality risks have caused serious concerns for the use of typical and atypical antipsychotic agents for elderly patients with dementia. The following overview will provide the results of studies investigating the effectiveness and side effects of antipsychotics prescribed for agitation in dementia, proceeding historically.

4.9.1.1. First generation antipsychotics (vs second generation)

Schneider et al. [524] performed a meta-analytic review of the existing literature as early as 1990. Results indicated that antipsychotics were significantly more effective than a placebo, but that the effect was small (r = .18). This indicates that 18 out of 100 dementia patients benefited from antipsychotic treatment (beyond that of a placebo) and is consistent with the modest efficacy described in previous qualitative reviews. In six studies comparing thioridazine with another antipsychotic, and in five studies comparing haloperidol with another antipsychotic, meta-analysis results did not show that these two medications differed significantly from the comparison medications, which is not inconsistent with the opinion that no single antipsychotic is better than another. This was the evidence base in 1990.

A Cochrane Review performed by Lonergan et al. [34] studied the effectiveness of haloperidol. Five trials were included and led to the following results: there was no significant improvement in agitation among haloperidol treated patients, compared with controls treated with a placebo. Aggression decreased among patients with agitated dementia treated with haloperidol; other aspects of agitation were not affected significantly. Although two studies showed increased drop-out rates due to adverse effects among haloperidol patients, there was no significant difference in drop-out rates when haloperidol-treated patients were compared with controls. The data were insufficient to examine response to treatment in relation to length of treatment and degree of dementia. Authors' conclusion: No evidence has been found of any significant general improvement in manifestations of agitation, other than aggression, among demented patients treated with haloperidol, compared with placebo-treated controls.

4.9.1.2. Comparison of first generation with second generation antipsychotics

De Deyn et al. [525] studied the effectiveness of risperidone and haloperidol compared with a placebo in patients with dementia. A 13-week double-blind study involving 344 patients with dementia randomly assigned patients to receive a placebo or flexible doses (0.5 to 4 mg/d) of

risperidone or haloperidol. Behavioural symptoms were assessed by the BEHAVE-AD, the CMAI, and the Clinical Global Impression (CGI) scale. The mean dose at the endpoint was 1.1 mg/d of risperidone and 1.2 mg/d of haloperidol. Although not significant, a higher percentage of patients receiving risperidone than those receiving a placebo showed clinical improvement (30% or more reduction from baseline to endpoint in BEHAVE-AD total score). Reductions in the BEHAVE-AD total score were significantly greater with risperidone than with a placebo at week 12. In a further analysis of aggression, the most dominant symptom in these patients, BEHAVE-AD and CMAI aggression cluster scores were significantly reduced compared with a placebo at the endpoint and at week 12. Severity of extrapyramidal symptoms with risperidone did not differ significantly from that of a placebo and was less than that of haloperidol. A post hoc analysis showed significantly greater reductions in the BEHAVE-AD aggressiveness score with risperidone than haloperidol at week 12. The authors concluded that low-dose risperidone (mean 1.1 mg/d) was well tolerated and associated with reductions in the severity and frequency of behavioural symptoms, particularly aggression, in elderly patients with dementia.

Chan et al. [526] conducted a RCT comparing risperidone with haloperidol in 58 patients with DSM-IV diagnosis of dementia of Alzheimer's type or vascular dementia. They were randomly assigned to receive flexible doses (0.5 to 2 mg/day) of haloperidol or risperidone. Clinical response was evaluated using the CMAI, the BEHAVE-AD, Simpson-Angus Scale (evaluates drug-related extrapyramidal syndromes), Functional Assessment Staging and Cantonese version of the Mini-Mental State Examination. The study obtained the following results: the mean doses during the last week were 0.90 mg/day of haloperidol and 0.85 mg/day of risperidone. Both haloperidol and risperidone significantly reduced the severity of BPSD (scores on CMAI and BEHAVE-AD), with no significant between-group differences. Haloperidol-treated patients showed a worsening on the Simpson-Angus scale, while there was no significant change in this measure in risperidone-treated patients.

Suh et al. [527] performed a similar study comparing haloperidol with risperidone. This was an 18-week double-blind, crossover study involving 120 patients who were randomly assigned to receive flexible doses (0.5-1.5 mg/day) of risperidone or haloperidol. BPSD were assessed using the BEHAVE-AD, the CMAI, and the Clinical Global Impression of Change scale (CGI-C). Both risperidone and haloperidol were efficacious in alleviating BPSD. However, when receiving risperidone, patients showed significantly greater improvement than when receiving haloperidol in the total and sub-scale scores of the BEHAVE-AD, the total and sub-scale scores of the CMAI, and the scores on the CGI-C scale. Also, risperidone

had an additional benefit on aggressiveness and anxiety/phobia. The risk of antipsychotic-induced parkinsonism throughout this study was significantly lower with risperidone than with haloperidol.

Gareri [528] evaluated the efficacy and safety of risperidone or olanzapine vs. promazine in the treatment of BPSD. In this study 60 patients were randomised to the intervention. The NPI was administered at baseline, after 4 and 8 weeks. Patients had at least a total score of 24 or more on NPI at baseline. The scale was administered by an clinical research assistant who was not aware of the kind of treatment of the patients. 20 patients were randomly assigned to 1 mg daily of risperidone in divided doses; 20 patients were randomly assigned to 5mg of olanzapine at bedtime, and 20 patients were randomly assigned to 50 mg of promazine daily. If there was a lack of clinical response after 4 weeks, the dose could be increased to 2 mg/day of risperidone, 10 mg/day of olanzapine, and to 100 mg/day of promazine in the respective groups. At the end of the 8th week, a global improvement was obtained in 80% of the patients treated with risperidone and olanzapine, vs. 65 % of patients treated with promazine ($p < 0.01$). The authors concluded that

> "risperidone in doses of 1-2 mg/day and olanzapine in doses of 5-10 mg/day are effective and safe in the treatment of BPSD. Risperidone presents a major and dose-dependent antidopaminergic action and seems to be preferable when hallucinations and delusions are the prevailing symptoms, though it also gives good results on aggression and wandering. Olanzapine seems to be faster in its sedative effect, probably because of its H1 receptor blockade. Moreover, 5-HT6 antagonism may favour acetylcholine release and this explains why these patients did not present with cognitive worsening. However, both drugs are comparable or even superior to promazine, with significantly fewer side effects of both anticholinergic and extrapyramidal character."

Tariot et al. [529] conducted a multicentre, double-blind, placebo-controlled, randomised trial of flexibly dosed quetiapine and haloperidol. Primary outcomes were change in the total Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions-Severity of Illness (CGI-S) scores at week 10. Secondary outcomes included BPRS factors, NPI, and the Physical Self-Maintenance Scale (PSMS). Of the 284 randomised participants, 63.4% completed the study. The median of the mean daily dose was 96.9 mg for quetiapine and 1.9 mg for haloperidol. BPRS agitation factor scores improved with quetiapine versus a placebo, but no difference was found between quetiapine and haloperidol. BPRS anergy scores worsened with haloperidol versus quetiapine, but not quetiapine versus a placebo. No NPI factors showed

change, including the agitation factor. PSMS total scores worsened with haloperidol treatment, but not in patients treated with quetiapine. Somnolence occurred in 25.3%, 36.2%, and 4.1% of the quetiapine, haloperidol, and placebo groups, respectively. Parkinsonism was most prevalent in the haloperidol group. Other safety and tolerability measures differed little between the groups. All treatment groups showed improvement in measures of psychosis without significant differences between them when planned comparisons were performed. Participants treated with quetiapine or haloperidol showed inconsistent evidence of improvement in agitation. Tolerability was better with quetiapine compared with haloperidol.

Gill et al. [530] performed a population-based, retrospective cohort study to investigate the risk of death at 30, 60, 120, and 180 days after the initial dispensing of antipsychotic medication. Two pairwise comparisons were made: atypical versus no antipsychotic use and conventional versus atypical antipsychotic use. A total of 27,259 matched pairs were identified. New use of atypical antipsychotics was associated with a statistically significant increase in the risk of death at 30 days compared with non-use in both the community-dwelling cohort and the long-term care cohort. Excess risk seemed to persist to 180 days, but unequal rates of censoring over time may have affected these results. The study concluded that atypical antipsychotic use is associated with an increased risk of death compared with non-use among older adults with dementia. The risk of death may be greater with conventional antipsychotics than with atypical antipsychotics.

Schneeweiss et al. [531] performed a retrospective cohort study in British Columbia, Canada, of 37,241 adults, 65 years of age or older, who were prescribed conventional (12,882) or atypical (24,359) antipsychotic medications for any reason between January 1996 and December 2004. The investigators compared the 180-day mortality from any cause with use of a conventional antipsychotic versus treatment with an atypical antipsychotic. They found that the risk of death in the group of patients treated with conventional antipsychotic medications was comparable to, or possibly greater than, the risk of death in the group of patients treated with atypical antipsychotic medications. The causes of death with the highest relative risk were cancer and cardiac disease. As a consequence of this study and the study performed by Gill et al., the FDA considered that the methodological limitations in these two studies preclude any conclusion that conventional antipsychotics carry a greater risk of death than atypical antipsychotics. FDA (FDA Allert 2008) has determined, however, that the overall weight of evidence, including these studies, indicates that the conventional antipsychotics share the increased risk of death in elderly patients with dementia-related psychosis that has been observed for the atypical antipsychotics

(http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm).

Tyrer et al. [532] investigated the use of antipsychotics compared with a placebo in the treatment of aggressive challenging behaviour for people with intellectual disabilities (the NACHBID trial). Mean daily dosages were 1.07 mg rising to 1.78 mg for risperidone and 2.54 mg rising to 2.94 mg for haloperidol. Aggression declined dramatically with all three treatments by 4 weeks, with the placebo showing the greatest reduction (79%, versus 57% for combined drugs) ($p = 0.06$). Placebo-treated patients showed no evidence of inferior response in comparison to patients receiving antipsychotic drugs. An additional study found that clinicians who had not participated in clinical trials before were less likely to recruit. The mean total cost of accommodation, services, informal care and treatment over the 6 months of the trial was £16,336 for the placebo, £17,626 for haloperidol and £18,954 for risperidone.

4.9.1.3. Second generation antipsychotics

Risperidone

Risperidone was the first atypical antipsychotic shown to be effective in treating BPSD and is currently the only atypical antipsychotic that is approved for the treatment of BPSD in a number of countries, including Norway.

Katz et al. [233] reported the findings from the first large, double-blind, placebo-controlled study conducted to evaluate the efficacy and safety of risperidone in the treatment of psychotic and behavioural symptoms in institutionalized elderly patients with dementia. Each patient was randomly assigned to receive a placebo or 0.5 mg/day, 1 mg/day, or 2 mg/day of risperidone for 12 weeks. The primary outcome measure was the BEHAVE-AD. The study was completed by 70% of the patients. At the endpoint, significantly greater reductions in BEHAVE-AD total scores and psychosis and aggressiveness sub-scale scores were seen in patients receiving 1 and 2 mg/day of risperidone than in placebo patients. More adverse events were reported by patients receiving 2 mg/day of risperidone than 1 mg/day. The most common dose-related adverse events were extrapyramidal symptoms, somnolence, and mild peripheral edema. The frequency of extrapyramidal symptoms in patients receiving 1 mg/day of risperidone was not significantly greater than in placebo patients.

Brodaty et al. [533] randomised elderly patients with dementia of the Alzheimer's type, vascular dementia, or a combination of the two in a RCT. The participants had significantly aggressive behaviour and received for a period of 12 weeks a flexible dose of either a placebo or risperidone solution up to a maximum of 2 mg/day. Outcome measures were the CMAI,

the BEHAVE-AD, and the Clinical Global Impression of Severity (CGI-S) and of Change (CGI-C) scales. The trial was completed by 67% of patients in the placebo group and 73% of patients in the risperidone group. The mean dose of risperidone was 0.95 mg/day. The primary endpoint of the study, the difference from baseline to endpoint in CMAI total aggression score, showed a significant reduction in aggressive behaviour for risperidone versus placebo. A similar improvement was also seen for the CMAI total non-aggression sub-scale and for the BEHAVE-AD total and psychotic symptoms sub-scale. Overall, 94% and 92% of the risperidone and placebo groups, respectively, reported at least 1 adverse event. Somnolence and urinary tract infection were more common with risperidone treatment, whereas agitation was more common with a placebo. There was no significant difference in the number of patients who reported extrapyramidal symptoms between the risperidone (23%) and placebo (16%) groups. The authors concluded: treatment with low-dose (mean = 0.95 mg/day) risperidone resulted in significant reduction in aggression, agitation, and psychosis associated with dementia.

From the year 2005 on, pooled analyses, systematic reviews and meta-analyses showed that there is a greater risk for serious adverse events connected to the use of atypical antipsychotics in patients with dementia. At the beginning, the conclusions were more favourable for the use of antipsychotics than later on. One example of this is the pooled analysis performed by De Deyn et al. [534], which included three randomised, placebo-controlled double-blind trials in NH residents treated with risperidone in the management of agitation, aggression, and psychosis associated with dementia. The aim of this analysis was to assess the risk and benefit of the use of risperidone in this population. The efficacy data (risperidone n=722, placebo n=428) were obtained from the CMAI and the BEHAVE-AD total and sub-scales. Additionally, clinical global impression (CGI) assessments were performed. The mean dose of risperidone at the end point was 1.0 mg/day. The observed mean change at the end point was significantly higher for risperidone than for placebo on CMAI total score, and total aggression score, BEHAVE-AD total score, and psychotic symptoms score. The main treatment effects of risperidone were similar in all subgroup analyses. Additionally, risperidone-treated patients scored significantly better than placebo-treated patients on the CGI scales at the end point. The incidence of treatment-emergent adverse events was comparable between risperidone (84.3%) and the placebo (83.9%). More patients discontinued due to adverse events in the risperidone-treated group (17.2%) than in the placebo group (11.2%). Differences in adverse event incidences between the placebo and

risperidone were observed for extrapyramidal symptoms (EPS), mild somnolence and the less common cerebrovascular adverse events (CAE).

Of all atypical antipsychotics, risperidone has the largest database of double-blind controlled trials to support its efficacy and safety in the treatment of agitation, aggression, and psychosis associated with dementia. At the recommended doses, risperidone displayed a favourable risk-benefit profile. In view of the risk for CAEs, risperidone should be targeted towards the treatment of those patients in whom psychotic and behavioural symptoms of dementia are prominent and associated with significant distress, functional impairment or danger to the patient.

Olanzapine

Street et al. [535] conducted a multicentre, double-blind, placebo-controlled, 6-week study in NH residents with AD who exhibited psychotic and/or behavioural symptoms. Patients were randomly assigned to placebo or a fixed dose of 5, 10, or 15 mg/d of olanzapine. The primary efficacy measure was the sum of the ‘agitation/aggression’, ‘hallucination’, and ‘delusion’ items (Core Total) of the NPI-NH. The conclusion of this study was that low-dose olanzapine (5 and 10 mg/d) was significantly superior to placebo and well tolerated in treating agitation/aggression and psychosis in this population of patients with AD.

Following a double-blind, 6-week exposure to fixed-dose olanzapine (5, 10, or 15 mg/d), patients entered an additional 18-week, open-label, flexible-dose treatment [536]. Baseline was defined from the start of the extension phase. Patients improved significantly on the primary efficacy measure, defined a priori, which consisted of the sum of the ‘agitation/aggression’, ‘delusion’, and ‘hallucination’ items ('Core') of the NPI-NH. Olanzapine also significantly improved scores for the NPI-NH total and the Core item.

De Deyn et al. [537] randomly assigned patients with AD and delusions or hallucinations to a 10-week double-blind treatment with a placebo or fixed-dose olanzapine (1.0, 2.5, 5.0, 7.5 mg/day). Repeated-measures analysis showed significant improvement from baseline in NPI-NH Psychosis Total scores (sum of Delusions, Hallucinations items - primary efficacy measure) in all five treatment groups, but no pairwise treatment differences were seen at the 10-week endpoint. However, under LOCF analysis, improvement in the 7.5 mg olanzapine group was significantly greater than with a placebo, while endpoint CGI-C scores showed the greatest improvement in the 2.5 mg olanzapine group compared to the placebo. Neither the incidence of any other individual events, including extrapyramidal symptoms, nor of total adverse events occurred with significantly higher frequency in any olanzapine group relative

to the placebo. No clinically relevant significant changes were seen across groups in cognition or any other vital sign or laboratory measure, including glucose, triglyceride, and cholesterol. While 1.0 mg olanzapine did not show significant differences from placebo, the 2.5 mg dose was a reasonable starting dose. Olanzapine at 7.5 mg/day significantly decreased psychosis and overall behavioural disturbances and was well tolerated.

Clark et al. [538] studied the effects of olanzapine in reducing the emergence of psychosis among NH patients with AD. Of the patients without hallucinations or delusions at baseline, the placebo-treated patients showed significantly greater development of these symptoms (NPI-NH hallucinations + delusions mean change score) compared with olanzapine-treated patients. Similarly, of the patients without baseline hallucinations, the placebo-treated patients showed greater hallucinations score increases than did olanzapine-treated patients. Patients without baseline delusions showed no significant treatment effect. The conclusion at this time was that olanzapine had a favourable safety profile in each patient subset.

Bigos et al [539] investigated, as part of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), the impact of sex, race, and smoking on the olanzapine exposure. Smokers cleared olanzapine 55% faster than those who had never smoked. Men cleared olanzapine 38% faster than women. Patients who identified themselves as black or African American cleared olanzapine 26% faster than other races. Differences in olanzapine exposure due to sex, race, and smoking may account for some of the variability in response to olanzapine.

Quetiapine

Ballard et al. [540] randomised 93 patients with AD and clinically significant agitation, measured by the CMAI, into three intervention groups: atypical antipsychotic (quetiapine), cholinesterase inhibitor (rivastigmine), or a placebo (double dummy). 80 (86%) patients started treatment (25 rivastigmine, 26 quetiapine, 29 placebo), of whom 71 (89%) tolerated the maximum protocol dose (22 rivastigmine, 23 quetiapine, 26 placebo). Compared with the placebo, neither group showed significant differences in improvement on the CMAI either at six weeks or 26 weeks. In this study, the Severe Impairment Battery (SIB) was used to measure cognition at baseline, at six weeks and 26 weeks. Compared with the placebo, quetiapine was associated with significantly greater cognitive decline as measured by SIB.

Kurlan et al. [541] assessed the efficacy and tolerability of quetiapine for agitation or psychosis in patients with dementia and parkinsonism by performing a multicentre

randomised, double-blind, placebo-controlled parallel group clinical trial. They involved patients with dementia with Lewy bodies (n=23), Parkinson disease (PD) with dementia (n=9), and Alzheimer disease with parkinsonian features (n=8). The main outcome measure for efficacy was change in the Brief Psychiatric Rating Scale (BPRS) from baseline to 10 weeks of treatment. For tolerability, the Unified PD Rating Scale (UPDRS) motor section was used. No significant differences in the primary or secondary outcome measures of efficacy were observed. An unexpectedly large placebo effect, inadequate dosage (mean 120 mg/day), and inadequate power may have contributed to lack of demonstrable benefit. Quetiapine was generally well-tolerated and did not worsen parkinsonism, but was associated with a trend toward a decline in functioning in daily activities.

Aripirazol

De Deyn et al. [542] compared the efficacy, safety, and tolerability of aripiprazole with placebo in patients with AD associated with psychosis. This 10-week, double-blind, multicentre study randomised outpatients with AD-associated psychosis to aripiprazole (n=106) or placebo (n=102). The initial aripiprazole dose of 2 mg/d was titrated upwards (5, 10, or 15 mg/d) according to efficacy and tolerability. Evaluations included NPI (Psychosis sub-scale) and Brief Psychiatric Rating Scale (BPRS), adverse event (AE) reports, extrapyramidal symptoms (EPS) rating scales, and body weight. Overall, 83% completed the study. Mean aripiprazole dose at the end point was 10.0 mg/d. The NPI Psychosis sub-scale score showed improvements in both groups (aripiprazole, -6.55; placebo, -5.52; P = 0.17 at the end point). Aripiprazole-treated patients showed significantly greater improvements from baseline in BPRS Psychosis and BPRS Core sub-scale scores at the end point compared with the placebo. Adverse events were generally mild to moderate in severity and included (aripiprazole vs. placebo): urinary tract infection (8% vs. 12%), accidental injury (8% vs. 5%), somnolence (8% vs. 1%), and bronchitis (6% vs. 3%). Somnolence was mild and not associated with falls or accidental injury. There were no significant differences from the placebo in EPS scores, or clinically significant ECG abnormalities, vital signs, or weight.

Mintzer et al. [543] assessed the efficacy and safety of aripiprazole in AD patients with psychosis in a double-blind, placebo-controlled multicentre study. 487 institutionalized patients were randomised to placebo or aripiprazole, 2, 5 or 10 mg/day. Primary efficacy assessment was the mean change from baseline to week 10 on the NPI-NH (Psychosis Sub-scale score). Secondary measures included NPI-NH Total, Clinical Global Impression-Severity of Illness (CGI-S), BPRS Core and Total, and the CMAI scores. Aripiprazole 10

mg/day showed significantly greater improvements than placebo on the NPI-NH Psychosis Sub-scale. Aripiprazole 5 mg/day showed significant improvements versus placebo on BPRS and CMAI scores. Aripiprazole 2 mg/day was not efficacious compared to placebo. Cerebrovascular adverse events were reported: aripiprazole 2 mg/day, N=1; 5 mg/day, N=2; 10 mg/day, N=4; placebo, N=0. No deaths in any group (aripiprazole 2 mg/day, 3%; 5 mg/day, 2%; 10 mg/day, 7%; placebo, 3%) were considered to be treatment-related.

In a review of three trials [542-544], Madhusoodanan and Shah [545] concluded that these studies showed that aripiprazole improved psychotic symptoms in AD patients compared to placebo. The safety and tolerability profile of aripiprazole suggests a low potential for negative impact on dementia and overall patient health, but there was increased incidence of CVAEs (e.g., stroke, transient ischemic attack), including death, in aripiprazole-treated patients. In the fixed-dose study of Mintzer et al. [543] there was a statistically significant dose-response relationship for CVAEs in patients treated with aripiprazole.

4.9.1.4. Comparison between second generation antipsychotics

In a double-blind parallel study allowing dose titration over 14 days, 39 agitated persons with dementia residing in long-term care facilities were administered olanzapine (N=20) or risperidone (N=19) as acute treatment [546]. The primary outcome measures were the CGI and the NPI. Both drugs produced significant reductions in CGI and NPI scores, but there was no significant difference between the two drugs. The mean olanzapine dose was 6.65 mg/day; for risperidone, the mean dose was 1.47 mg/day. The positive drug effect was not accompanied by decreased mobility, and there was improvement on a quality-of-life measure. The main adverse events were drowsiness and falls. At baseline, 42% of subjects in both groups had extrapyramidal symptoms that increased slightly, but not significantly, by the end of the study. Low-dose, once-a-day olanzapine and risperidone appear to be equally safe and equally effective in the treatment of dementia-related behavioural disturbances in residents of care facilities.

Schneider et al. [547] assessed the effectiveness of three atypical antipsychotic drugs in outpatients with AD, as part of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). In this 42-site, double-blind, placebo-controlled trial, 421 AD outpatients with psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose 5.5 mg per day), quetiapine (mean dose, 56.5 mg per day), risperidone (mean dose 1.0 mg per day), or a placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason, and the number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks. There were no

significant differences between treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median 8.1 weeks), quetiapine (median 5.3 weeks), risperidone (median 7.4 weeks), and the placebo (median 8.0 weeks) (P=0.52). The median time to the discontinuation of treatment due to a lack of efficacy favoured olanzapine (22.1 weeks) and risperidone (26.7 weeks) as compared with quetiapine (9.1 weeks) and the placebo (9.0 weeks) (P=0.002). The time to the discontinuation of treatment due to adverse events or intolerance favoured the placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, and 5% of patients who received the placebo discontinued their assigned treatment owing to intolerance (P=0.009). No significant differences were noted among the groups with regard to improvement on the CGIC scale. Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to the placebo (P=0.22). The authors concluded that adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with AD.

4.9.1.6. Long-term follow up of antipsychotic use in NHs

Alanen et al. [548] designed a retrospective study in Finland with three identical cross-sectional samples originating from the same long-term care facilities, and collected data from 1 July to 31 December in 2001, 2002 and 2003. The prevalence of the use of one or more antipsychotic drugs decreased from 42% in 2001 to 39% in 2003. The overall confounder-adjusted decrease in antipsychotic use was not statistically significant. However, the use of antipsychotics decreased among residents for whom wandering was a behavioural problem and increased among residents with concomitant use of anxiolytic medications.

Kleijer er al. [549] observed the course of behavioural problems in elderly NH patients with dementia when treated with antipsychotics (N=556). During treatment of NH residents with dementia with antipsychotics the severity of most behavioural problems continues to increase in most patients, with only one out of six patients showing improvement. After withdrawal of antipsychotics, behavioural problems remained stable or improved in 68% of patients after 3 months and 58% after 6 months.

Selbaek et al. [261] reported the natural 12-month course of psychiatric and behavioural symptoms and the concomitant use of psychotropic medication in NH patients with dementia. At baseline a representative sample of 1,163 NH patients participated, of whom 933 had dementia. At the follow-up interview after 1 year, 633 of the patients who had dementia at

baseline were assessed. Individual symptoms, such as depression (58%), delusions (56%), and agitation/aggression (47%) had resolved at a high rate. Persistent use of antidepressants (79%), antipsychotics (75%), or any psychotropic drug (88%) was common. There were no differences between users and non-users of antipsychotics or antidepressants regarding the course of psychosis, agitation, or depression over the 1-year observation period.

4.9.1.5. Use of antipsychotic medication in NHs and some studies about physical restraints

Nijk et al. [550] registered psychotropic drug use in 1,322 patients on 59 dementia special care units (SCUs) in 25 nursing-homes. Psychotropic drugs in general and antipsychotics in particular were most frequently prescribed in GDS stage 6, and in patients aged between 65 and 75 years. Psychotropic drugs in general were positively associated with depression, night-time behaviour disturbances and agitation. Antipsychotic drug use was positively associated with psychosis, agitation and night-time behaviour and was negatively associated with apathy. In particular, the association with neuropsychiatric symptoms raises questions of the efficacy of these drugs and the risk of chronic use.

Feng et al.'s [551] study compared inter- and intra-country differences in the prevalence of the use of physical restraints and antipsychotic medication in NHs, and examines aggregated resident conditions and organizational characteristics correlated with these treatments. Population-based, cross-sectional data were collected using a standardized Resident Assessment Instrument (RAI) from 14,504 long-term care facilities providing NH level services in five countries participating in the inter-RAI consortium, including Canada, Finland, Hong Kong (Special Administrative Region, China), Switzerland, and the United States. Facility-level prevalence rates of physical restraints and antipsychotic use were examined both between and within the study countries. The prevalence of the use of physical restraint varied more than five-fold across the study countries, from an average 6% in Switzerland, 9% in the US, 20% in Hong Kong, 28% in Finland, and over 31% in Canada. The prevalence of antipsychotic use ranged from 11% in Hong Kong, 26 to 27% in Canada and the US, 34% in Switzerland, and nearly 38% in Finland. Within each country, substantial variations existed across facilities in both them use of physical restraint and antipsychotic use rates. In all countries, neither facility case mix nor organizational characteristics were particularly predictive of the prevalence of either treatment or the use of restraints. There exists large, unexplained variability in the prevalence of physical restraint and antipsychotic use in nursing-home facilities both between and within countries.

4.9.1.6. Reviews and meta-analyses of antipsychotic trials against agitation

Up to the year 2001, at least 35 trials have investigated the efficacy and safety of the use of conventional antipsychotics for this condition [552].

Lee et al. [553] reviewed 77 abstracts. Five randomised trials (1570 patients) evaluating risperidone and olanzapine were identified. Most participants lived in institutions (> 96%) and had AD (76.3%). Trials lasted 6 to 12 weeks. Treatment with atypical antipsychotic drugs was superior to placebo for the primary endpoint in three of the five trials. Two trials comparing risperidone with haloperidol did not find any differences in the primary measures of efficacy. Adverse events were common and included extrapyramidal symptoms, somnolence, and abnormal gait.

Sink et al. [35] evaluated the evidence of the efficacy of pharmacological agents used in the treatment of BPSD by performing a systematic review of articles published from 1966 to July 2004. For typical antipsychotics, 2 meta-analyses and 2 RCTs were included. Generally, no difference between specific agents was found, efficacy was small at best, and adverse effects were common. Six RCTs with atypical antipsychotics were included. The results showed modest, statistically significant efficacy of olanzapine and risperidone, with minimal adverse effects at lower doses. Atypical antipsychotics were associated with an increased risk of stroke.

Ballard and Howard [32] presented a meta-analysis to assess the efficacy of the antipsychotic drugs for the treatment of psychiatric symptoms in AD, and discussed the more limited evidence for their potential benefits in other dementias. They recommended that these treatments should be limited to the short-term treatment of psychiatric symptoms associated with serious distress or risk. Table 4.9.1 shows the number needed to treat (NNT) and the number needed to harm (NNH) for haloperidol and risperidone.

Schneider at al. [30] performed a meta-analysis of randomised, placebo-controlled trials to study the efficacy and adverse effects of atypical antipsychotics prescribed for people with dementia. Sixteen trials comparing atypical antipsychotics with a placebo, met the selection criteria: aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), and risperidone (n=5). A total of 3,353 patients were randomised to a drug and 1,757 to a placebo.

Efficacy on rating scales was observed by meta-analysis for aripiprazole and risperidone, but not for olanzapine. Response rates were frequently not reported. There were smaller effects for less severe dementia, outpatients, and patients with psychosis. Approximately one-third dropped out. Adverse events were mainly somnolence and urinary tract infection or incontinence across drugs, and extrapyramidal symptoms or abnormal gait

Table 4.9.1. Number Needed to Treat (NNT) and Number Needed to Harm (NNH) for different antipsychotics (Ballard and Howard 2006).

	Haloperidol	**Risperidon**
Efficacy (NNT)	3-6	6-8
EPS (NNH)	4-9	7-13
Somnolence (NNH)	8	10-13
	Typical antipsychotics	**Atypical antipsychotics**
Death risk	++	+

with risperidone or olanzapine. Cognitive test scores worsened with drugs. There was no evidence for increased injury, falls, or syncope. There was a significant risk of cerebrovascular events, especially with use of risperidone. Small statistical effect sizes on symptom rating scales support the evidence for the efficacy of aripiprazole and risperidone.

Aupperle [554] made a review searching medical databases for clinical trials with a focus on atypical antipsychotics. Because of the safety concerns associated with the use of atypical antipsychotics in this population, he recommended that these drugs should be used judiciously. For patients with severe BPSD such as psychosis, agitation, or aggression, for whom there are few options, atypical antipsychotics, particularly risperidone and olanzapine, should be considered.

A Cochrane systematic review [555] included studies published up to December 2004. The evidence suggested that risperidone and olanzapine are useful in reducing aggression and risperidone in reducing psychosis, but both are associated with serious adverse cerebrovascular events and extrapyramidal symptoms. Despite the modest efficacy, the significant increase in adverse events confirms that neither risperidone nor olanzapine should be used routinely to treat dementia patients with aggression or psychosis, unless there is severe distress or risk of physical harm to those living and working with the patients. Although insufficient data were available from the considered trials, a meta-analysis of 17 placebo-controlled trials of atypical antipsychotics for the treatment of behavioural symptoms in people with dementia conducted by the FDA suggested a significant increase in mortality (OR 1.7). A peer-reviewed meta-analysis [556] of 15 placebo-controlled studies (nine unpublished) found similarly increased risk in mortality (OR=1.54) for the atypical antipsychotics.

Herrmann and Lanctot [557] published another systematic review. Studies of reasonably high quality indicate that risperidone and olanzapine are more effective than a placebo in institutionalized patients with severe agitation, aggression, and psychosis. The efficacy of

antipsychotics is counterbalanced by safety concerns that include the risk of cerebrovascular adverse events and mortality. They concluded that although there have been numerous well-designed studies of the pharmacotherapy of neuropsychiatric symptoms in AD, safer and more effective treatments are urgently needed.

Jeste et al. [558] produced an update, the ACNP White Paper: Update on Use of Antipsychotic Drugs in Elderly Persons with Dementia. They concluded that there is insufficient evidence to suggest that psychotropics other than antipsychotics represent an overall effective and safe, let alone better, treatment choice for psychosis or agitation in dementia.

Ballard et al. [31] authored a review to describe the current state of knowledge regarding the management of agitation and aggression associated with AD and discussed the controversies and possible solutions. There is increasing evidence to support the value of simple psychological interventions and staff-training programmes as a first-line management strategy for agitation prior to pharmacotherapy. The most widely prescribed pharmacological treatments - atypical antipsychotics - have a modest but significant beneficial effect in the short-term treatment of aggression (over 6 to 12 weeks), but limited benefits in longer-term therapy. In addition, there have been increasing concerns regarding the potential for serious adverse outcomes, including stroke and death. The potential pharmacological alternatives to atypical antipsychotics with the most encouraging preliminary evidence include memantine, carbamazepine and citalopram.

Rochon et al. [559] compared the rate of developing any serious event, a composite outcome defined as an event serious enough to lead to an acute care hospital admission or death within 30 days of initiating antipsychotic therapy, so as to give a better estimate of the overall burden of short-term harm associated with these agents. In this population-based, retrospective cohort study, they identified 20,682 matched older adults with dementia living in the community and 20,559 matched individuals living in NHs. Relative to those who received no antipsychotic therapy, community-dwelling older adults newly dispensed an atypical antipsychotic therapy were 3.2 times more likely, and those who received conventional antipsychotic therapy were 3.8 times more likely to develop any serious event during the 30 days follow-up period. The pattern of serious events was similar but less pronounced among older adults living in a NH. Therefore, antipsychotic drugs should be used with caution even when short-term therapy is being prescribed.

4.9.1.7. Cerebrovascular adverse events (CVAE)

Herrmann et al. [560] examined the association between atypical antipsychotic use and stroke in the elderly. The authors conducted a retrospective population-based cohort study of patients over the age of 66 by linking administrative health care databases. Three cohorts - users of typical antipsychotics, risperidone, and olanzapine - were identified and compared. Model-based estimates adjusted for covariates hypothesized to be associated with stroke risk revealed relative risk estimates of 1.1 (95% CI=0.5-2.3) for olanzapine and 1.4 (95% CI=0.7-2.8) for risperidone. They concluded that the use of olanzapine and risperidone was not associated with a statistically significant increased risk of stroke compared with the use of a typical antipsychotic.

Wooltorton et al. [561] studied the incidence of CVAE related to risperidone. In 4 placebo-controlled trials lasting 1–3 months and involving more than 1,200 patients with AD or VaD, CVAE were twice as common in the risperidone-treated group (4%) as in the placebo group (2%). A further search of international databases of postmarketing adverse events revealed 37 cases of such events in elderly dementia patients taking risperidone, of which 16 (43%) were fatal. Similar to warnings issued about risperidone and associations with hyperglycemia and cerebrovascular events, two years later a warning was issued for another second-generation drug, olanzapine. The same research group [562] studied the incidence of CVAE in patients using olanzapine. According to information supplied by the manufacturer, only 2 of the 5 studies have been published in full. The duration of the published trials was between 6 and 10 weeks, with doses of the drug ranging from 1 to 15 mg. Overall, the relative risk of a cerebrovascular event among patients taking olanzapine in the 5 trials was 3.1 and the absolute increased risk was 0.9%. The rates of cerebrovascular events were similar to those reported for risperidone.

Herrmann and Lanctot [563] investigated the question of whether atypical antipsychotics cause stroke. Post hoc analyses of pooled results from 11 randomised controlled trials of risperidone and olanzapine in elderly dementia subjects revealed an increased incidence of CVAE compared with a placebo. Re-analysis of the risperidone trials suggests that some of the increased incidence may be accounted for by nonspecific events that were not strokes. A larger number of subjects with vascular and mixed dementias were included in the risperidone studies compared with the olanzapine studies, which is likely to account for the increased incidence of cerebrovascular adverse events in the risperidone trials compared with the olanzapine studies. Potential mechanisms proposed to explain an association between atypical

antipsychotics and cerebrovascular adverse events include thromboembolic effects, cardiovascular effects (e.g. orthostatic hypotension, arrhythmias), excessive sedation resulting in dehydration and haemoconcentration, and hyperprolactinaemia. However, there is little evidence to support these hypothesised mechanisms at present. Therefore, the authors concluded that association between atypical antipsychotics and cerebrovascular adverse events requires further clarification.

Zheng et al. [564] analysed data from the CATIE-AD study to discover metabolic changes associated with second-generation antipsychotic use in AD patients. Women showed significant weight gain while change was not significant in men. Clinically significant weight gain was seen among patients with antipsychotic use of up to 12 weeks (OR=1.56), between 12 and 24 weeks (OR=2.89), and more than 24 weeks (OR=3.38) relative to patients who did not use antipsychotics during the trial. Olanzapine and quetiapine treatments were significantly associated with weight gain. In addition, olanzapine was significantly associated with decreases in HDL cholesterol and increased girth relative to the placebo group. No treatment effects were noted for changes in blood pressure, glucose, and triglycerides.

4.9.1.8. Mortality risk

Wang et al. [565] conducted a retrospective cohort study involving 22,890 patients 65 years of age or older who had drug insurance benefits in Pennsylvania and who began receiving a conventional or atypical antipsychotic medication between 1994 and 2003. Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after the initiation of therapy with an antipsychotic medication. They controlled for potentially confounding variables. Conventional antipsychotic medications were associated with a significantly higher adjusted risk of death than were atypical antipsychotic medications at all the intervals studied (up to 180 days: relative risk, 1.37; less than 40 days: relative risk, 1.56; 40 to 79 days: relative risk, 1.37; and 80 to 180 days: relative risk, 1.27) and in all subgroups defined according to the presence or absence of dementia or NH residency. The greatest increases in risk occurred soon after therapy was initiated and with higher dosages of conventional antipsychotic medications. Increased risks associated with conventional as compared with atypical antipsychotic medications persisted in confirmatory analyses. These results suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should not be used to replace atypical agents discontinued in response to the FDA warning.

Bronskill et al. [566] reported the difference in rate of antipsychotic prescription and the consequences of that. Average antipsychotic dispensing ranged from 11.6% in the lowest quintile to 30.0% in the highest. Among residents with no recent hospitalization, all-cause mortality at 30 days was 2.5% in the lowest compared with 3.3% in the highest quintile and at 120 days was 9.3% compared with 11.7%. Residents were at increased risk of death simply by being admitted to a facility with a higher intensity of antipsychotic drug use, despite similar clinical characteristics at admission.

Kales et al. [567] compared in a retrospective cohort study the mortality rates in the year following new antipsychotic medication starts for neuropsychiatric symptoms of dementia with rates after starts of other psychiatric medications. All groups taking antipsychotics had significantly higher mortality rates (22.6% to 29.1%) than patients taking non-antipsychotic medications (14.6%). Adjusted mortality risks for atypicals and for combined atypical and conventional antipsychotics were similar to those for conventional antipsychotics. The mortality risk was significantly lower for non-antipsychotic medications than conventional antipsychotics. Except for anticonvulsants, the adjusted risks for all individual classes of non-antipsychotics were significantly lower than the risk for antipsychotics. Mortality risks did not change over 12 months. The proportions of patients taking antipsychotics who died from cerebrovascular, cardiovascular, or infectious causes were not higher than the rates for those taking non-antipsychotic psychiatric medications. The authors concluded that the association between mortality and antipsychotics is not well understood and may be due to a direct medication effect or the pathophysiology underlying neuropsychiatric symptoms that prompt antipsychotic use.

4.9.1.9. Antipsychotics and cognition

There are some concerns that antipsychotic use may worsen cognition in patients with dementia. McShane et al. [568] investigated this issue by performing a two year prospective, longitudinal study with interviews and autopsy follow up. The mean decline in cognitive score (score from expanded MMSE) in the 16 patients who took first-generation antipsychotics was twice that of the patients who did not receive antipsychotics. An increased rate of decline was also associated with aggression, disturbed diurnal rhythm, and persecutory ideas. However, only the use of antipsychotics and the severity of persecutory ideas were independently associated with more rapid cognitive decline when all other variables were adjusted for. The start of antipsychotic treatment coincided with more rapid cognitive decline: the median rate of decline was 5 points per year before treatment and 11 points per year after

treatment. Cortical Lewy body pathology did not account for an association between antipsychotic use and the more rapid decline of cognition. In conclusion, antipsychotics used to treat behavioural complications of dementia may worsen already poor cognitive function.

Scharre and Chang [569] performed a pilot study to examine cognition in patients treated with quetiapine. This study provided initial evidence that quetiapine does not significantly worsen cognition in AD outpatients, but Ballard et al. [540] showed that treatment with quetiapine resulted in cognitive decline measured by SIB.

4.9.1.10. Antipsychotics in delirium

Elie et al. [570] performed a retrospective, exploratory, secondary analysis of the association between antipsychotic use and mortality in elderly patients with delirium. The goal of this study was to compare mortality in delirious elderly medical inpatients treated with antipsychotics with those who did not receive antipsychotics. 326 elderly hospitalized patients were identified with delirium at an acute care community hospital. A nested case-control analysis was conducted on this cohort. Cases consisted of all patients who died in hospital within eight weeks of admission. Each case was matched for age and severity of illness to patients (controls) alive on the same day post-admission. Conditional logistic regression was used to assess the impact of exposure to antipsychotics on mortality. Covariates used for adjustment were the Charlson comorbidity score and the acute physiology score. 111 patients received an antipsychotic. A total of 62 patients died, 16 of whom were exposed to an antipsychotic. The OR of association between antipsychotic use and death was 1.53 in univariate and 1.61 in multivariate analysis. In elderly medical inpatients with delirium, the administration of antipsychotics was not associated with a statistically significant increased risk of mortality. Larger studies are needed to clarify the safety of antipsychotic medication in elderly patients with delirium.

4.9.1.11. Antipsychotics and anticholinergic activity

Older individuals with dementia are highly sensitive to the effects of muscarinic receptor blockade. Mulsant et al. [571] randomly assigned patients with probable AD, VaD, or mixed-etiology dementia to treatment with olanzapine or risperidone. Anticholinergic activity was measured with a radioreceptor assay, and plasma levels of antipsychotic medications were determined. Primary outcomes were assessed with the Udvalg for Kliniske Undersøgelser (UKU) scale and for somnolence adverse events; secondary outcome measures included scores on the NPI and other scales. There were no between-treatment differences in the UKU

scale or in somnolence adverse events. Statistically significant improvements from baseline were found for the NPI measures, with no between-treatment group differences. Olanzapine was associated with significant increases from baseline in anticholinergic activity, while risperidone was not; the between-treatment group differences were not statistically significant. Increase in anticholinergic activity was associated with an increase in anticholinergic side effects and slower performance on the Trail Making Test Part A. Higher endpoint anticholinergic activity was associated with higher endpoint scores on several items from the NPI, including delusions, anxiety, and aberrant motor behaviour. Efficacious doses of olanzapine increased anticholinergic activity in older patients with dementia, while similarly efficacious doses of risperidone did not. Patients whose anticholinergic activity increased were more likely to experience anticholinergic side effects and to have worsening in certain cognitive domains. These data suggest that certain patients may be vulnerable to the anticholinergic activity associated with antipsychotic treatment.

4.9.1.12. Antipsychotic drug withdrawal studies

Longitudinal cohort studies [572] and placebo-controlled antispychotic withdrawal studies [573-575] did not indicate benefit from antipsychotic therapy. However, all of the withdrawal studies continued for 3 months or less, leaving some uncertainty regarding long-term symptom outcome. In addition, the largest study did suggest a benefit for treatment with atypical antipsychotics in people with scores greater than 14 on the NPI.

Ballard et al. [576] performed a study with the aim of determining the impact of long-term treatment with antipsychotic agents upon global cognitive decline and neuropsychiatric symptoms in patients with AD. They randomised patients currently prescribed the antipsychotics thioridazine, chlorpromazine, haloperidol, trifluoperazine or risperidone for behavioural or psychiatric disturbance in dementia for at least 3 months. The study was designed as a blinded, placebo-controlled parallel two-group treatment discontinuation trial for 12 months; patients continued with their antipsychotic drug or switched to an identical placebo. The primary outcome was the total Severe Impairment Battery (SIB) score. Neuropsychiatric symptoms were evaluated with the NPI. 165 patients were randomised (83 to continue treatment and 82 to placebo, i.e., discontinue treatment), of whom 128 (78%) commenced treatment (64 continue/64 placebo). Of those, 26 were lost to follow-up (13 per group), resulting in 51 patients per arm analysed for the primary outcome. There was no significant difference between the continued treatment and placebo groups in the estimated mean change in SIB scores between baseline and 6 months. For neuropsychiatric symptoms,

there was no significant difference between the continue treatment and placebo groups in the estimated mean change in NPI scores between baseline and 6 months. Both results became more pronounced at 12 months. There was some evidence to suggest that those patients with initial NPI of at least 15 benefited with respect to neuropsychiatric symptoms from continuing treatment. For most patients with AD, withdrawal of antipsychotics had no overall detrimental effect on functional and cognitive status. Antipsychotics may be considered as maintenance treatment of more severe neuropsychiatric symptoms, but this benefit must be weighed against the side effects of therapy.

Ballard et al. [577] followed up the afore mentioned study because of mounting concerns about increased mortality in patients with AD who are prescribed antipsychotics; however, until now, there have been no mortality data from long-term placebo-controlled trials. They aimed to assess whether continued treatment with antipsychotics in people with AD is associated with an increased risk of mortality. This additional follow-up was done by telephone assessment to establish whether each participant was still alive 24 months after the enrollment of the last participant (range 24 to 54 months). Causes of death were obtained from death certificates. Kaplan-Meier estimates of mortality for the whole study period showed a significantly increased risk of mortality for patients who were allocated to continue antipsychotic treatment compared with those allocated to placebo. The hazard ratio for the ITT group was 0.58 for the ITT population after 12 months. The more pronounced differences between groups during periods of follow up longer than 12 months were evident at specific timepoints (24-month survival 46% vs 71%; 36-month survival 30%vs 59%). There is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medication; these results further highlight the need to seek less harmful alternatives for the long-term treatment of neuropsychiatric symptoms in these patients.

4.9.1.13. Antipsychotics and Public Advisory Warnings

The discussion, if antipsychotics are as dangerous as the FDA and other drug regulatory agencies are presenting in their warnings, was launched anew by Suh [578] who wrote the following:

> "In 2003, Brodaty et al. (2003) reported higher rates of cerebrovascular adverse events (CVAEs) and mortality in patients with dementia-associated agitation and psychosis who were treated with risperidone compared with those receiving placebo in a randomised trial. In 2004, the U.K. Committee on Safety of Medicines (CSM) informed clinicians that risperidone and olanzapine should not be used to treat BPSD

because of increased risk of strokes with both drugs and an increased mortality with olanzapine.

In 2005, the US Food and Drug Administration (FDA) issued a public advisory warning alerting health care providers and the public about new safety information regarding all atypical antipsychotic medications. When 17 placebo-controlled trials relating to the use of olanzapine, arpiprazole, risperidone and quetiapine in dementia patients with BPSD (N=5106) were pooled, the mortality of the drug-treated group was 1.6 or 1.7 times that of the placebo group (4.5% vs 2.6%), predominantly due to heart-related or infectious causes (FDA, 2005; revised 2009)."

Suh, then, discussed *Simpson's paradox*, a statistical paradox, wherein the successes of groups seem reversed when the groups are combined [579]:

"Simpson's paradox occurs when we combine data. If a very large trial is poorly conducted and is part of a meta-analysis, the results of the meta-analysis can be adversely impacted by that trial ("garbage in, garbage out") [580]….Data were combined by agent (i.e. risperidone only, olanzapine only) [581] or even by the supposed same category (i.e. atypical antipsychotics) [30] . There is no rationale for considering all atypical antipsychotics to be the same. Profiles of adverse events vary widely across different atypical antipsychotics. Even sociodemographic and clinical characteristics (i.e. age, gender, levels of cognition and behavioural disturbances) of the active treatment group and the comparator group vary widely across RCTs. In addition, none of the RCTs were initially designed to look for CVEs or mortality… There have been reports from non-experimental studies which contradict those of the U.K.'s CSM and the U.S.A.'s FDA."

Furtheron, Suh referred to the following studies in his arguments against the warnings launched by the FDA. In 2005, Suh and Shah [582] reported results of a one-year prospective study comparing antipsychotic users and antipsychotic non-users in a NH (N=273). They reported that the mortality rate in those who had not received antipsychotics (26.8%) was higher than that in those who had received antipsychotics (20.8%). The mortyality rates of the two groups were statistically significantly different, even after controlling for possible confounding factors.

In 2006, Schneider et al. [547] reported results of a prospective study entitled Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer's Disease (CATIE-AD). In this study doses were adjusted as needed. Neither the incidence of CVE (two cases in the olanzapine group, one in the quetiapine group, one in the risperidone group, one in the

placebo group; p=0.92) nor mortality rates were statistically different in the overall comparison (one case in the olanzapine group, three in the quetiapine group, one in the risperidone group, three in the placebo group; p=0.68). The CATIE-AD study reported that the sum total of the risk/benefit equation of atypical antipsychotic therapy was no greater than that achieved by placebo.

In 2006, Nonino et al. [583] reported that the long-term survival of 294 dementia patients with BPSD treated with atypical antipsychotics may not significantly differ from that of dementia patients not treated with these drugs, using data from a population-based cohort study conducted in Modena, Italy. In 2006 and 2007, Barnett et al. [584] [585] reported a retrospective review of the clinical outcomes of a large cohort of elderly patients admitted to hospital for pneumonia or for dementia. They found no increased risk of mortality in pneumonia patients treated with atypical antipsychotics, and no increased risk for CVE-related hospital admission in dementia patients treated with atypical antipsychotics.

In 2007, Raivio et al. [586] reported results of a two-year prospective study with 254 very frail dementia patients from seven NHs and two hospitals in Finland, which concluded that neither atypical nor conventional antipsychotics increased mortality or hospital admissions among dementia patients.

A population-based retrospective cohort study (1997 to 2002) in Canada that included 11,400 patients found no difference in the rate of strokes requiring hospitalization among users of the conventional antipsychotics, risperidone and olanzapine [560]. The same research group reported an increased risk of death in the use of atypical antipsychotics compared to non-use among dementia patients, using data including the additional year of 2003 [530].

Simoni-Wastila [587] examined retrospectively the prevalence of antipsychotics use and the association of antipsychotics and other drug use variables with hospital events and mortality. A total of 2,363 long-term care (LTC) Medicare beneficiaries, 1999 to 2002, were included in the analysis. Antipsychotic use rose markedly from 1999 to 2002 (26.4% to 35.9%), predominantly due to increased use of atypical agents. After controlling for sociodemographic and clinical factors, antipsychotic use is not related to hospital events (hazard ratio [HR] = 0.98). Antipsychotic use is associated with a slightly reduced mortality (HR = 0.83). The authors suggested that disease and drug burden factors may confound the antipsychotics-mortality relationship. This study provided no evidence of increased hospital events or mortality in LTC residents who use antipsychotic medications.

Suh concluded that *none* of the reports except one [530] support the findings from previous experimental clinical trials. Almost all non-experimental clinical studies have shown no increase in the risk of CVAE and mortality associated with the use of atypical antipsychotics. The results also suggest that they may be associated with a *lower* mortality rate than conventional antipsychotics [531 588 589]. The final word in this case is not said yet, but we think that antipsychotics should be used with precaution as Ballard et al. [577]mentioned in their latest antipsychotic withdrawal trial.

4.9.2. Anticonvulsants

4.9.2.1. Theoretical background for the use of anticonvulsive drugs

Alzheimer's disease is characterized by disruptions in multiple major neurotransmitters like the noradrenergic [590], the cholinergic [591] and serotonergic [592] transmissions in both cortical and subcortical areas of the brain. The damage of serotonergic (5-HT) neurons seemed to be more generalised and more severe than that of noradrenergic neurons. GABA's association with such neuropsychiatric symptoms as anxiety [593], aggression [594] and psychosis [593], as well as its ability to regulate acetylcholine, dopamine, and serotonin, make it a therapeutic target for controlling BPSD.

Rissman et al. [595] described the research that has focused on the role of calcium permeable glutamate receptors in promoting glutamate mediated excitotoxicity in AD cell death. Specifically, an 'over-stimulation' of post-synaptic N-methyl-D-aspartate (NMDA) and alpha-**a**mino-3-hydroxy-5-**m**ethyl-4-isoxazole**p**ropionic **a**cid (AMPA) receptors by glutamate has been demonstrated to induce cell death by calcium-dependent pathways [596]. Approximately 90% of hippocampal neurotransmitter neurons are glutamatergic. The remaining 10% of hippocampal neurons are inhibitory in nature, of which the majority is GABAergic. While the hippocampal glutamatergic cell populations are lost very early in the progression of AD, the hippocampal GABAergic system has been found to be relatively resistant to AD neuropathology. It is reasonable to consider that altered drug responses in elderly individuals may be related to a compensatory modulation of the molecular composition of the GABA-A receptor subunits.

Lanctot et al. [597] reviewed the evidence for change in GABA's function among patients with AD and suggest that the variable findings reflect subtypes of the disease that are possibly manifested clinically by differing behavioural symptoms. GABA, the major

inhibitory neurotransmitter, has long been a target for anxiolytics, hypnotic sedatives, and anticonvulsants.

Carbamazepine (CBZ)

The mechanism of action of CBZ and its derivatives is relatively well understood. Voltage-gated sodium channels are the molecular pores that allow brain neurons to generate action potentials, the electrical events that allow neurons to communicate over long distances. After the sodium channels open to start the action potential, they inactivate, essentially closing the channel. CBZ stabilizes the inactivated state of sodium channels, meaning that fewer of these channels are available to open up, making brain cells less excitable. CBZ has also been shown to potentiate GABA receptors made up of alpha1, beta2, gamma2 subunits. CBZ reduces L-type calcium channel activation by depolarisation, and may block the excitatory transmitter glutamate at NMDA-type receptors.

CBZ has been reported effective in the management of agitation/aggression associated with primary psychiatric disease (schizophrenia, affective disorder) and episodic dyscontrol and interictal and ictal aggression related to temporal lobe epilepsy in children and adolescents. The theoretical reasons and clinical experiences caused the researchers to think whether CBZ could be effective in treating aggression and agitation in dementia too.

Table 4.9.2. Placebo-controlled trials of carbamazepine (CBZ) in the treatment of BPSD (Konovalov 2008), revised.

Name	Subjects	Design	Results (-/+)	Author's conclusion
Chambers et al., 1982	19 female Inpatients	Nonrandom., crossover	Overactivity: - Cogn.funct.: - Poorly tolerated	CBZ is not effective in tx of agitation in dementia
Tariot et al., 1994	25 NH-patients	Nonrandom., crossover (6 weeks)	Low dose; 16 pts improved globally	CBZ can reduce agitation in some patients
Cooney et al., 1996	6 inpatients	Nonblinded, crossover	Aggression significantly reduced	CBZ can be an effective antiaggressive agent in dementia
Tariot et al., 1998	51 NH-patients	Physician monitor and pharmacist were not blinded; randomised (6 weeks)	Significant effect significantly more adverse events	Short-term use of CBZ for agitation can be efficient
Olin et al., 2001	21 outpatients	Physician adjusting dosage was not blinded, randomised (6 weeks)	Not significant difference between groups	CBZ is not effective in the treatment of behavioural symptoms

Placebo-controlled [36 37 598-600] and non-controlled studies [601-604] and case reports [605 606] have investigated the effect of CBZ in the management of agitation and aggression in patients with dementia (Table 4.9.2).

Sink et al. [35] performed a systematic review, excluded three of the placebo-controlled studies because of methodological problems, and concluded that two small RCTs [36 37] of CBZ had conflicting results.

There are some more concerns related to the use of CBZ in this population: central nervous system (dizziness, drowsiness, ataxia), hematologic (aplastic anemia, agranulocytosis), and hepatotoxic adverse effects may occur. In addition, the drug interaction potential with this potent hepatic enzyme-stimulating agent (stimulation of metabolism of phenytoin, warfarin, theophylline, haloperidol, oral contraceptive steroids, and valproate and inhibition of carbamazepine metabolism by macrolides, cimetidine, propoxyphene, isoniazid, fluoxetine, calcium-channel blockers) may make this a difficult agent to use in patients receiving multiple drug therapies. In addition, autoinduction of metabolism can result in decreased effectiveness after the first or second month of therapy.

Oxcarbazepine

Oxcarbazepine (OXC) as an alternative to CBZ with less interaction potential and less side-effects will be revisited in chapter 5.

Valproic acid

On the basis of valproate's anti-aggressivity properties in animal studies and its ability to augment brain GABA and serotonin concentrations, valproate was theoretically a promising agent in the management of agitation/aggression in patients with dementia.

Reports on the use of valproate for treating BPSD in dementia patients have long been dominated by retrospective chart reviews [607 608] and reports or case series [38 609 610].

In a Cochrane Review Lonerghan et al. [611] examined three randomised, placebo-controlled trials that investigated the effect of valproic acid on older people with dementia who were agitated. Meta-analysis of the pooled results of the included trials could not be performed because of the following problems. According to Porsteinsson [40], the physician who controlled the therapy knew which patients were receiving divalproex. Therefore, the trial did not satisfy the criterion of concealed allocation. In Tariot [612], 54% of the treated patients dropped out compared with 29% of the control patients. Of all treated patients, 22% dropped out because of adverse effects, and the study had to be discontinued prematurely. The third trial [41] had a cross-over design. No results from the first phase of the study were

available, and although the statistical section stated, "the t-test for independent samples is used to analyze the two-period cross-over trial", because the samples were not independent - they are the same patients in the treatment and placebo groups - a question must be raised about the correctness of the analyses. A limited meta-analysis, pooling the results concerning adverse effects [349] [613] revealed the following: sedation occurred more frequently in patients treated with valproic acid than in controls. Urinary tract infection was more common among patients treated with valproic acid than controls. Because of differences in identifying adverse effects, it was not possible to pool other observations concerning adverse effects between the two studies that were examined. They concluded that on the basis of current evidence, valproate preparations cannot be recommended for the treatment of agitation in dementia.

An updated systematic review (October 2008) [614] of two new studies [39] [42] applied meta-analysis to the effect of valproate on agitation in demented patients. This new meta-analysis of pooled results showed no improvement of agitation among valproate-treated patients, compared with controls, and showed an increase in adverse events (falls, infection, gastrointestinal disorders) among valproate-treated patients.

Gabapentin

Gabapentin is structurally related to GABA. It probably acts by interfering with calcium channels to alter transmitter release [615].

One of the first reports of the successful use of gabapentin in the elderly with AD was by Regan and Gordon [616]. Sheldon et al. [617-619] authored promising case reports. Herrmann et al. [620] performed a prospective open-label case-series study with gabapentin including twelve patients with moderate to severe dementia and severe behavioural disorders who were non-responders to previous trials of antipsychotics. Average patient scores for the CMAI and the NPI remained unchanged after treatment with gabapentin. The authors concluded that gabapentin may have a role in treating a subgroup of dementia patients with severe behavioural disorders who have not responded to antipsychotics. Hawkins et al. [621] did a retrospective chart review of 24 NH residents. Gabapentin was used in cases where other anti-aggressive medication (including haloperidol, risperidone, olanzapine, quetiapine, carbamazepine, valproic acid, buspirone and trazodone) failed to control aggressive behaviour. They found that 17 of 22 patients were much or greatly improved; 4 were minimally improved; and only 1 remained unchanged. Two of the 24 patients discontinued use of the medication because of excessive sedation. No other significant side effects were noted in treatment lasting up to 2 years.

4.9.2.2. Reviews and meta-analyses of mood stabilisers

Sink et al. [35] included five RCTs with anticonvulsants in their systematic review [36 37 41 349 612] and concluded: valproate does not appear to be effective for the treatment of neuropsychiatric symptoms of dementia whether in short- or long-acting preparations. In addition, valproate caused significantly more adverse events than a placebo, sedation being the most common. Based on 2 small trials (1 positive and 1 negative), there is currently not enough evidence of benefit to recommend the use of carbamazepine for treatment of neuropsychiatric symptoms, especially in light of the black box warning for hematologic toxicity and the potential drug-drug interactions between carbamazepine and other drugs commonly prescribed to elderly individuals.

Konvalov et al. [622] reviewed the data on the use of anticonvulsant mood stabilisers (carbamazepine, valproic acid, gabapentin, lamotrigine, topiramate) in the treatment of BPSD to determine whether these medications can be recommended for routine clinical use. They analysed a total of seven RCTs (two for carbamazepine and five for valproate). One study showed statistically significant improvement of BPSD in the medication group compared to the placebo group; five studies showed no significant differences; one study showed statistically significant worsening of the symptoms in the medication group vs. placebo. The majority of the studies reported significantly more frequent adverse effects in the medication group. The report concluded that, although clearly beneficial in some patients, anticonvulsant mood stabilisers cannot be recommended for routine use in the treatment of BPSD.

The newest update over the use of anticonvulsants in agitation and aggression in dementia was authored by Amann et al. [623]. They concluded, as other authors already had done, that the data on anticonvulsants used by patients with dementia and behavioural disturbances are not convincing.

4.9.3. Serotonergic agents

In this part, we will present the use of serotonergic agents as treatment for agitation.

Trazodone

Trazodone has specific but complex effects on the serotonergic system (mixed serotonin agonist and antagonist effects) and has a lesser effect on dopamine, histamine and cholinergic systems. It has a sedative and hypotensive effect due to α-adrenergic antagonism. The use of trazodone for the treatment of behavioural disturbances in dementia was examined in two uncontrolled studies with a total of 38 patients. 84% experienced at least mild improvement

and 32% were described as markedly improved [624] [625]. In a structured approach for selecting pharmacotherapy [626], 11 patients in a NH got trazodone in doses ranging from 50 to 100 mg/day (mean dosage 70 mg/day). Nine of the patients demonstrated satisfactory treatment responses as shown by a decreased BEHAVE-AD score of 30% or more (average BEHAVE-AD scores at baseline and 1 month after treatment were 13 +/- 4 and 4 +/- 3, respectively), and no clinical side effects were observed.

In the Cochrane Database of Systematic Reviews, the evidence of the use of trazodone for agitation in dementia is described [627]. Only two randomised studies comprising 104 participants with dementia met the inclusion criteria: Teri et al. [628] and Lebert et al. [629]. The authors' conclusion was: there is insufficient evidence to recommend the use of trazodone as a treatment for behavioural and psychological manifestations of dementia. In order to assess effectiveness and safety of trazodone, longer-term randomised controlled trials are needed, involving larger samples of participants with a wider variety of types and severities of dementia.

Fluvoxamine

In a double-blind, controlled trial comparing fluvoxamine with a placebo given to 46 patients with dementia, there were no significant benefits in the fluvoxamine group compared to the placebo group [630].

Citalopram

Nyth and Gottfries [631] performed a Nordic multicentre study investigating the clinical efficacy of citalopram in the treatment of emotional disturbances in dementia disorders. In this multicentre study, the clinical efficacy of citalopram was investigated in 98 patients with moderate AD or VaD using a combined double-blind and open technique with placebo and citalopram. Analyses were made for each diagnosis after four weeks of double-blind treatment. Patients with AD treated with citalopram showed a significant reduction in emotional bluntness, confusion, irritability, anxiety, fear/panic, depressed mood and restlessness. Those improvements were not found after treatment with a placebo. There were no significant improvements in patients with VaD. No improvements were recorded in motor or cognitive impairment. Citalopram provoked few and comparatively mild side-effects. None of the changes observed during the double-blind withdrawal period were identified as withdrawal symptoms or rebound phenomena.

Pollock et al. [632] conducted a double-blind, placebo-controlled study to compare the acute efficacy of the selective serotonin reuptake inhibitor (SSRI) citalopram and the

antipsychotic perphenazine with placebo for the treatment of psychosis and behavioural disturbances in non-depressed patients with dementia. Eighty-five hospitalized patients with at least one moderate to severe target symptom (aggression, agitation, hostility, suspiciousness, hallucinations, or delusions) were randomly assigned to receive either citalopram, perphenazine, or a placebo under double-blind conditions for up to 17 days. Patients treated with citalopram or perphenazine showed statistically significant improvement on several Neurobehavioural Rating Scale factor scores. Compared to those receiving a placebo only patients treated with citalopram showed significantly greater improvement in their total Neurobehavioural Rating Scale score, as well as in the scores for the agitation/aggression and lability/tension factors. Side-effect scores were similar among the three treatment groups. In another study, Pollock et al. [633] compared citalopram with risperidone in a 12-week randomised, controlled trial in non-depressed patients with dementia hospitalised because of behavioural symptoms (N=103). Participants were consecutively recruited on an inpatient unit if they had at least one moderate to severe target symptom (aggression, agitation, hostility, suspiciousness, hallucinations, or delusions). Once they improved sufficiently, they were discharged to NHs, personal care homes, or residential homes for continued treatment. Completion rates did not differ for citalopram and risperidone (overall completion rate: 44%). Agitation symptoms (aggression, agitation, or hostility) and psychotic symptoms (suspiciousness, hallucinations, or delusions) decreased in both treatment groups but the improvement did not differ significantly between the two groups. There was a significant increase in side-effect burden with risperidone but not with citalopram, such that the two groups differed significantly. The authors concluded that these findings need to be replicated before citalopram or other serotonergic antidepressants can be recommended as alternatives to antipsychotics for the treatment of agitation or psychotic symptoms associated with dementia.

Previous trials have shown reductions with SSRI treatment in impulsive aggression in subjects with personality disorders, decreases in irritability in non-depressed AD patients, and significantly greater improvements in behavioural symptoms in non-depressed dementia patients treated with citalopram compared with placebo. Siddique et al. [634] analysed data of patients who were enrolled in CATIE-AD. Of the 421 patients enrolled, 44 were started on a placebo and were, after phase 1 (36 days), randomly assigned to citalopram treatment. There were data available for 34 subjects who took a placebo for at least 14 days. In this citalopram group, there was a 60% reduction in irritability and apathy scores without sedation, no effect on scores for delusions, and a clinically insignificant drop in scores for hallucinations.

The National Institute on Aging intends to start a multi-centre randomised placebo-controlled clinical trial study of citalopram for the treatment of agitation in AD. It will also investigate pharmacogenomic, genetic, and clinical predictors of response to citalopram therapy. The arguments for this study are that selective serotonin reuptake inhibitors (SSRIs) show promise as a treatment for agitation in AD, based on evidence of a link between agitation and brain serotonin system abnormalities in AD patients, and on preliminary clinical data from RCTs in which citalopram was superior to perphenazine, risperidone and a placebo.

Sertraline

Finkel et al.'s [635] study was a randomised, placebo-controlled study. Patients with probable or possible AD, and a NPI total score greater than 5 (with a severity score of at least 2 in at least one domain), were treated with donepezil (5 to 10 mg) for 8 weeks, then randomly assigned to 12 weeks of double-blind augmentation therapy with either sertraline (50 to 200 mg) or placebo. Primary efficacy measures were the 12-item NPI and the Clinical Global Impression Improvement (CGI-I) and Severity (CGI-S) scales. Twenty-four patients were treated with donepezil and sertraline and 120 patients treated with donepezil and placebo. There were no statistically significant differences at the endpoint of three primary efficacy measures. Sertraline augmentation was well tolerated in this sample of AD outpatients. In addition, post hoc analyses demonstrated a modest but statistically significant advantage of sertraline over placebo augmentation, and a clinically and statistically significant advantage in a sub-group of patients with moderate-to-severe behavioural and psychological symptoms of dementia.

4.9.3.1. Reviews

A Cochrane review [636] elucidated the evidence of the use of antidepressants for depression in dementia. They concluded that

> "available evidence offers weak support to the contention that antidepressants are an effective treatment for patients with depression and dementia. However, only three studies are included in the meta-analysis relating to efficacy, and sample sizes are small. Moreover, only one of the studies included in the analysis of efficacy data investigated the properties of the more commonly used selective serotonin reuptake inhibitors and no studies investigated the properties of newer classes of antidepressants (e.g. selective noradrenergic reuptake inhibitors). This review draws attention to the paucity of research and evidence in this area. It is not that

antidepressants are necessarily ineffective but there is not much evidence to support their efficacy either."

A new systematic review "Antidepressants for agitation and psychosis in dementia" is under elaboration by Seitz et al. from the Dementia and Cognitive Improvement Group, Canada. Sink et al. [35], see Table 4.9.3, described five RCTs; we added the trial performed by Pollock et al. in 2007 [633]. Sink et al.'s conclusion was that although serotonergic agents are

Figure 4.9.3. Studies of antidepressants : Outcomes (Sink 2005), edited.

Source	**Drug**	**Number of partici-pants**	**Outcomes**	**Significance of primary outcome Statistic. - Clinical**		**Adverse events and comments**
Auchus & Bissey-Black 1997	Haloperidol, Fluoxetine, Placebo	15 outpatients	No positive effect for CMAI, CSI BEHAVE-AD	No		Haloperidol + Fluoxetine groups more AE
Teri et al. 2000	Trazodone, Haloperidol, BMT	149 Outpatients (16 weeks)	No difference	No		No significant differences in AE
Pollock et al. 2002	Citalopram, Perphenazine, Placebo	84 hospitalised patients (17 days)	Significant effect for NRS total, agitation	Yes	Possibly	52% Citalopram and 57% Placebo patients dropped out
Lyketsos et al. 2003	Sertraline,	44 outpatients (12 weeks)	No difference in NPI total	Depression: yes Agitation: no		No significant differences in AE
Finkel et al. 2004	Sertraline + Donepezil	24 outpatients	No difference NPI, CGIC, CMAI, BEHAVE-AD	No	Probably	12% dropped out in both groups due to AE
	Donepezil + Placebo	120 outpatients (8 weeks)				
Pollock et al. 2007	Citalopram, Risperidone, Placebo	103 Hospitalised patients (12 weeks)	NRS,	No	Possibly	Significant increase of AE with risperidone

References: [628] [632] [633] [635] [637] [638] AE: Adverse events; BEHAVE-AD: Behavioural Pathology in Alzheimer's Disease rating scale; BMT: Behaviour Management Techniques; CGIC: Clinical Global Impression of Change; CMAI: Cohen-Mansfield Agitation Inventory; CSI: Community Screeing Instrument; NRS: Neurobehavioural Rating Scale;

well tolerated, they do not appear to be very effective in the treatment of neuropsychiatric symptoms. In the light of the results from Pullock et al.'s study from 2007, the use of cipramil as treatment against agitation may be judged more favourably.

4.9.4. Acetylcholinesterasis inhibitors

Acetylcholinesterasis inhibitors (AChEI) are used to slow down cognitive and functional decline in AD. Furthermore, trials showed that they may have some effect in reducing BPSD. This will be elucidated in the following.

Donepezil

Tariot et al. [211] performed a 24-week, randomised, multicentre, double-blind, placebo-controlled trial. Two hundred and eight nursing-home patients with a diagnosis of probable or possible AD, or AD with cerebrovascular disease were randomised to the trial; the mean age was 85.7 years. The primary outcome measure was the NPI-NH-12 total score. Eighty-two per cent of donepezil - and 74% of placebo-treated patients completed the trial. Eleven perm cent of donepezil - and 18% of placebo-treated patients withdrew because of AEs. Mean NPI-NH 12-item total scores improved relative to baseline for both groups, with no significant differences observed between the groups at any assessment. No significant differences were observed between the groups on the Physical Self-Maintenance Scale (PSMS). Overall rates of occurrence and severity of AEs were similar between the two groups (97% placebo, 96% donepezil). Patients treated with donepezil maintained or improved in cognition and overall dementia severity in contrast to placebo-treated patients who declined during the 6-month treatment period. The authors concluded that given the apparent improvement in behaviour in the placebo group, and the high use of concomitant medications in both groups, the impact of donepezil on behaviour in the nursing-home setting is unresolved and merits further investigation.

Feldman et al. [219] randomised 290 patients to treatment in a 24-week, double-blind, placebo-controlled trial. Patients received either 5 mg/day donepezil for the first 28 days and 10 mg/day thereafter as per the clinician's judgement (n=144) or a placebo (n=146). Patients receiving donepezil showed benefits on the CIBIC+, compared with a placebo, at all visits up to week 24. All other secondary measures, including the MMSE, Severe Impairment Battery (SIB), Disability Assessment for Dementia (DAD), Functional Rating Scale, and the NPI, showed significant differences between the groups in favour of donepezil at week 24. Eighty-four per cent of donepezil- and 86% of placebo-treated patients completed the trial. 8% of

donepezil- and 6% of placebo-treated patients discontinued because of AE. These data suggest that donepezil has a significant effect on BPSD in more advanced stages of AD.

Gauthier et al. [221] performed a sub-analysis of a double-blind, placebo-controlled trial to examine the prevalence of behavioural symptoms in moderate to severe AD, and the effect of treatment with donepezil. Two hundred and ninety patients with moderate to severe AD (MMSE scores 5-17) were randomised to receive 24 weeks of 5 mg/day daily doses of donepezil for 28 days, and 10 mg/day thereafter per the clinician's judgment. The outcome measure of interest was the 12-item NPI. At baseline, the most common symptoms were apathy/indifference (67%), aberrant motor behaviour (53%), depression/dysphoria (52%), anxiety (49%), and agitation/aggression (45%). NPI individual item change from baseline scores at Week 24 using a LOCF analysis showed benefits with donepezil treatment compared with placebo for all items, with significant treatment differences for depression/dysphoria, anxiety, and apathy/indifference. When patients who were not receiving psychoactive medications at baseline were analysed separately, significant improvements in NPI 12-item total score were observed with donepezil compared with placebo at most visits and at Week 24 LOCF. The agitation/aggression sub-score showed, however, no significant response to treatment with donepezil.

Holmes et al. [639] conducted a study to determine the efficacy of donepezil in the treatment of neuropsychiatric symptoms in patients with Alzheimer disease (AD) in a randomised withdrawal study. Patients with mild to moderate AD with marked neuropsychiatric symptoms at baseline (NPI > 11 points) were treated openly with donepezil 5 mg daily for 6 weeks followed by 10 mg daily for a further 6 weeks. Patients were then randomised (60:40) to either placebo or 10 mg donepezil daily. All patients were assessed at 6 weeks and provided there was no marked cognitive deterioration their blinded treatment was continued for a further 6 weeks. NPI and carer distress were assessed at 6 weekly intervals throughout the study. A total of 134 patients participated. Following randomisation patients who continued on donepezil 10 mg for 12 weeks had improvements in NPI compared with the placebo group and in NPI-Distress scores. During the open-label phase the total NPI and NPI-Distress scores were lower after 12 weeks treatment with open label donepezil compared with baseline (total NPI 22 points vs13 points; NPI-Distress 13.5 vs 7.9 points). In the open-label phase all domains of the NPI (with the exception of elation) were improved (all $p < 0.05$ after Bonferroni correction). The conclusion was that donepezil has a significant effect in the treatment of neuropsychiatric symptoms in patients with mild to moderate AD.

Cummings et al. [460] conducted an exploratory analysis of data pertaining to the efficacy of donepezil treatment of patients with severe behavioural disturbances. Most patients included in clinical trials have had low levels of psychopathology at baseline, and the effect of cholinesterase inhibitors on patients with more severe behavioural disturbances is unknown. The authors report the effects of donepezil on behavioural disturbances in patients with relatively severe psychopathology at baseline. This is a hypothesis-driven secondary analysis of a three-phase study involving donepezil and sertraline. In phase 1, psychotropic agents were withdrawn; in phase 2, patients were treated in an open-label fashion with donepezil for 8 weeks; and in phase 3, patients on donepezil were randomised to receive placebo or sertraline for an additional 12 weeks. The data set that was analysed comprised patients treated with donepezil (without sertraline) for 20 weeks. One hundred twenty patients were included in the analyses. Mean age was 76 years, average Mini-Mental State Examination Score was 18, and mean Neuropsychiatric Inventory (NPI) total score was 30. Primary efficacy assessments were the NPI, the Clinical Global Impression-Improvement, and the Clinical Global Impression-Severity scales. Secondary measures included the BEHAVE-AD, the Hamilton Depression Rating Scale, and the Alzheimer's Disease Functional Assessment and Change Scale. The total score of the NPI was significantly reduced over the 20 weeks of therapy with donepezil. Sixty-two per cent of patients had at least a 30% reduction in the total NPI score (significantly greater than the number with no meaningful response). Likewise, more patients had total or partial resolution of depression and delusions than those who had no meaningful change. The results of these analyses suggest that donepezil reduces behavioural symptoms, particularly mood disturbances and delusions, in patients with AD with relatively severe psychopathology.

Howard et al. [640] randomly assigned 272 patients with AD who had clinically significant agitation and no response to a brief psychosocial treatment programme to receive 10 mg of donepezil per day (128 patients) or a placebo (131 patients) for 12 weeks. The primary outcome was a change in the score on the CMAI at 12 weeks. There was no significant difference between the effects of donepezil and those of the placebo on the basis of the change in CMAI scores from baseline to 12 weeks. Twenty-two of 108 patients (20.4%) in the placebo group and 22 of 113 (19.5%) in the donepezil group had a reduction of 30% or greater in the CMAI score. There were also no significant differences between the placebo and donepezil groups in scores for the NPI, or the Clinician's Global Impression of Change.

Birks et al. [641] authored a Cochrane review including 24 trials, involving 5,796 participants, of which 15 reported results in sufficient detail for the meta-analyses. Most trials

lasted 6 months or less. Patients in 20 trials had mild to moderate disease, in two trials moderate to severe, and in two severe disease. People with mild, moderate or severe dementia due to AD, treated for periods of 12, 24 or 52 weeks with donepezil, experienced benefits in cognitive function, performing the activities of daily living and behaviour but not on the quality of life score.

Rivastigmine

Some studies showed that rivastigmine is better tolerated and has a better effect than donepezil [642] [643]. Donepezil is a selective acetylcholine esterase (AChE) inhibitor, while rivastigmine inhibits both AChE and butyrylcholine esterase (BuChE). Analysis of response by BuChE genotype suggested that this differential effect may be due to the inhibition of BuChE, in addition to AChE, by rivastigmine [644].

Cummings et al. [645] enrolled a total of 173 patients in a study. After 26 weeks of rivastigmine treatment, patients showed statistically significant improvements of NPI sub-scores from baseline (delusions, hallucinations, agitation, apathy/indifference, irritability/lability, aberrant motor behaviour, nighttime disturbances, and appetite/eating changes). The study was open label and not restricted to patients with behavioural disturbances at baseline, which limit the results.

Burn et al. [646] included a total of 541 PDD patients in a study, 188 with visual hallucinations (118 on rivastigmine, 70 on a placebo) and 348 with non-visual hallucinations (239 on rivastigmine, 109 on a placebo). Greater behavioural benefits in the hallucinating sub-group were evident on NPI-10 individual items, as well as overall NPI-10 change from baseline. The baseline mean NPI-10 score was, however, twice as high in the visual hallucinating sub-group compared with the non-hallucinating sub-group, raising the possibility of a ceiling effect to account for the intergroup difference in efficacy. Although the study was not powered to detect significant differences on the individual NPI items, a significant treatment effect was noted on one item: agitation/aggression. Low patient numbers reporting symptoms captured by other individual items on the scale might have contributed to non-significant effects on other items such as apathy. Visual hallucinations may appear to predict more rapid decline and possibly greater therapeutic benefit from rivastigmine treatment in PDD.

Emre et al. [647] reviewed data from large, placebo-controlled clinical trials conducted with rivastigmine in patients with PDD and AD to evaluate similarities and differences in response to treatment. In placebo groups, AD patients appeared to show more rapid cognitive

decline than those with PDD. Treatment effects (rivastigmine versus placebo) on cognitive performance over 6 months were quantitatively similar in both populations, but qualitatively different: in AD, cognitive abilities were stabilized by rivastigmine compared to declines in placebo groups, whereas in PDD symptomatic improvements above baseline drove treatment effects while placebo patients had limited change. In the activities of daily living, stabilization (rather than improvement) was observed in both dementia types. A more aggressive course of placebo decline, and greater treatment differences (rivastigmine versus placebo), were seen in sub-populations of both PDD and AD patients with hallucinations at baseline. The safety and adverse event profiles were comparable in the two populations. In conclusion, the magnitude of effect with rivastigmine versus placebo is quantitatively comparable in patients with AD and PD, but the treatment effect tended to be one of stabilization in AD, while in PDD improvements over baseline were seen. In both populations, hallucinations may identify patients who are likely to be more treatment-responsive.

Birks et al. [648] included in a Cochrane review analysis nine trials, involving 4,775 participants. They concluded that rivastigmine appears to be beneficial for people with mild to moderate Alzheimer's disease. In comparisons with placebo, improvements were seen in the rate of decline of cognitive function, performance of the activities of daily living, and the severity of the dementia with daily doses of 6 to 12 mg. Adverse events were consistent with the cholinergic actions of the drug. Two studies assessed behavioural disturbance using the NPI-10 and NPI-12; there was no difference between rivastigmine and placebo.

Galantamine

Tariot et al. [649] reported the results from a 5-month multicentre, placebo-controlled, double-blind trial. Following a 4-week placebo run-in, patients were randomised to one of four treatments: a placebo or galantamine escalated to final maintenance doses of 8, 16, or 24 mg/day. Compared with placebo, the galantamine 16- and 24-mg/day groups also had a significantly better outcome on CIBIC-plus, performing the activities of daily living, and behavioural symptoms.

Wilkinson et al. [650] performed a post hoc analysis on pooled data from four pivotal studies in patients with 'advanced moderate' AD: baseline MMSE mean score 11 or Alzheimer's Disease Assessment Scale-cognitive sub-scale (ADAS-cog) mean score 39. Over 5 to 6 months, cognitive abilities were improved with galantamine versus placebo. Cognitive and functional abilities were maintained around baseline; behavioural symptoms were

delayed. Over 6 months, galantamine provided a broad spectrum of benefits to patients with 'advanced moderate' AD.

Cummings et al. [651] assigned 978 patients with mild to moderate Alzheimer's disease to placebo or galantamine (8, 16, or 24 mg/day). Behavioural changes were the primary outcome and were assessed with the NPI, and alterations in carer distress were measured by the NPI distress scale. Data collected at baseline and 12 and 21 weeks postbaseline were analysed. NPI scores worsened with the placebo, whereas patients treated with 16 or 24 mg/day of galantamine had no change in total NPI scores. Treated patients, asymptomatic or symptomatic at baseline, had better NPI sub-scale scores than did patients receiving the placebo. Behavioural improvement in patients symptomatic at baseline ranged from 29% to 48%. Changes were evident in patients receiving 16 or 24 mg/day of galantamine. High-dose galantamine was associated with a significant reduction in carer distress. Galantamine therapy was associated with reduced emergence of behavioural disturbances and improvement in existing behavioural problems in patients with mild to moderate Alzheimer's disease.

Suh et al. [652] enrolled a total of 300 patients (76, 78, 80, and 66 patients in the 8-, 16-, 24-mg/d and community control groups, respectively). Significant improvements in all 3 treatment groups were observed in mean BEHAVE-AD, and CIBIC-plus scores. Galantamine was relatively well tolerated. This study found that galantamine effected significant benefits on the cognitive, functional, and behavioural symptoms of mild to moderate AD. The tolerability results suggest that galantamine is well tolerated in these patients.

4.9.4.1. Combination therapy

Tariot et al. [653] performed the first study combining a cholinesterase inhibitor with memantine. They hypothesised that administration of memantine to patients with moderate to severe AD receiving stable donepezil therapy would result in clinical benefit and would be safe and well tolerated. Of the 404 patients who entered the study, 201 were randomised to placebo and 203 were randomised to memantine, added on to donepezil. Specifically, measures of cognitive function, performance of the activities of daily living, behaviour, and clinical global status were significantly improved with memantine compared with the placebo. Treatment with memantine during the 6-month trial in patients with MMSE scores of 5 to 14 resulted in the maintenance of cognitive function (0.9 increase in SIB score compared with baseline), whereas treatment with the placebo was associated with cognitive decline (2.5 decrease in SIB score compared with baseline). McShane [654] commented on this article in

Evidence Based Mental Health and concluded: Memantine significantly improves physical and mental health in people with severe to moderate Alzheimer's taking donepezil.

Atri et al. [655] compared the clinical effectiveness in patients with AD treated with combination (COMBO) therapy consisting of cholinesterase-inhibitor (CI) plus memantine (MEM) versus CI alone versus no treatment with either. Three hundred eighty-two subjects with probable AD underwent serial clinical evaluations at a memory disorders unit. One hundred forty-four subjects received standard care without CI or MEM (NO-RX), 122 received CI monotherapy, and 116 received COMBO therapy with CI plus MEM. The mean follow-up period was 30 months (4.1 visits) and the mean cumulative medication treatment time was 22.5 months. The COMBO group had significantly lower mean annualised rates of deterioration compared with the CI and NO-RX groups. Similar comparisons significantly favoured the CI over the NO-RX group. COMBO therapy slowed cognitive and functional decline in AD compared with CI monotherapy and no treatment. These benefits had small-to-medium effect sizes that increased with time on treatment and were sustained for years.

Lopez et al. [656] performed an observational study investigating the time to NH admission and death in 943 probable AD patients who had at least a 1-year follow-up evaluation. Of these patients, 140 (14.9%) used both ChEIs and memantine, 387 (41%) used only ChEIs, and 416 (44.1%) used neither. The mean follow-up time was 62.3 months. Compared with those who never used cognitive enhancers, patients who used ChEIs had a significant delay in NH admission (HR 0.37); this effect was significantly augmented with the addition of memantine (HR 0.29) (memantine+ChEI vs ChEI alone). ChEIs alone, or in combination with memantine had no significant association on time to death. This study revealed that the addition of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine to the treatment of AD with ChEI significantly altered the treated history of AD by extending time to NH admission by factor 3.5.

4.9.4.2. Reviews and consensus statements

Trinh et al. [657] conducted a systematic review and meta-analysis to quantify the efficacy of cholesterinase inhibitors for neuropsychiatric and functional outcomes. Ten trials included the ADAS-noncog and six included the NPI. Compared with the placebo, patients randomised to cholinesterase inhibitors improved 1.72 points on the NPI, and 0.03 points on the ADAS-noncog. For functional outcomes, 14 trials used ADL and 13 trials used IADL scales. There was no difference in efficacy among various cholinesterase inhibitors. The results indicated

that cholinesterase inhibitors have a modest beneficial impact on neuropsychiatric and functional outcomes for patients with AD.

Burns et al. [658] authored a consensus statement from the British Association for Psychopharmacology. They concluded that there is type 1b evidence for AChEIs for the treatment of people with Lewy body disease (particularly neuropsychiatric symptoms).

Birks et al. [659] performed a Cochrane review of 13 randomised, double- blind, placebo-controlled trials and could demonstrate that treatment for periods of 6 months and one year, with donepezil, galantamine or rivastigmine at the recommended dosage for people with mild, moderate or severe dementia due to AD produced improvements in cognitive function. Benefits of treatment were also seen on measures of performance in the activities of daily living and behaviour. None of these treatment effects are large. It was not possible to identify those who will respond to treatment prior to treatment.

Raina et al. [660] performed a large review of 96 publications representing 59 unique studies. Both cholinesterase inhibitors and memantine had consistent effects in the domains of cognition and global assessment, but summary estimates showed small effect sizes. Outcomes in the domains of behaviour and quality of life were evaluated less frequently and showed less consistent effects. Most studies were of short duration (6 months), which limited their ability to detect delay in onset or progression of dementia. Three studies directly compared different cholinesterase inhibitors and found no differences in cognition and behaviour. Of the 9 studies that evaluated behaviour, all but 1 used the NPI. Summary estimates for this outcome were not significant in patients with AD.

Rodda et al. [661] did a systematic review of randomised, placebo-controlled trials of donepezil, rivastigmine and galantamine to answer whether cholinesterase inhibitors are effective in the management of the BPSD of dementia in AD. Fourteen studies were identified that matched the inclusion criteria. Nine were of donepezil, three of galantamine and two of rivastigmine. Median study treatment length was 24 weeks (range 12 to 170). Most studies used the NPI as a behavioural outcome measure although three used specific scales for either agitation or apathy. Four studies were specifically designed to assess behavioural outcomes whilst in the majority of studies behavioural outcomes were only secondary measures. Three studies found statistically significant, albeit modest, differences in the change of NPI total score between drug and placebo. The interpretation of the results of many studies is limited by methodological considerations, including generally low NPI scores at baseline and the investigation of BPSD as secondary outcomes. The evidence base regarding the efficacy of cholinesterase inhibitors in BPSD is limited, in part due to methodological considerations. In

the absence of alternative safe and effective management options, the use of cholinesterase inhibitors is an appropriate pharmacological strategy for the management of BPSD in Alzheimer's disease.

4.9.5. Memantine

Memantine is a low- to moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and has a totally different pharmacological target than the cholinesterase inhibitors. It may prevent excitatory neurotoxicity in dementia.

The objective of Cummings et al. [662] was to investigate the behavioural effects of memantine in moderate to severe AD. The authors conducted an exploratory analysis of a 24-week, double-blind, placebo-controlled trial comparing memantine (20 mg/day) with a placebo in subjects with moderate to severe AD on stable donepezil treatment. They employed the NPI-NH, administered at baseline, week 12, and week 24, to assess the effects of memantine on behaviour. Global, cognitive, and functional measures were collected and relationships between these assessments and changes in behaviour were determined. Patients treated with memantine had significantly lower NPI total scores than patients treated with placebo. Analyses of the 12 NPI domains revealed significant effects in favour of memantine on agitation/aggression, eating/appetite, and irritability/lability. Of patients who exhibited agitation/aggression at baseline, those treated with memantine showed significant reduction of symptoms compared with placebo-treated patients. Memantine-treated patients without agitation/aggression at baseline evidenced significantly less emergence of this symptom compared with similar patients receiving the placebo. Carers of patients receiving memantine registered significantly less agitation-related distress.

Aarsland et al. [663] aimed to test the safety and efficacy of memantine in patients with PDD and DLB in a parallel-group, 24-week, randomised controlled study of memantine (20 mg per day) versus placebo at four psychiatric and neurological outpatient clinics in Norway, Sweden, and the UK. The primary outcome measure was the CGIC. Seventy-two patients with PDD or DLB were randomly assigned and started treatment: 34 with memantine and 38 with placebo; 56 (78%) completed the study. All withdrawals were owing to adverse events, but the proportion of withdrawals was similar in both groups. At week 24 the patients in the memantine group had better CGIC scores than those taking placebo. With the exception of improved speed on attentional tasks (A Quick Test on cognitive speed - AQT) in the memantine group, there were no significant differences between the groups in secondary outcome measures (NPI, MMSE, DAD). Murat Emre [664] commented on this study and

elucidated some limitations but concluded that "although not conclusive, these results are encouraging, but they await confirmation before memantine can be added to the list of treatments for these patients. A larger, randomised placebo-controlled, multicentre trial including 199 patients with either DLB or PDD has just been completed and the results are being analysed. Should these results of Aarsland and colleagues be confirmed, the choices of treatment for physicians managing such patients might be expanded."

4.9.5.1. Reviews

McShane et al. [665] published the results of a systematic Cochrane review: (1) Moderate to severe AD. Two out of three six-month studies show a small beneficial effect of memantine. Pooled data indicate a beneficial effect at six months on cognition, activities of daily living and behaviour (2.76 points on the 144 point NPI, 95% CI 0.88 to 4.63, P=0.004), supported by clinical impression of change. (2) Mild to moderate AD. Pooled data from three unpublished studies indicate a marginal benefical effect at six months on ITT cognition, which was barely detectable clinically but no effect on behaviour, activities of daily living or OC analysis of cognition. (3) Mild to moderate vascular dementia. Pooled data from two six-month studies indicated a small beneficial effect of memantine on cognition, and behaviour but this was not supported by clinical global measures. (4) Patients taking memantine were slightly less likely to develop agitation (134/1739 [7.7%] versus 175/1873 [9.3%]; OR=0.78, 95% CI 0.61 to 0.99, P=0.04). This effect was slightly larger, but still small, in moderate to severe AD (58/506 [12%] vs 88/499 [18%]; OR=0.6, 95% CI 0.42 to 0.86, P=0.005). There is no evidence either way about whether it has an effect on agitation which is already present.

Wilkinson and Andersen [666] pooled data from 6 randomised, double-blind, placebo-controlled, 6-month studies and a subgroup of patients (867 on placebo, 959 on memantine) with moderate to severe AD (MMSE <20) was analysed. More placebo-treated than memantine-treated patients showed some clinical worsening (28% vs. 18%), and 21% of the placebo-treated patients compared to 11% of the memantine-treated patients had marked clinical detoriation. In this population of moderate and severe AD patients, treatment with memantine was associated with reducing worsening of clinical symptoms in AD during the 6-month study period.

Winblad et al. [212] summarised the efficacy data for memantine by a meta-analysis of 1,826 patients in six trials. Efficacy was assessed using measures of global status, cognition, function, and behaviour (NPI). Results (without replacement of missing values) showed statistically significant effects for memantine (vs. placebo) in each domain. Memantine was

well tolerated, and the overall incidence rates of adverse events were comparable to placebo. This meta-analysis supports memantine's clinically relevant efficacy in patients with moderate to severe AD.

Wilcock et al. [667] reported the results of a pooled analysis of three studies. Sixty percent of the total patient group had baseline symptoms of agitation/aggression, delusions, or hallucinations on the NPI. At both 12 and 24/28 weeks, there was a significant treatment advantage for memantine over placebo for the proportion of patients showing improvement on the defined neuropsychiatric symptom cluster (55.6% vs. 44.4% at week 12; 58.0% vs. 44.8% at week 24/28) and specifically for the treatment of agitation/aggression (55.3% vs. 43.1% at week 12; 61.0% vs. 45.0% at week 24/28). Placebo-treated patients in this population demonstrated an accelerated disease progression for global, cognitive, and functional outcomes, but memantine conferred statistically significant benefit for all measures. Tolerability in this population remained good, and fewer memantine-treated patients than placebo-treated patients withdrew due to adverse events. This post hoc analysis provides important evidence from placebo-controlled trials that memantine may be a safe and effective treatment in AD patients with agitation/aggression or psychosis, who are otherwise prone to rapid progression.

Gauthier et al. [668] performed a pooled data analysis of six 24/28-week, randomised, placebo-controlled, double-blind studies. Of the 2,311 patients included in these studies, 1,826 patients with moderate to severe AD (MMSE <20) were included in this analysis, corresponding to the extended indication for memantine in Europe. In this subgroup, 959 patients received memantine 20 mg/day and 867 received a placebo. Behavioural symptoms were rated using the NPI total and single-item scores at weeks 12 and 24/28. At weeks 12 and 24/28, ITT analysis demonstrated that memantine treatment produced statistically significant benefits over placebo treatment in the NPI total score, and in NPI single items: delusions, hallucinations, agitation/aggression, and irritability/lability, LOCF population. Analysis of the patients without symptoms at baseline indicated reduced emergence of agitation/aggression ($p=0.002$), delusions ($p=0.047$), and disinhibition ($p=0.011$), at week 12, and of agitation/aggression ($p=0.002$), irritability/lability ($p=0.004$), and night-time behaviour ($p=0.050$) at week 24/28 in those receiving memantine. The data suggest that memantine is effective in treating and preventing the behavioural symptoms of moderate to severe AD. Specific persistent benefits were observed on the symptoms of delusions and agitation/aggression, which are known to be associated with rapid disease progression, increased carer burden, early institutionalisation, and increased costs of care.

Grossberg et al. [669] provided an overview of the prevalence, assessment, and treatment of behavioural disturbances in AD, and summarized current knowledge regarding the effects of memantine on the behaviour of community-dwelling patients. They searched EMBASE and PubMed (January 1992 to October 2008) for reports on memantine trials that involved outpatients with moderate to severe AD. All previously unpublished data were obtained from Forest Laboratories, Inc. Behavioural outcomes were assessed in three completed, double-blind, placebo-controlled trials. Overall, patients who received memantine performed better on behavioural measures than those treated with placebo. Post-hoc analyses suggest that memantine treatment was associated with a reduced severity or emergence of specific symptoms, particularly agitation and aggression. Prospective, well-designed trials are warranted to evaluate the efficacy of memantine in patients with significant behavioural symptoms.

4.9.6. Benzodiazepines and others

The GABA receptor comprises various binding sites for GABA, benzodiazepines, barbiturates, and steroids. Each of these sites may be involved in the regulation of GABAergic neurons with respect to its inhibitory effects on other neuronal systems. Administration of exogenous agents that bind specifically to each site on the GABA receptor may be useful in producing or inhibiting typical GABA-related phenotypes, such as anxiety, aggression, and sleep. The benzodiazepine class of drugs has been used for many years to reduce anxiety and promote sleep. Unfortunately, these agents may produce tolerance after long-term use, as well as other side effects such as sedation, dizziness, and ataxia. Therefore, there is a concern with benzodiazepine use among the elderly. Stahl and colleagues [670] showed that a large proportion of AD patients receiving donepezil also received hypnotics for the management of behavioural symptoms.

Alprazolam (Xanor®), lorazepam (Temesta®, Ativan®), clonazepam (Rivotril®), diazepam (Valium®, Stesolid®), oxacepam (Sobril®, Alopam®)

The different benzodiazepines have been tested, on average in small RCTs and chart reports [671-684]. They compared benzodiazepines either to antipsychotics and/or a placebo. With respect to efficacy, the authors did not find significant differences between the medication groups and the placebo.

Meehan et al. [685] published the only RCT using benzodiazepines for acutely agitated patients with dementia. They reported the results using intramuscular lorazepam treatment,

compared with those treated with placebo in a double-blind, randomised study. Significant adverse events noted with lorazepam were drowsiness and dry mouth.

The Dementia and Cognitive Improvement Group from Cochrane is planning a review of benzopdiazepines in dementia, led by Huang from China.

In summary, though many of the benzodiazepines lack data from RCTs, they are widely used in NHs in Norway [13]. To date, there seems to be limited evidence for the use of benzodiazepines in managing BPSD. The primary concern with these agents is the potential for serious adverse events such as confusion, falls, depression of respiration, and they may paradoxically increase agitation in patients with dementia [686] [687]. Consistent with this information, the report published by the Expert Consensus Panel for Agitation in Dementia generally recommended against the use of benzodiazepines except for short-term or occasional use for anxiety symptoms [688].

4.9.7. Beta Blocker

Peskind et al. [208] randomised 31 subjects (age 85, SD 8) with probable or possible AD and persistent disruptive behaviour that interfered with necessary care to propranolol (n=17) or a placebo (n=14) in a double-blind study. Stable doses of previously prescribed psychotropics were maintained at pre-study dose during the study. Following a propranolol or placebo dose titration period, subjects were maintained on the maximum achieved dose for 6 weeks. Primary outcome measures were the NPI and the CGIC. Propranolol augmentation (mean achieved dose 106, SD 38 mg/d) was significantly more effective than the placebo for improving overall behavioural status on the total NPI score and CGIC. Improvement in individual NPI items within propranolol subjects was significant only for ‘agitation/aggression’ and ‘anxiety’, and reached borderline statistical significance favouring propranolol over the placebo only for ‘agitation/aggression’.

4.9.8. Aroma therapy

Ballard et al. [574] randomly assigned 72 people residing in care facilities to aromatherapy with Melissa essential oil (N=36) or a placebo (sunflower oil) (N=36). These patients had clinically significant agitation in the context of severe dementia. The active treatment or placebo oil was combined with a base lotion and applied to patients' faces and arms twice a day by carers. Changes in clinically significant agitation (CMAI) and the QoL indices (percentage of time spent socially withdrawn and percentage of time engaged in constructive activities, measured with DCM) were compared between the 2 groups over a 4-week period of treatment. Seventy-

one patients completed the trial. No significant side effects were observed. Sixty percent (21/35) of the active treatment group and 14% (5/36) of the placebo-treated group experienced a 30% reduction of CMAI score, with an overall improvement in agitation (mean reduction in CMAI score) of 35% in patients receiving Melissa balm essential oil and 11% in those treated with placebo. QoL indices also improved significantly more in people receiving essential balm oil.

Shortly, Burns et al. will publish the Essence study presenting a 24 week placebo-controlled, double-blind trial comparing donepezil, melissa aromatherapy, with a placebo. The study with better blinding showed significant benefits in both therapy groups, but no statistically significant difference between the groups. This raises a question that is relevant in all trials: Is this a negative study or does it demonstrate non-specific benefits?

4.9.9. Different subjects related to drug therapy in dementia

4.9.9.1. Anticholinergic drugs

Medications prescribed to elderly persons often have an anticholinergic effect, as do many commonly used over-the-counter drugs. Anticholinergic medications are known to produce psychomotor and cognitive slowing, especially in older persons.

Mulsant et al. [689] measured the serum anticholinergic activity (SAA), as measured by a radioreceptor assay, in 201 subjects who were randomly selected among the participants in an epidemiological community study, based on their age and sex. Cognitive performance was assessed with use of the MMSE. Serum anticholinergic activity was detectable in 180 (89.6%) participants (range 0.50 to 5.70 pmol/mL). Univariate testing showed a significant association between SAA and MMSE scores. Logistic regression analysis indicated that subjects with SAA at or above the sample's 90th percentile (i.e., SAA >/=2.80 pmol/mL) were 13 times (OR 12.81; 95%CI 1.08-152.39) more likely than subjects with undetectable SAA to have a MMSE score of 24 or below. This confirmed that even low SAA is associated with cognitive impairment.

Nebes et al. [690] found that an elevated SAA was associated with a significant slowing in both gait speed and simple response time. Cumulative anticholinergic burden may be one of the factors contributing to an increased risk of falls in the older population.

Landi et al.'s [691] results confirmed that among old-old subjects the use of anticholinergic drugs is associated with impaired physical performance and functional status.

Chew et al. [692] measured the anticholinergic activity (AA) of 107 medications commonly used by older adults. Six clinically relevant concentrations were assessed for each

medication. The authors presented a list with medications in typical doses administered to older adults, categorising them into ‘no AA’, ‘mild AA’ (AA values less than 5 pmol/mL), ‘moderate AA’ (AA values of 5 to 15 pmol/mL), ‘severe AA’ (AA values exceeding 15 pmol/mL).

Carnahan et al. [693] described the Anticholinergic Drug Scale (ADS) as a measure of drug-related anticholinergic burden and investigated the scale’s associations with serum anticholinergic activity. ADS scores were significantly associated with SAA. Therefore, the ADS may be a clinically useful tool for preventing anticholinergic adverse effects.

4.9.9.2. Inappropriate prescribing

Blix et al. [694] performed a prospective study with the aim of describing the frequency and types of drug-related problems (DRPs) in hospitalised patients, and to identify risk factors for DRPs and the drugs most frequently causing them. The patients used an average of 4.6 drugs on admission. Of the 827 patients, 81% had DRPs, and an average of 2.1 clinically relevant DRPs was recorded per patient. The DRPs most frequently recorded were dose-related problems (35.1% of the patients) followed by need for laboratory tests (21.6%), non-optimal drugs (21.4%), need for additional drugs (19.7%), unnecessary drugs (16.7%) and medical chart errors (16.3%). A multivariate analysis showed that the number of drugs on admission and the number of clinical/pharmacological risk factors were both independent risk factors for the occurrence of DRPs, whereas age and gender were not.

4.9.9.3. Covert medication

Kirkevold and Engedal [695] reported that nearly a quarter (23.5%) of patients in Norwegian nursing-homes who received medications had drugs mixed in food or beverages. Fourteen per cent of the patients in SCUs and nearly 10% of the patients in RUs received medicine blended in food or beverages without their knowledge (covert medication). Compared with patients who were treated openly, a significantly higher proportion of patients who were treated covertly received antipsychotics (20% vs 30%, respectively; $p < 0.001$). In most cases, the decision to administer covert medication was made by the staff together with the physician or by the physician alone (61.4% of occasions in SCUs and 52.8% in RUs). About two-thirds of cases of covert medication had been documented to some extent in the patients' records. Low mental capacity, low ADL function and the presence of agitation and learning disability were associated with covert medication.

4.9.9.4. Drug related problems

Ruths et al. [696] performed a multidisciplinary review of drug use in nursing-home-residents with the aim of identifying the most frequent clinically relevant medication problems and to analyse them according to the drugs involved and types of problems; 2,445 potential medication problems were identified in 1,036 (76%) residents. Psychoactive drugs accounted for 38% of all problems; antipsychotics were the class most often involved. Multiple psychoactive drug use was considered particularly problematic. Potential medication problems were most frequently classified as risk of adverse drug reactions (26%), inappropriate drug choice for indication (20%), and underuse of beneficial treatment (13%).

4.9.10. Summary of chapter 4.9.

Ballard, C. G., Gauthier, S., Cummings, J. L., Brodaty, H., Grossberg, G. T., Robert, P., and Lyketsos, C. G. [697] have published a paper on 'Management of agitation and aggression associated with Alzheimer disease' and concluded that the most widely prescribed pharmacological treatments for these symptoms - atypical antipsychotics - have a modest but significant beneficial effect in short-term treatment (over 6 to 12 weeks) of aggression but limited benefits in longer-term therapy. Benefits are less well established for other symptoms of agitation. In addition, concerns are growing over the potential for serious adverse outcomes with these treatments, including stroke and death. A detailed consideration of other pharmacological and non-pharmacological approaches to agitation and aggression in patients with AD is, therefore, imperative. This article reviewed the increasing evidence in support of psychological interventions or alternative therapies (such as aromatherapy) as a first-line management strategy for agitation, as well as the potential pharmacological alternatives to atypical antipsychotics - preliminary evidence for memantine, carbamazepine, and citalopram is encouraging.

4.10. Oxcarbazepine in the treatment of agitation and aggression in dementia

4.10.1. Pharmacology

Oxcarbazepine (OXC) is a structural derivative of carbamazepine, with a ketone in place of the carbon-carbon double bond on the dibenzazepine ring. This difference helps to reduce the impact on the liver during the metabolising of the drug, and also prevents the serious forms of anemia or agranulocytosis occasionally associated with carbamazepine. In vitro

electrophysiological studies indicated that OXC blocks the voltage-sensitive sodium channels, resulting in stabilization of hyper excited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of OXC with brain neurotransmitter or modulator receptor sites have been demonstrated.

Following oral administration, OXC is completely absorbed and is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect. The half-life of the parent is about two hours, while the half-life of MHD is about nine hours, so that MHD is responsible for most antiepileptic activity. Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. MHD is metabolized further by conjugation with glucuronic acid and cleared from the body mostly by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged OXC. There is a linear correlation between creatinine clearance and the renal clearance of MHD. When OXC (Trileptal®) is administered as a single 300-mg dose in renally-impaired patients (creatinine clearance <30 mL/min), the elimination half-life of MHD is prolonged to 19 hours. Following administration of single (300 mg) and multiple (600 mg/day) doses of Trileptal to elderly volunteers (60 to 82 years of age), the maximum plasma concentrations of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance. No gender-related pharmacokinetic differences have been observed in children, adults, or the elderly.

Clinically significant hyponatremia (sodium <125 mmol/L) can develop during OXC use. In the 14 controlled epilepsy studies, 2.5% of Trileptal-treated patients (38/1,524) had a sodium level of less than 125 mmol/L at some point during treatment, compared to no patients assigned to a placebo or active control. When OXC was discontinued due to hyponatremia patients experienced normalization of serum sodium within a few days without additional treatment.

4.10.2. Oxcarbazepine's (OXC) use in psychiatry

Previous clinical studies in psychiatric disorders, clinical experience, and published individual cases of BPSD [698] [699] indicated that OXC may be an effective alternative to existing treatments in BPSD. This has not been investigated in prospective RCTs. OXC is effective in affective disorders, especially in mania [700] [701]. In Benedetti et al.'s study, OXC was as

effective as haloperidol. OXC was used as add-on therapy to lithium in bipolar disorders, especially mania and mixed states. It has been shown to be significantly more effective than lithium alone in 60 % of the patients [702]. In some recommendations, OXC is preferred to carbamazepine (CBZ) in mania (Texas Guidelines, 2002). OXC has shown a CBZ-like effect [703 704]. CBZ was effective in BPSD [36] and its efficacy and tolerability was not limited to any particular type of dementia [705].

5. Characteristics of the studies included in the thesis

5.1. Background

Dementia is a serious health problem that becomes more prevalent in a population as its average age increases. It is the main reason for institutionalizing elderly people. Disruptive and agitated behaviour affects 30 to 50% of all individuals with dementia at some point in the course of the illness. Such behaviour decreases the quality of life of patients and carers, puts heavy strains on relatives as well as professional carers and poses a diagnostic, therapeutic and economic challenge.

There is a need for new pharmacological and non-pharmacological treatments, because the existing drugs have shown only limited benefits and are associated with poor tolerance and serious side effects. Furthermore, there is a need for validated assessment tools to evaluate patients before therapy and during a follow-up period. Given the daily routine in nursing-homes with many competing demands on staff time brief instruments are preferable.

5.2. Objectives

The thesis had three aims:

1) To evaluate the effect of oxcarbazepine (OXC) in the treatment of severe agitation and aggression in patients residing in nursing-homes with Alzheimer's disease or vascular dementia or a mixture of both.
2) To study the psychometric properties of the Norwegian version of the Brief Agitation Rating Scale (BARS) by performing a factor analysis on a large sample of Norwegian nursing-home patients and testing the reliability and validity on another sample.
3) To test the reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, Nursing-home Version (NPI-NH).

5.3. Design

5.3.1. Main study

This was an eight-week, multicentre, double-blind, randomised, placebo-controlled trial performed independently of the pharmaceutical industry. The pharmaceutical company Novartis donated the supply of the drug, but was neither involved in the study design, analyses, interpretation of the results, nor in the writing of reports or scientific papers. The authors and a protocol committee designed the trial and wrote the protocol (see appendix). For safety reasons and to track adverse events, patients were followed up for an additional 4 weeks after the trial medication had been discontinued. The study was approved by the Norwegian state authorities in charge of regulating research and the Regional Ethics Committee.

Patients were randomly assigned in blocks of four to treatment with 300–900 mg OXC (Trileptal®, Novartis) per day or a placebo in a 1:1 ratio (for study assignment, see Fig. 1). Personalised dosing, similar to Pierre N. Tariot's study, was chosen in view of the limited amount of published data on the safety, tolerance, and efficacy of this agent for this kind of population. Treatment started with 75 mg in the morning and 225 mg in the evening. Doses were increased stepwise, reaching a total daily dose of 900 mg OXC after 3 weeks. For this quite old and frail population, we followed the principles of geriatric medicine and reduced the dose to half of the highest possible dose. Our clinical experience using OXC in elderly patients also led us to use 900 mg as a maximum dose. The highest well-tolerated dose for each patient was maintained for the rest of the study. Dose adjustments were permitted if there were adverse events or other problems. All personnel involved in conducting the study remained unaware of the treatment groups until all the data had been retrieved, double data entry had been checked, a blind review had been performed, and the report of the analysis had been written.

Efficacy assessments were made at baseline and at weeks 2, 4, 8, and 12. The primary efficacy variable was change in the agitation and aggression sub-score of NPI-NH. This sub-score is the product of intensity scores (0–3 points) and frequency scores (0–4 points) and ranges from 0 to 12, with higher scores indicating more severe symptoms. Secondary clinical outcome variables were change in agitation, as measured by the Norwegian version of the Brief Agitation Rating Scale (BARS) and change in the burden of care as measured by NPI-NH. The Norwegian version of BARS is a 10-item scale, for which each score ranges from 1

(never) to 7 (more than once an hour); the total score ranges from 10 to 70, higher scores indicating more frequent symptoms of agitation.

5.3.2. Study of the factor analysis of BARS

We used a set of previously published data from a cross-sectional study that analysed the effect of patient and ward characteristics on the use of restraints in Norwegian nursing-homes, Kirkevold et al. [363], and performed a factor analysis of the BARS.

5.3.3. Study of the reliability and validity of the Norwegian version of the Brief Agitation Rating Scale (BARS) in dementia

We used the existing Norwegian translation of the BARS because it had already been introduced and widely used, especially in clinical trials. It consists of ten items, which are scored from 1 (never) to 7 (several times an hour), retrospectively reporting the frequency of the agitated behaviour during the preceding two weeks. Thus, the sum score may range from 10 to 70. Normally, the total score of BARS is used. Another way is to sum up the scores of the types of agitation related to factors of the BARS. After conducting a factor analysis we identified three factors, 'physically aggressive behaviour', 'physically non-aggressive behaviour' and 'verbal agitation', in a large sample (n=1,870) of Norwegian nursing-home patients. In the present study we used the scores of these three sub-scales in our analysis.

5.3.4. Study of the reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, Nursing-home Version (NPI-NH)

The NPI rates the occurrence, frequency and severity of psychiatric symptoms and behavioural disturbances commonly seen in dementia. The structure and the scoring-rules of the scale have been comprehensively described by Cummings et al., and the validity and the reliability are reported to be satisfactory [706].

The NPI-NH was translated into Norwegian, translated back into the original language, and then harmonized into Norwegian by Aarsland and Dramsdahl according to procedures recommended for the translation of psychometric scales (Aarsland, personal communication).

5.4. Materials

5.4.1. Main study

The patients included both males (29.1%) and females (70.9%) resident in nursing-homes for at least 4 weeks prior to inclusion. They had a median age of 84 years (range: 63–98) and had

received a diagnosis of Alzheimer's disease or vascular dementia according to ICD-10, Diagnostic Criteria for Research [134]. We did not differentiate between Alzheimer's disease and vascular dementia, because it is difficult to discriminate between Alzheimer's disease and vascular dementia in this age-group and in the late stages of dementia [707 708]. We followed Pierre N. Tariot's [36] study design to make our study comparable to the only trial using antiepileptics that showed a significant effect. The dementia was of moderate to severe degree as defined by a Mini Mental State Examination score of 0 to 20 [709], and the patients had a history of agitation or aggression for at least 1 week and a score of ≥ 6 on the NPI-NH sub-scale for agitation and aggression [26 200]. Our definition of agitation and aggression was pragmatic: the sub-scale agitation/aggression of the NPI-NH was used to identify eligible patients. Patients with the following clinical abnormalities were excluded: low sodium serum levels (< 135 mmol/L); severely impaired renal function (creatinine clearance < 30 ml/min, calculated with Cockroft and Gault's formula); or hepatic failure (transaminases γ-GT and ALAT three times or more above the upper normal limit). Furthermore, patients with the following diseases were excluded: AV-block II and III and all kinds of arrhythmia necessitating treatment; severe somatic diseases that might demand a change of medication; severe or acute neurological disease (e.g., epilepsy, acute cerebrovascular events, severe Parkinson's disease, acute confusion) or a severe psychiatric disorder such as bipolar disorder or schizophrenia; dementia other than Alzheimer's disease or vascular dementia. Patients who had participated in another clinical trial during the previous 3 months or who earlier had been randomly assigned to the same study were excluded. Finally, patients were excluded if they had used cholinesterase-inhibitors or memantine for less than 3 months or if any change in the dosage had been introduced during the previous 2 weeks; the following concomitant medications were an exclusion criterion: cyclosporin or strong analgesics such as opioids, like codeines, and all morphines; carisoprodol; antiepileptics or antipsychotics; MAOI or lithium.

Participants were allowed to take 1 g of paracetamol three to four times a day. Those who used a psychotropic drug were not allowed to make any dose changes within 2 weeks before or during the study, nor was the commencement of treatment with new psychotropic medication (except rescue medication with haloperidol) permitted during this period.

5.4.2. Study of the factor analysis of BARS

Data were collected from two samples: The first comprised 1,501 patients in nursing-homes in 54 out of 430 municipalities in Norway. The patients were randomly selected from 222 wards in large, medium and small municipalities in all the four health regions of the country.

The second sample consisted of 425 patients; it included all the patients from four teaching nursing-homes (TNH), and in addition all the patients from two wards of a fifth TNH. Thus the study comprised 1,926 patients in 251 wards, 1,362 patients in 160 regular units (RUs) and 564 patients in 91 special care units, specializing in the care of patients with dementia (SCUs). Further details can be found in Kirkevold *et al*. [363].

5.4.3. Study of the reliability and validity of the Norwegian version of the Brief Agitation Rating Scale (BARS) in dementia

The study of the internal consistency and the test-retest reliability was performed by enrolling 56 patients in three nursing-homes in rural Norway. The mean age of the patients was 85.6 years (SD 6.22); 67.9% were women.

In the validation study, we included 138 patients from six nursing-homes, 56 who took part in the reliability study and an additional 82 who were only included in the validation study. Their mean age was 84.7 years (SD 7.4); 65.9% were women.

5.4.4. Study of the reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, Nursing-home Version (NPI-NH)

5.4.4.1. Reliability study

A sample of 41 patients from a nursing-home in a rural area of Norway was enrolled in the reliability study. The mean age of the sample was 84.3 years (SD 7.38, range 54-97). Seventy-one per cent were female. Eighty-five per cent suffered from dementia (CDR $\geq$ 1).

5.4.4.2. Validity study

A sample of 50 patients from two other nursing-homes in the same area was included in the validation study. The mean age of the sample was 84.4 years (SD 5.50, range 70-94). Sixty-four per cent were female.

5.5. Data Collection

5.5.1. Main study

Patients were recruited from 35 nursing-homes across Norway under the guidance of 15 investigators who had specialised either in geriatric psychiatry or geriatric medicine. Prior to inclusion, the diagnosis of each patient's dementia, mental and physical capacity, and mental health status were assessed. Except for one patient who had the capacity to consent to the

study himself, the legally authorized representatives of the patients gave written informed consent.

Specialized registered nurses from departments of geriatric psychiatry or geriatrics carried out the assessments by interviewing the patients' primary professional carers. In addition, the study nurses always interviewed the same carer. Prior to the study they attended a 1-day training course in the use of the NPI-NH and the BARS. We organised this in order to increase the test-retest reliability. The Norwegian version of NPI-NH was tested for reliability and validity and found excellent [227].

Safety evaluations included recording adverse events, laboratory tests conducted at screening and in weeks 2 and 6, electrocardiography obtained at screening and in week 2, and measurements of blood pressure and pulse rates. Adverse events were coded with the use of a standard glossary related to body systems. A central laboratory conducted all of the laboratory tests; if some results were out of the normal range, a safety manager warned the investigators at the relevant study site by telephone. Concomitant medication and dose changes were recorded.

5.5.2. Study of the factor analysis of BARS

The data were collected during the period March-November 2000. Twelve research nurses were trained to use the interview questionnaires. They carried out a structured interview with the nursing-home member of staff who knew the patient best and the nurses in charge of the wards. The age and gender of each patient were recorded. In addition, the number of beds in the ward, the staff ratio (i.e. the number of patients per staff member on an ordinary morning shift), education level of the staff and whether the ward was organized as a RU or SCU, were recorded. To measure aggression and agitation the BARS was applied. It scores agitation on a 7 point scale: 1=never; 2=once in two weeks; 3=two or more times in two weeks; 4=once a week; 5=two or more times a week; 6=once a day; 7=several times an hour. Carers, who knew the patients well, were interviewed and the symptoms were rated as they occurred over the preceding two weeks. The original American version consists of ten symptoms (hitting, grabbing, pushing, pacing/aimless wandering, repetitious mannerisms, restlessness, screaming, repetitive sentences or questions, making strange noises, complaining) and the total score ranges from 10 to 70. In the Norwegian version of BARS, the item "screaming" differed from the English version, and was rejected in the analysis. Therefore, we performed the analysis of BARS with the remaining nine items. In addition, the patients' level of functioning in the activities of daily living (ADL) were classified with the Physical Self-

Maintenance Scale (PSMS) [710]. The PSMS sum score ranges from 6 to 30; a higher score indicates poorer ADL functioning. The severity of dementia symptoms was categorised by means of the Clinical Dementia Rating Scale (CDR) [711]. The overall score ranges from zero to three; a higher score indicates poorer mental functioning.

5.5.3. Study of the reliability and validity of the Norwegian version of the Brief Agitation Rating Scale (BARS) in dementia

5.5.3.1. Reliability study

The respondents were the nursing-home staff (registered nurses and nursing assistants) who knew the patients well. Staff members were interviewed twice by a psychiatrist (OS) about each patient, using the BARS, with an interval of seven days and preferably with the same respondent for each patient on both occasions. In the second interview, he did not have access to the results of the first interview. Demographic characteristics and ward characteristics were collected.

In addition, patients were tested with the Mini Mental State Examination (MMSE) [709], examining cognitive abilities of patients in different areas (range 0-30), and the Clinical Dementia Rating Scale (CDR) [711], an observational scale that measures the degrees of dementia (categories: no dementia – 0 and 0.5; dementia – 1, 2 and 3, where 3 indicates severe dementia).

5.5.3.2. Validation study

For the validity study, we used the BARS results from the first interview for those who participated in both studies. In addition, we collected the biographical data and applied the following measures: the CDR, the MMSE, the Cornell Scale for Depression in Dementia (CSDD) [238], an observational scale measuring depression in dementia (range 0-38) and the NPI-NH, an observational scale evaluating 12 psychological and behavioural symptoms in dementia (the total score ranging from 0 to 144; and the product score of frequency and intensity ranging from 0 to 12 per item). It has an item called agitation/aggression (NPI-NH/AA) that was used for our analyses.

5.5.4. Study of the reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, Nursing-home Version (NPI-NH)

All of the patients were assessed by a geriatric psychiatrist (GS) or a medical doctor specializing in geriatric psychiatry (OS). Patients went through a physical examination and

data from their medical records were collected. The Mini Mental State Examination (MMSE) was completed. On the basis of these findings and an interview with a carer, the BEHAVE-AD was completed. A diagnosis of dementia and the type of dementia, as well as a diagnosis of major depression, were established according to DSM-IV criteria. Seventy-eight per cent suffered from dementia. Of the patients with dementia, 61.5 per cent had Alzheimer's disease, 28.2 per cent had vascular dementia and 10.3 per cent had other types of dementia. The MMSE scores ranged from 0 to 28, the mean was 14.3 (SD 9.1).

A research nurse, who was blind to the results of the physical examination, interviewed the patient's professional carer, the registered nurse who was most knowledgeable about the patient, using the NPI-NH scale and the Cornell scale [238]. The research nurse and the psychiatrist did not use the same nurse as an informant. The research nurse attended, prior to the interviews, a two-day course on the use of the NPI.

5.6. Ethical and legal considerations

5.6.1. Main study

We distributed three different information letters, one for patients with full mental capacity, one for patients with reduced capacity, and one for the next of kin. Only one patient had the capacity to give consent. Therefore, the next of kin of all the other patients were informed about the study and all the possible risks and disadvantages, like side effects of the drug and that there were restrictions for using other drugs against agitation, and how we planned to make the study as safe as possible. The next of kin had the authority to reject the inclusion of the patient in the trial and also to decide to interrupt his/her participation in the study after it had begun.

Safety evaluations included recording adverse events, laboratory tests conducted at screening and in weeks 2 and 6, electrocardiography obtained at screening and in week 2, and measurements of blood pressure and pulse rates. Adverse events were coded with the use of a standard glossary related to body systems. A central laboratory conducted all of the laboratory tests; if some results were out of the normal range, a safety manager warned the investigators at the relevant study site by telephone. For security reasons and to track adverse events, patients were followed up for an additional 4 weeks after the trial medication had been discontinued.

The study was approved by the Norwegian state authorities in charge of regulating research and the Regional Ethics Committee. The capacity of the patients was evaluated and consents signed.

5.6.2. Study of the factor analysis of BARS

Information on the patients was identified by the year of birth, gender, type of ward and type of nursing-home. No patients or family members were asked any questions or otherwise involved in the study. Identification of the carers, who were interviewed, was not recorded. The Regional Ethics Committee for Medical Research accepted the study design; the Data Inspectorate and the Directorate for Health and Social Affairs approved the procedure.

5.6.3. Study of the reliability and validity of the Norwegian version of the Brief Agitation Rating Scale (BARS) in dementia

The Regional Ethics Committee for Medical Research in Eastern Norway accepted the study design and approved the study. The Data Inspectorate and the Directorate for Health and Social Affairs approved the procedure. All participants, or their next-of-kin, got verbal and written information about the study and signed a consent form.

5.6.4. Study of the reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, Nursing-home Version (NPI-NH)

Information about the reliability study was given in advance to the patients and their family members. Explicit consent was not required for enrolment but the patients or their next of kin were informed that they could refuse to participate at any stage in the study. In the validity study written consent was obtained from those of the patients who were able to consent. In the other cases, family carers confirmed that they did not object to the patient participating in the study. This procedure was approved by the Regional Ethics Committee, the Data Inspectorate and the Directorate for Health and Social Affairs.

5.7. Statistical methods

5.7.1 Main study

The sample size necessary to demonstrate a statistically significant difference between the two treatments was determined prior to beginning the study. The standard deviation of the sub-scale for aggression and agitation in NPI-NH was estimated to be 1.8. Based on a two-sided *t*-test with an assumed difference between the two treatments of 1.2 on the aggression and agitation sub-scale in NPI-NH (for the active drug an estimated reduction of 30% and for

the placebo an estimated reduction of 15%), a total of 78 randomised patients would be needed to detect this difference with 80% power. Adjusting for possible dropouts, we decided to enrol 100 patients in the study. All the patients who received at least one dose of the study medication were included in the primary and safety population and they made up the intention-to-treat population. Patients who dropped out were regarded as lost to follow-up, but the information on them that had already been collected was used in the analysis. A last-observation-carried-forward approach was used for the imputation of missing values. Data were described by the mean and standard deviation; for variables that were not normally distributed, we used the median and the range.

The differences between the treatment groups for primary and secondary variables were analysed by a repeated measures model with an autoregressive covariance structure, including the baseline value as a covariate in the model. The normal distribution assumption was assessed using QQ-plots and histograms of residuals. Statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Cary, NC). An alternative analysis was performed, where the data were treated as categorical and non-parametric methods were used. However, the results were very similar to the results achieved when using the more 'classical approach'.

Table 5.7.1. Materials of the four studies

Materials	**Study I OXC - Plac.**		**Study II RU - SCU**		**Study III Reliab - Valid**		**Study IV Reliab - Valid**	
Number of participants	103		1870		138		91	
	52	51	1353	517	56	138	41	50
Women (%)	67.3	74.5	67.9	74.6	67.9	65.9	71	64
Age in years	83	84	84	83	86	85	84	84

Table 5.7.2. Scales and statistics of the four studies

Study I OBAD	**Study II BARS Factor anal.**	**Study III BARS Reliab - Valid**	**Study IV NPI Reliab - Valid**
NPI-NH, MMSE, BARS	BARS, CDR, CCSD, NPI-NH	BARS, CDR,MMSE CCSD, NPI-NH	NPI-NH, CDR, MMSE, CCSD, BEHAVE-AD
Repeated measures model, Two-sided t-test	Cronbach's α, Principal component analysis (Varimax), linear & multiple regression	Cronbach's α, Spearman's ρ, partial correlation	Cronbach's α, Spearman's ρ, κ -statistic,

5.7.2. Study of the factor analysis of the BARS

All statistical analyses were performed using SPSS version 15.0. First, the distribution of the continuous variables was examined. Second, we conducted preliminary analyses to examine whether any explanatory variable correlated with other variables, causing multicollinearity. These examinations proved that there was no need to exclude any variables from the analyses and that the data set was a reliable basis for performing factor analyses (multicollinearity 0.119; Kaiser-Meyer-Olkin 0.74 and Bartlett's Test of Sphericity < 0.001). Third, we performed an exploratory factor analysis by applying a principal component analysis (PCA) using an orthogonal rotation procedure (Varimax). The number of factors to extract was determined using the eigenvalue ≥1.0 criterion and by examining the 'scree plot'. Factor loadings > 0.40 were considered statistically significant, which left us with three factors.

Cronbach's alpha was calculated to measure the internal consistency of the factors. To validate the factors, we constructed three sub-scales by adding the items in each factor. Because of skewness, we calculated the logarithms of the three scores before we used them as dependent variables in three linear regression analyses.

5.7.3. Study of the reliability and validity of the Norwegian version of the Brief Agitation Rating Scale (BARS) in dementia

All the statistical analyses were performed using SPSS version 15.0. To test the internal consistency of the BARS and the two sub-scales, we used Cronbach's alpha coefficient. The test-retest reliability was examined by measuring the Spearman's rank correlation coefficient rho because the data were not normally distributed.

In the validation study, we examined the correlations between both the BARS total sum and the single BARS items with the NPI-NH/AA and the CSDD sub-scale Agitation (CSDD/A). None of the variables were normally distributed. Therefore, we applied a non-parametric statistic using Spearman's correlation coefficient as a test for the concurrent validity. In a further analysis, we performed a first-order partial correlation analysis and looked at the difference in the correlations between the two test variables, controlling for the stage of dementia as a third modifying variable, to get a more accurate picture of what is happening. In this analysis, we controlled for the different stages of CDR, collapsing together the patients scoring 0, 0.5 and 1 into one group (<2), since the size of the groups would otherwise have been too small to conduct a valid statistical test.

5.7.4. Study of the reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, Nursing-home Version (NPI-NH)

The data were analysed using a SPSS (Statistical Program for Social Science) package version 14.01. We used Cronbach's alpha coefficient as an indicator of the internal consistency of the scale. The inter-rater reliability was established with kappa (κ) statistics. In order to use ordinary κ-statistics we combined NPI frequency scores 1 and 2 into one category. Thus, we had symmetrical 4x4 tables for both frequency and severity. The concurrent validity was analysed by calculating the Spearman correlation coefficients of the NPI sub-scales and the corresponding BEHAVE-AD sub-scales.

6. Abstracts of the papers included in the thesis

Paper I. Effect of Oxcarbazepine in the Treatment of Agitation and Aggression in Severe Dementia

Background/Aims:

To evaluate the efficacy of oxcarbazepine (OXC) in the treatment of agitation and aggression in patients with Alzheimer's disease, vascular dementia or both.

Methods:

This is an eight-week, multicenter, randomised, double-blind, placebo-controlled trial carried out independently of the pharmaceutical industry. Changes in the agitation and aggression sub-score of the Neuropsychiatric Inventory (NPI) were the primary outcomes. The secondary outcomes were the changes in the caregivers' total burden scores (measured by the NPI) and change in the Brief Agitation Rating Scale (BARS).

Results:

In total, 103 institutionalized patients residing at 35 different sites were randomised to the trial. After eight weeks, no statistically significant differences were found between the two groups for all outcomes. A trend was observed in favour of the OXC group in the reduction of the scores on the BARS ($p = 0.07$).

Conclusion:

This study found no significant effect of OXC in treatment of agitation and aggression in patients with dementia.

Paper II. Factor Analysis of the Brief Agitation Rating Scale (BARS) in a Large Sample of Norwegian Nursing-Home Patients

Background:

Agitation and aggression are prevalent in dementia and put heavy strains on caregivers. Validated assessment tools measuring these symptoms are required to evaluate patients before therapy and during the follow-up period. Given the daily routine in nursing-homes, abbreviated instruments are preferable. The Brief Agitation Rating Scale (BARS) is a short form of the Cohen-Mansfield Agitation Inventory (CMAI). Our aim was to examine the Norwegian version of the BARS by performing a factor analysis.

Methods:

The data came from 1,870 nursing-home patients. The primary caregivers were interviewed by research nurses using the Clinical Dementia Rating Scale (CDR), Lawton's Physical Self-Maintenance Scale (PSMS) and the BARS.

Results:

The exploratory factor analysis of the BARS revealed three dimensions: physically aggressive behaviour, physically non-aggressive behaviour and verbal agitation. Linear regression analysis showed that reduced functioning in activities of daily living (ADL) was associated with physically aggressive behaviour and verbal agitation, whereas increased severity of dementia and better ADL functioning were related to physically non-aggressive behaviour. In addition, verbal agitation was positively related to a higher number of drugs being taken per day.

Conclusions:

The factor analyses **c**onfirmed that the Norwegian version of the BARS measures the clinically relevant dimensions of agitation in dementia.

Paper III. Reliability and Validity of the Norwegian Version of the Brief Agitation Rating Scale in Dementia

Objective:

To examine the test-retest reliability and validity of the Norwegian Brief Agitation Rating Scale (BARS), a short form of the Cohen-Mansfield Agitation Inventory (CMAI), assessing the frequency of agitation in dementia.

Methods:

We investigated the internal consistency, the test-retest reliability and the validity of the BARS. In the validity study, we compared the BARS scores with the Neuropsychiatric Inventory – Nursing-Home Version sub-scale Agitation/Aggression (NPI-NH/AA) and the Cornell Scale for Depression in Dementia sub-scale Agitation (CSDD/A).

Results:

In the reliability study, Cronbach's alpha was 0.76; the test-retest reliability of the BARS showed a Spearman's rho of 0.64, but this increased to 0.86 when we deleted the item 'complaining'. In the validation study the BARS score correlated with the NPI-NH/AA and the CSDD/A scores, Spearman's rho was 0.55 and 0.52 respectively. These correlations changed when controlling for the Clinical Dementia Rating Scale (CDR) stages. The highest correlations between the BARS and the NPI-NH/AA and the BARS and the CSDD/A were found among patients with CDR score 2.

Conclusions:

The study indicates that the Norwegian version of BARS is a reliable and valid instrument to test agitation in dementia, but a version without the item 'complaining' would be better.

Paper IV. The Reliability and Validity of the Norwegian Version of the Neuropsychiatric Inventory, Nursing-Home Version (NPI-NH)

Background:

Psychiatric symptoms and behavioural disturbances are highly prevalent in the residents of nursing homes. The Neuropsychiatric Inventory (NPI) is a commonly used scale for the assessment of such symptoms in diverse settings. We have conducted a study of the reliability and the validity of the Norwegian version of the NPI nursing-home version (NPI-NH).

Methods:

The reliability study comprised 41 patients. We established inter-rater reliability between raters with various levels of health education using kappa (κ) statistics. Fifty patients were included in the validity study. The patients were examined by a physician, who also rated the patient's behaviour using "behavioural pathology in Alzheimer's disease" (BEHAVE-AD). Subsequently, a research nurse performed a standardized interview using the NPI and the Cornell scale. Concurrent validity of the NPI and the BEHAVE-AD were analyzed.

Results:

Internal consistency, as measured by Cronbach's α, was above 0.8. Inter-rater reliability was, except for one item, between 0.85 and 1.0 across assessors with different levels of health education. All correlations between the NPI and the BEHAVE-AD were significant, ranging from 0.38 to 0.72. The weakest correlations were between items assessing affective and anxiety symptoms.

Conclusion:

The Norwegian version of the NPI-NH is a reliable and valid instrument for assessing psychiatric symptoms and behavioural disturbances in the residents of nursing homes. The investigation of depressive symptoms merits particular attention.

7. Discussion of the main results

7.1. Main study

7.1.1. OBAD study

This randomised, placebo-controlled trial examined the effect of OXC in the treatment of agitation and aggression in patients with dementia. This study was neither designed nor financed by the pharmaceutical industry. Mood stabilizers as valproate and carbamazepine have been investigated in four and two RCTs respectively. Only one study with carbamazepine showed a statistically significant effect. Our data failed to prove that OXC is efficacious in treating aggression and agitation in patients with dementia. We observed a trend, however, that patients randomly assigned to OXC performed better than those assigned to the placebo ($p = 0.07$), as measured by the BARS.

Poor statistical power may be one reason why we could not prove that OXC was efficacious. Our power calculation, done prior to the study, was based on a much larger estimated difference between the groups and a lower placebo effect. The placebo group showed a 36.3% reduction in agitation and aggression score on the NPI-NH compared to 39.0% in the OXC group, but our estimates were 15% and 30% respectively for the two groups. In order to detect a significant effect with such a small difference, the study would have required the enrolment of 232 patients. Other short-term studies in similar populations have reported high placebo response rates, ranging from 21% to 58% [36 37 40]. A high placebo effect may be caused by the disease's fluctuating course or by the Hawthorne effect [712], that is, people being observed in a research context tend to behave in a different way than they otherwise would [713]. Indirectly, a high placebo effect may also indicate that approaches other than psychotropic drugs can improve behaviour in patients with dementia in nursing-homes. The choice of the patient population could also influence the placebo effect. In our study the patients had high scores for symptoms such as agitation and aggression at baseline, thus increasing the probability of a lower score later (i.e., the regression toward the mean phenomenon) [714].

Another aspect that ought to be considered is the sensitivity of the outcome measures. Items 1 to 4 of the agitation and aggression sub-scale of NPI-NH are directed to a passive form of aggression, whereas items 5 to 8 address active aggression, including an impulsive type of behaviour. The form of aggression that causes the most stress for nursing-home staff

and other patients is the striking out, impulsive, uncontrolled form of aggression. This type of aggression is often the reason why psychotropic drugs are prescribed. This may be why we found a nearly statistically significant improvement in favour of the OXC group compared with the placebo group using the BARS as a measure of efficacy. We speculate that the treatment with OXC could be effective in dementia patients with uncontrolled and impulsive aggression. Although BARS seems to capture uncontrolled aggression better than NPI-NH, there is still a need for a more specific instrument that can measure the kind of aggressive behaviour that we are most interested in: the impulsive, unexpected, physical form of aggression directed toward carers and the other patients in nursing-home wards. In post hoc sub-analyses we found that a high level of aggression (NPI-NH agitation/aggression score 9 or 12) showed a tendency to a better response to the active drug after four weeks (p=0.095), but not after eight weeks (p=0.30).

Despite the potential variability that might have been caused by our use of many sites, we do not believe that there are large differences between the various nursing homes in Norway. Extensive care was taken to select study nurses and give them special training so that the inter-rater variability was kept to a minimum. The adverse event profile of OXC in older patients is similar to that in younger patients. No special age-related adverse events have been observed. Safety data from more than 6,600 patients with epilepsy in the files of the producer of OXC, including elderly patients, support the safe use of OXC. Friis et al. [715] published safety data on 947 patients taking OXC. However, clinical practice and a vast majority of clinical studies show that patients with dementia respond differently from the healthy elderly to psychotropic drugs, those with dementia being more sensitive to side-effects. In our trial the profile of adverse events shows that OXC led to sedation in 25% of the patients, a side-effect that must be considered as a particular disadvantage for physically and mentally ill patients. Consequently, there was a stronger tendency toward ataxia and falls among this group. In sum, our study results, these side-effects and serious concerns lead to the conclusion that the prescription of OXC could not be recommended in this population.

There is a great need for further research to enhance our understanding of the neurobiological changes in agitation and aggression in dementia, which might lead to more adequate drug therapy, if that is the best treatment strategy. The present study and other drug studies have shown that the placebo response in patients with dementia is high, which highlights the importance of psychosocial, environmental, and educational strategies in treating behavioural and psychological symptoms of dementia.

7.1.2. Placebo effect in studies of dementia

While neurotransmitter changes have been shown to affect behaviour and they provide support for a biological theory of agitation in dementia, pharmacological treatment for dementia and for agitation have had only limited effectiveness. This may be the result of the limited types of pharmacological agents available, and/or that other factors in addition to neuropathological changes are responsible for agitated behaviour in dementia. All the trials investigating the effect of drugs showed a quite clear placebo effect. Target symptoms improve in trials with psychotropics, to varying degrees, in approximately a third of patients given a placebo [716]. Side effects also occur; the so-called nocebo effect. Although pharmacologically inert, a placebo can cause direct physiological effects, at least in the short term, that are consistent with the effects of active drugs; this has been demonstrated in neuroimaging studies [717] [718]. The activation of pain-suppressive, endogenous opioid neurotransmission after administration of a placebo with the expectation of analgesia has been directly demonstrated in recent work with humans using molecular imaging techniques [719]. These initial data suggest that in the case of endogenous opioid mediated placebo analgesic responses, the individual experience of pain, in particular its affective elements, the internal affective state of the individuals during pain and a measure of sustained pain sensitivity are important factors contributing to the formation of a placebo effect.

Many of the placebo-effect papers have investigated the placebo effect in depression, which is quite high, but the same principles apply to the treatment of other disorders.

In the OBAD study, only one out of 103 participants had the mental capacity to give consent. The mean MMSE score was 5.4 (95% CI 5.4) and 6.2 (95% CI 5.7) in the placebo and OXC group, respectively, indicating that the participants were suffering from a severe stage of dementia. It is reasonable to conclude that the majority of the patients did not know that they were part of a study. Therefore, the explanation that the placebo effect is caused by the patient's belief in the positive outcome of the intervention could not be applied to our study. However, the conviction of the carers and relatives that the intervention could be effective, the excitement of the staff taking part in a trial, the more intense observation of and focus on the patient, all these may be pieces in the puzzle of the placebo effect. In addition, there are other well-known facts that may explain the placebo response, like the Hawthorne effect, the participants and staff getting more attention, that the use of an assessment scale is a kind of educational intervention, and that the staff got additional training by being interviewed and realised that the different kinds of behaviour were part of the disease. As

consequence, they may have developed more tolerance, which may have resulted in lower scores. The CRAs in our study also often discussed other patients with the staff, a fact that may have contributed to debriefing the staff and a form of supervision with a positive influence on the environment in the ward from which, consequently, patients may have profited. A further fact is the fluctuating nature of agitation. A certain percentage of the placebo effect may be explained by the spontaneous resolution of agitation. It is difficult to separate the placebo effect from spontaneous remission. The higher the spontaneous remission rate, the more difficult it is to calculate the study power to show treatment effects [720].

Patients in our study were bound to have high scores in agitation/aggression. Symptoms are likely to improve in the majority, irrespective of the intervention. This is the so-called 'regression to the mean' phenomenon [721].

More generally, twenty years ago, the placebo effect in studies with psychopharmacological drugs was not as high as it is now [722]. We believe that the ethical regulations and the legal position have contributed to patients, carers and next of kin being better informed. This fact may contribute to a higher expectation of an effect. A further explanation may be the increasing recruitment of mildly ill patients into trials because of clinicians' reluctance to risk randomising severely ill patients into the placebo-receiving group. This reason may not apply to our study.

Not all placebos are the same. Patients perceive two brightly coloured tablets to be more effective than one small white one. Capsules, injections and branding also increase expectations of efficacy [716]. This may partly explain different placebo response rates in studies with a similar design. In our study the tablets were not brightly coloured; they were a light brown colour.

Placebo responses may be short-lived. Studies are usually too short to pick up placebo relapsers [723]. Our study could show that the placebo response rate was deteriorating during the four week follow-up period.

The placebo response increases according to expectancy. That can be demonstrated because the placebo effect is greater in studies randomising 2:1 active:placebo than in those randomising 1:1; the chance of receiving the active drug, and thereby the expectation, is greater in the 2:1 administration.

Also other effects may operate: a 'wish bias' probably exaggerates the efficacy of new drugs compared with established agents [724].

Rothwell and Robertson [725] studied 26 meta-analyses of 241 trials and found that when the trials within each meta-analysis were ordered according to year of publication; there was a significant variation in the proportion of trials in which the treatment was better than the control, with a significant excess of positive outcomes in the earlier trials and often a lower percentage of placebo effect. This variation is independent of trial size. Therefore, it is reasonable to assume that the trials conducted by Tariot in 1997 with carbamazepine showed a better effect than our study did years later. Early trials overestimated the treatment effect in comparison with subsequent trials in 20 out of 26 meta-analyses studied. One explanation for this phenomenon may be the publication bias: If an initial trial is positive, it is likely to be published – and sooner – than if it is negative. However, once a treatment is considered to be effective and established, a negative trial becomes interesting. Thus meta-analyses done early in the evolution of published trials overestimate a positive treatment effect. Another reason for this observation may be that earlier trials had fewer legal or ethical constraints – especially because the participants were given less information and the rules for Good Clinical Practice (GCP) and monitoring were not so well established. It is much more time-consuming to conduct a study nowadays than it was ten to twenty years ago. This means, in practice, that the staff involved have to spend more time filling in reports and are, therefore, more observant and are spending more time with the participants nowadays.

Brunoni [726] performed a meta-analysis of the placebo response of non-pharmacological and pharmacological trials concerning major depression (MDD). Forty-one studies met the inclusion criteria - 29 in the repetitive transcranial magnetic stimulation (rTMS) group and 12 in the escitalopram group. They extracted the mean and standard deviations of the depression scores in the placebo group of each study. Then, they calculated the pooled effect size for the escitalopram and rTMS groups separately, using Cohen's *d* as the measure of effect size. They found that placebo responses are large for both escitalopram (Cohen's d: 1.48; 95%C.I. 1.26 to 1.6) and rTMS studies (0.82; 95%C.I. 0.63 to 1). Thereby, they confirmed that the placebo response in MDD is large regardless of the intervention and they speculated that the placebo response is associated with the resistance of depression to treatment and treatment combinations (add-on rTMS studies). They concluded that the magnitude of the placebo response seems to be related to the study population and study design rather than the intervention itself.

Schneider and Sano [727] studied the effect of drugs developed for AD compared to a placebo. They concluded that increasing variability and relatively little change overall in the ADAS-cog placebo groups, eg, about 25% of patients do not worsen by more than 1 point,

might make it more unlikely than previously assumed that a modestly effective drug can be reliably recognized, especially when the drug might work only to attenuate decline in function and not to improve function. These observations would be strengthened by pooling data from individual trials, and pharmaceutical sponsors should participate in such efforts.

Tyrer et al. [532] studied the effects and cost-effectiveness of haloperidol, risperidone and a placebo on aggressive challenging behaviour in adults with intellectual disabilities (NACHBID). There is no evidence from this trial that either risperidone or haloperidol, given in conventionally low doses, offer any advantages over a placebo, on the contrary, over 4 weeks the placebo was found to be more effective in reducing aggression. Placebo treatment was also cheaper in terms of total cost than the other two treatments over a 6-month period.

In summary, the large placebo effect in our study may well be more a treatment effect of the unintended psychosocial activities and more thorough physical and psychological examination of patients using instruments like the NPI and the BARS; thereby, they got more quantitative and qualitative attention from the carers, and that is known to have a positive therapeutic influence on problem behaviour.

7.1.3. What can be done to prevent high placebo effects?

Shah et al. [360] recommended a "run in" period of at least 4 weeks in intervention studies using the SOAS to reduce contamination by spontaneous decline. The total number of aggressive incidents on the SOAS, the SOAS total score, spontaneously declined after week four and became established by week five. Thereby, a more normalised experience of being part of a trial may be reached and the Hawthorne effect of getting involved into a trial may be reduced and, consequently, the placebo effect will be less prominent.

The properties of the measurements should be considered more thoroughly. Treating the patients' 'agitation' as the endpoint is too unspecific as an aim. The symptoms of agitation one wants to treat should be defined and the scale that is appropriate to inform about the change over time should be carefully chosen. As our studies show, it looks as though the BARS is more sensitive to change than the NPI. In addition, it may be of interest to use the factors of BARS as specific goals of interest.

7.2. BARS factor analysis

This study is, to our knowledge, the largest factor analytic study of a scale measuring agitation in an unselected nursing-home population. Our sample represents 4.4% of the Norwegian nursing-home population (N=42,236 in the year 2000) (Statistics Norway:

http://www.ssb.no/pleie/tab-2009-07-02-02.html) and had the same demographic characteristics as described in a large epidemiological survey including all Norwegian nursing-homes in 1999 [728]. These statistics demonstrate that our study sample is representative of the nursing-home population in Norway.

We could replicate the findings of Finkel et al. [230], who published a factor analysis of the BARS. Shah et al.'s [362] study provided evidence of the concurrent validity of the BARS, the CMAI and the RAGE. Because it is the shortest one, the BARS was recommended by Shah et al. as the easiest to incorporate into nursing care plans both in psychogeriatric wards and in nursing-homes. Finkel et al. edited the BARS to represent the three factors that Cohen-Mansfield et al. found, using the items that were most frequent. Therefore, Finkel et al.'s factor analysis of the BARS conformed to the previous factor analyses of the CMAI [24 320], which produced the following components: physically aggressive behaviour, physically non-aggressive behaviour and verbally agitated behaviour. The same factors were found in later studies [19 334 339 340 342 343 345]. The Norwegian version of the nine items of the BARS represents the same factors and is therefore congruent with the original ten items of the BARS and the 29 items of the CMAI. The third factor, verbal agitation, was not represented as clearly as in the analyses of the original English version of the BARS and the CMAI. It could be argued that it may be caused by the rejection of the item 'screaming' in the Norwegian version. Nonetheless, three out of the nine items of the Norwegian version of the BARS represent verbal expressions (repetitive sentences and questions, making strange noises and complaining). Screaming did not contribute essentially to the factors of the CMAI found in various studies using a factor analysis of the CMAI [19 24 334 339 343]. Additionally, Rabinowitz reports that in six studies performing a factor analysis on the CMAI only three showed a loading of 'screaming' as ≥0.40. In Rabinowitz et al.'s study comparing three study samples [233 525 533], 'screaming' loaded to different factors. Therefore, it may be legitimate to omit screaming from a further reduced version of the BARS.

The three multiple linear regression analyses showed a different pattern for the three factors of the BARS. The degree of cognitive impairment as measured by CDR was a significant explanatory variable only for physically non-aggressive behaviour. The total number of drugs per day was related to verbal agitation, but there was no association between psychotropic drugs and the factors we found, although we would have expected that side effects like akathisia or other extrapyramidal symptoms would contribute to some of the factors.

We found an apparently contradictory association between level of functioning in the activities of daily living (ADL) and physically non-aggressive behaviour and between physically aggressive behaviour and ADL. It is reasonable to assume that patients who function better in the ADL have more symptoms related to physically non-aggressive behaviour than those who function less well in the ADL because Lawton and Brody's ADL scale assesses walking abilities [710]. Wandering, as an expression of physically non-aggressive behaviour, has often been observed in patients with dementia. Patients who function less well in the ADL are more aggressive than those who function better in the ADL. Perhaps physically aggressive behaviour is related to frustration resulting from being more dependent on others and the difficulty of communicating unmet needs [729].

The type of ward was significant both for physically aggressive behaviour and for physically non-aggressive behaviour, indicating that the selection of patients with dementia to SCU works. The regulations governing residence in a SCU for dementia in Norway require that patients can walk and take part in simple everyday activities, like setting a table. The staff ratio had no influence on any of the factors.

A weakness of our study is that our sample comprised the whole nursing-home population and not just patients with dementia. Some studies, performing a factor analysis of the CMAI, included only those patients with moderate to severe dementia [19] or patients with dementia exhibiting behavioural problems [343]. A further limitation of our study is that the results cannot be generalized, but are restricted to Norwegian nursing-home patients.

One strength is that we could replicate the same three factor solution which was found in the majority of previous factor analyses of the CMAI and the BARS in nursing-home samples. This may support the assumption that the factors 'physically aggressive behaviour', 'physically non-aggressive behaviour' and 'verbal agitation' are three separate phenomena.

7.3. BARS reliability and validity study

With a huge increase in the number of people with dementia and the challenge of how to deal with the related behavioural disturbances, caregivers require instruments that are reliable, easy and quick to apply, given the daily routine in nursing-homes with its many competing demands on staff time. The BARS has ten items, and is a short form of the CMAI with its 29 items. It was designed to meet the requirements of a busy clinical setting. As the Norwegian version of the BARS was increasingly being applied in Norwegian nursing-homes, we saw that it was important to validate it.

We performed a literature search in PubMed ('Brief AND Agitation AND Rating' in the Title field) to find studies investigating the reliability and validity of the BARS, resulting in the articles by Finkel et al. [230] conducting a factor analysis and by Shah et al. [362] comparing the CMAI, the RAGE and the BARS with each other.

7.3.1. Reliability

The test-retest reliability, expressed by Spearman's correlation coefficients, was good, taking into consideration that agitation is, along with depression and delusions, one of those behaviour symptoms in dementia that resolves over a one-year period in nearly 50 per cent of patients [261] and shows considerable short-term fluctuation.

Cronbach's alpha showed good internal consistency for the BARS total sum, especially when 'complaining' was omitted. The item 'complaining' was a symptom that lowered the internal consistency of the scale, implying that the psychometric properties of the scale would have been better without this item. As 'complaining' also results in lower test-retest reliability, we suggest that this item should be omitted from the Norwegian version of the BARS.

In their sample, Finkel et al. did not find that the item 'complaining' created reliability problems. This may be a reflection of cultural differences between the American and Norwegian ways of reacting to discomfort. Complaining may be less prominent in a health system like Norway's, where the social welfare system is quite good and, i.e., the stay in a nursing home is affordable for everyone. Furthermore, Finkel et al. recruited their patients from a skilled nursing, long-term care facility for the Jewish elderly with possible differences in staff density and care settings. The residents' religion, forming behavioural patterns throughout their lifetime, might create other ways of expressing agitation in dementia. Some studies indicate that pre-morbid personality traits do cause differences in behaviour in persons with dementia [730 731], i.e. that pre-morbid agreeable behaviour was negatively correlated with agitation and irritability. Another possible explanation for the discrepancy between the results may be that Finkel's research was conducted 15 years ago. The agitation observed in a new generation of elderly patients may present itself by a different symptom spectrum, but that has yet to be proven by further research.

7.3.2. Validity

Agitation is a poorly defined fragment in the mosaic of neuropsychiatric symptoms and syndromes in dementia, although many have investigated and tried to define it. Therefore, we

find quite a number of different scales and are confronted with the fact that many studies are difficult to compare because the results are dependent on which scale has been used. As an example, in a study of treating patients with oxcarbazepine against agitation and aggression in dementia, Sommer et al. [210] found an almost statistically significant outcome measured with the BARS, but no significance at all with the agitation/aggression sub-scale of the NPI (NPI-NH/AA). In the present study, we have found that the BARS correlates better with the Cornell Scale for Depression in Dementia/Agitation (CSDD/A) than with the NPI-NH/AA, reinforcing the belief that agitation as measured by the BARS contains some other information than the NPI-NH/AA.

This difference increased further when we deleted the item 'complaining' from the BARS. The agitation questions in the CSDD address aspects of agitated behaviour related to restlessness, playing with one's hands or hair, hand-wringing, hair-pulling, and/or lip-biting, as such behaviour can be seen in depressed patients. The NPI-NH/AA contains different aspects of agitation and aggression such as getting upset, resisting bathing or changing clothes, wanting things their own way, being uncooperative, resisting help from others, slamming doors, kicking furniture and throwing things. These aspects are not found in the BARS or in CSDD/A. Therefore it may be possible that the concepts of agitation in the BARS and the CSDD/A are more congruent than that of the BARS and the NPI-NH/AA. It might also be that depression and agitation have a closer connection. Others have also come to similar conclusions: Ellis [324] found in a sample of 64 persons with dementia, residing in assisted living accommodation, that depression is one of the main co-morbid disorders related to agitation. Bartels et al. [732] found that dementia is often complicated by a mix of agitation and depression, and Cohen-Mansfield and other researchers [286 322 733] found that depression may play a role in verbally aggressive behaviour. One may argue that, in many cases, agitation is an expression of depression or that the same patho-physiological processes are causing similar and overlapping symptoms. Decreased levels of serotonin are related to depressive disorders and impulsive/aggressive behaviours [734-737].

A limitation of our study is that the population in Norwegian nursing-homes may differ from those in other countries and, therefore, the generalizability of our results to other countries may be biased. The validation part of our investigation has a weakness because no scale has been established as a "gold standard". We used the NPI-NH/AA and CSDD/A for our validation because both are parts of instruments widely used in clinical practice in nursing-homes and in research. Finally, we used an already existing and much-used translation, rather than creating a new one, applying strict research criteria. A further

limitation may be that we did not diagnose the patients' dementia according to ICD-10 or DSM-IV criteria, but used the CDR and the MMSE. However, studies have shown that the CDR is a valid instrument for evaluating the stages of dementia [738].

7.4. NPI reliability and validity study

The reliability and validity of the Norwegian version of the NPI-NH was tested in two unselected nursing-home populations. This is to our knowledge the first study of the reliability and validity of a Scandinavian version of the NPI. In this study the internal consistency was high even though the sample studied was more heterogeneous than the majority of earlier studies. The high internal consistency is concurrent with most previous studies. As could be expected, the two last items, night-time behaviour and eating behaviour, correlated least well with the total.

The inter-rater reliability was excellent for all items, apart from the severity score of the item 'eating behaviour'. One explanation could be that a registered nurse might see changes in eating behaviour in another context, and rate it more positively, than psychiatric health-workers would do. The high inter-rater reliability in our study indicates that the NPI is robust and can be used by assessors from different professions and with different levels of medical education.

The concurrent validity of most NPI items, when compared with the BEHAVE-AD, was satisfactory, though somewhat lower than in the initial study by Cummings [706]. This might be due to the greater heterogeneity of our sample and the fact that we used professional carers and not family carers as informants.

The low correlation of depressive symptoms of the NPI with the BEHAVE-AD is consistent with previous studies. The BEHAVE-AD presents a relatively narrow concept of depression, taking only crying and a depressed mood into account, whereas the NPI has a broader approach to depressive symptoms. Furthermore, the correlation between items concerning depression in the BEHAVE-AD and the Cornell scale is low. However, the diagnosis of depression correlated poorly with all three scales. This result is a bit odd, bearing in mind that the diagnosis of depression and the rating of the BEHAVE-AD, as well as the Cornell scale and the NPI had been done by the same assessors. It might reflect the fact that depression in dementia is an elusive disorder that is poorly described by diagnostic criteria and current psychiatric rating scales.

The possibility of generalising our results to more specific dementia populations is limited. However, we have demonstrated that the NPI can also be useful in unselected nursing-home populations. Reliable and valid instruments for research and clinical purposes in nursing-homes are sorely needed.

7.5. Methodological issues

One of the unsolved issues in the field of dementia research is the clear definition of agitation and aggression. That leads to the use of different scales and, thereby, to difficulties in comparing and interpreting the results. There is no generally agreed definition of aggressive behaviour. Many studies [362 739-741] have failed to define aggressive behaviour clearly. Varying definitions of aggressive behaviour have included verbal abuse or threatening behaviour [742 743], excessive vocal activity [744], damage to property [745 746], physical attacks on people including other patients, staff and informal caregivers [743 747], sexually aggressive behaviour [328 742] and self-harm [746 748]. Differing combinations of these facets have been used in different studies. One of the most comprehensive definitions of aggressive behaviour in the elderly is that by Patel and Hope [331]: "Aggressive behaviour is an overt act, involving the delivery of noxious stimuli to (but not necessarily aimed at) another organism, object or self, which clearly is not accidental." Cohen-Mansfield produced the widely used, but still not unanimously accepted, definition of agitation in dementia: 'Inappropriate verbal, vocal or motor activity that is not explained by needs or confusion per se'. But, one may ask: Inappropriate for whom? In addition, this definition excludes need driven behaviour and, therefore, all the studies investigating agitation as an expression of the unmet needs of the disabiled or agitation as result of lack of proper verbal communication and interaction between caregiver and patient. Cohen-Mansfield's definition seems to be influenced by the important emphasis in her research on agitation resulting from unmet needs, but it seems to be too exclusive and confines the definition of agitation to the unexplainable cases alone. The lack of a precise definition and the complexity of the problem may lead to research difficulties in terms of defining research questions and relevant outcome measures.

In the main study there were considerable difficulties in recruiting patients because of ethical and consent doubts, but also because there was no established research network and no tradition of conducting drug trials in nursing-homes. Therefore, we had to recruit new research centres and nursing-homes during the ongoing trial. Our original plan to conduct the study in two enrolment periods in autumn 2005 and spring 2006 with an ongoing evaluation process of the progress and the safety of the participants had to be supplemented by a third

enrolment period in summer 2006. We have been confronted with the 'law' attributed to Lasagna [749], according to which clinical experience shows there are more patients who could be recruited to a trial than are found during an ongoing trial.

Designing the OBAD study we tried to make it as comparable as possible with Tariot's study [36], which investigated carbamazepine's effect on agitation in dementia. At the same time, we applied different scales because we wanted to use NPI as this instrument was used in many drug trials in dementia. It would have been an advantage to use the CGI scale too. Tariot et al.'s results showed an improvement in the Clinical Global Impression Scale (CGI) in 77% of the patients taking carbamazepine and 21% of those taking a placebo. That misled us into underestimating the placebo effect. We learned that the comparison of studies, and consequently the designing of a new study, has to take into consideration similar precautions as reviews or meta-analyses. Verstraete [580] published a paper that focused on these issues: Differences in patients' characteristics (selection bias), the care provided (performance bias), assessment of outcomes (detection bias) and exclusion of randomised patients (attrition bias). Turner et al. [750], in a widely discussed article in the *New England Journal of Medicine*, asked the question: "How accurately does the published literature convey data on drug efficacy to the medical community?" The investigators compared data from 74 FDA-registered randomised controlled trials submitted for regulatory approval, with the published literature. They found evidence for the "file drawer effect," that is, publication bias in favour of positive studies. Selective reporting [751] of scientific research, the "adverse effects" of industry influence [752], and also other reasons for underreporting of trials is haunting the validity of reviews and meta-analyses: It appears that only about half of the abstracts presented at conferences are later published in full [753] (publication bias). Based on research proposals approved by the ethics committees of four leading medical schools, only 49 to 67% are fully published in medical journals [754 755]. Of trials funded by the National Institutes of Health, 20% are still unpublished several years after completion [754 756]. This hidden information is unfortunately not a random process but mainly affects trials with negative results. In future investigations, we would take even more time to search the literature before designing a study. Anyway, one aspect of the publishing bias that may also in the future lead to similar problems in planning intervention trials is that it is not easy to get a negative study published, as we ourselves have experienced, because the journal editors have to look to the economic consequences and tend to publish papers that are likely to "sell" best.

Suh [578] discussed some critical points related to RCTs in patients with dementia, mainly focusing on trials with antipsychotics:

"RCTs are considered the most reliable form of scientific evidence in healthcare because they eliminate spurious causality and bias. As the name suggests, RCTs involve the random allocation of different treatments to patients. This ensures that known and unknown confounding factors are evenly distributed between the groups. However, patients who are allocated to the active treatment group may be at higher risk of SAE than those allocated to the placebo group. This might be due to following reasons:

(i) Contrary to steadily declining cognition and function in dementia patients, BPSD is not constantly presenting, but sometimes spontaneously goes into remission. BPSD often fluctuates and can have an episodic course. Most BPSD are expected to respond to antipsychotics within one or two weeks, and most symptoms go into remission soon. Then, in usual clinical practice, ideally clinicians maintain antipsychotics for a time-limited period and then taper and discontinue the medication. Medication is often used on an "as needed" basis. However, in RCTs, patients in the active treatment group continue to take antipsychotics to the end of the trial, most for 8 to 36 weeks, even though they do not need antipsychotics any longer because their symptoms are now very mild or in remission. This means that patients in the active treatment group are unnecessarily exposed to a higher risk of harm.

(ii) The experimental condition itself may put patients on the active treatment at higher risk for harm. Once recruited for RCTs, every patient takes the trial medication as scheduled. To guarantee the safety of patients, protocols of RCTs of antipsychotics for BPSD did not exclude patients using drugs which had been regularly used to control stable general medical conditions (e.g. hypertension, diabetes) throughout the trial period. Older people are dangerously overmedicated in the real world, yet many frequently omit to take medications. However, in the experimental condition, they have to take medications without omission throughout the trial period. The compulsory continuous use of these different drugs in RCTs may increase the chance of drug-disease interactions or drug-drug interaction with the trial medication. In RCTs of antipsychotics for BPSD, by fixing the doses and requiring that patients be kept on medication throughout the trial, many patients are placed at increased risk for adverse events and do not have the potential to benefit from individualised dosing adjustments. By comparison, in usual clinical practice, medication might have been discontinued, decreased, increased or switched. Thus, the clinical trial may reflect both more AE and less efficacy than are actually experienced by patients in 'real life'."

Therefore, we used a model with variable dosing of the trial medication and by that means tried to avoid exposing the patients to additional risk of adverse events (AEs) and to come closer to the every day clinical management of agitation.

Causes of BPSD in dementia patients are heterogeneous and complex to manage. This is something that those administering a drug trial do not usually take into consideration. Although we instructed all those who were involved in the recruitment of patients that psychosocial interventions had to be tried first and only when it had failed should the patient be considered as qualified for inclusion, we believe that this was not always done in the real world of screening for inclusion.

Another problem we faced that posed methodological challenges was, how to react to AE. As mentioned, 25% of patients taking OXC experienced sedation. This may have led to more apathy, less food and fluid intake, resulting in dehydration and haemoconcentration. Herrmann [563] mentioned this problem as one of the causes of stroke in antipsychotic trials. Although we did not have any incidents of stroke in our trial, we may have exposed our patients to a higher risk. Sedation may also have caused a reduction in their quality of life (QoL). If we were to do a similar trial again, we would include a scale like CGI as a measurement that reflects the clinical state of the patient and a scale measuring QoL, e.g. QUALID, in addition to the registration of patients' fluid intake.

After the intervention period of eight weeks in the OBAD trial, both curves, that representing the placebo and that for the OXC group respectively, showed a tendency for agitation to have increased. We wonder whether this reflects the decreasing influence of the Hawthorne effect on the trial, as it represents the decreasing interest of the staff involved in the care of the patients or the study nurses. It would be interesting to have a scale that measures not only the burden of the carers as the NPI does, but also the satisfaction of the carers with the response to the treatment. The OBAD study results showed an impressively high placebo effect, which made us curious about the reason for it.

8. Future directions for research

All Cochrane Reviews, 'Evidence Based Medicine'-reviews, meta-analyses and expert consensus statements in the field of dementia research recommend more research. As recent years have showen, there is increasing interest in the research community and from politicians in contributitions augmenting knowledge about the aetiology, pathology, prevention and treatment of the different forms of dementia and their behavioural and psychological symptoms.

Until now, the focus has mainly been on psychosocial factors contributing to agitation and other behavioural challenges. Concerning drug treatments, it is essential to get more insight into the biological processes of dementia, and that is the only way that drug treatments can be designed more specifically. This is still a widely unexplored field.

The past 30 years have seen many attempts to demonstrate the safety and efficacy of drugs for dementia, predominantly those aiming to treat the symptoms [757]. Most of the benefit of the dementia drugs, such as tacrine, donepezil, rivastigmine, galantamine and memantine, has been in slowing down the progress of the symptoms rather than producing an improvement over the baseline condition of the patient. There have also been attempts at arresting the progress of AD, but so far all have failed. Studies treating agitation with psychosocial intervention strategies and drugs showed limited effectiveness and a high placebo response. Especially in drug trials, there has been quite an alarming number and severity of adverse events.

So far we have only just begun to understand the dementia diseases and persons with dementia and are far from treating them properly. Gauthier and Schelters proposed to start

> "clinical trials where proof of concept can be done in populations enriched with certain clinical and biological characteristics, including cognitive symptoms, APOE ε4 carrier status, CSF AD profile, and hippocampal atrophy. Success in these studies would require a confirmatory follow-up study with more broadly representative populations. These two studies (proof of concept and confirmatory) should satisfy regulatory requirements for efficacy. Designs such as delaying disease milestones should receive equal considerations to fixed endpoint studies, which are currently favoured but not convincing to payers and users."

As the changes in the brain in AD start decades before a dementia diagnosis can be made, efforts to find ways to prevent the development of dementia pathology as early as possible should be reenforced. Delaying the onset of dementia by treating preclinical states as

subjective cognitive impairment and mild cognitive impairment, might make it possible to prevent most of the non-cognitive symptoms such as agitation. Could we learn something from coronary heart disease prevention and the partly successful strategies there? Prevention should always be the primary goal in medicine.

References

1. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health* 1998;88(9):1337-42.
2. Ebly EM, Parhad IM, Hogan DB, Fung TS. Prevalence and types of dementia in the very old: results from the Canadian Study of Health and Aging. *Neurology* 1994;44(9):1593-600.
3. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;366(9503):2112-7.
4. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* 2007;29(1-2):125-32.
5. Bharucha AJ, Pandav R, Shen C, Dodge HH, Ganguli M. Predictors of nursing facility admission: a 12-year epidemiological study in the United States. *J Am Geriatr Soc* 2004;52(3):434-9.
6. Hurt C, Bhattacharyya S, Burns A, Camus V, Liperoti R, Marriott A, et al. Patient and caregiver perspectives of quality of life in dementia. An investigation of the relationship to behavioural and psychological symptoms in dementia. *Dement Geriatr Cogn Disord* 2008;26(2):138-46.
7. Rabins PV, Mace NL, Lucas MJ. The impact of dementia on the family. *JAMA* 1982;248(3):333-5.
8. Rosness TA, Ulstein I, Engedal K. Stress affects carers before patient's first visit to a memory clinic. *Int J Geriatr Psychiatry* 2009.
9. Sourial R, McCusker J, Cole M, Abrahamowicz M. Agitation in demented patients in an acute care hospital: prevalence, disruptiveness, and staff burden. *Int Psychogeriatr* 2001;13(2):183-97.
10. Teri L. Behavior and caregiver burden: behavioral problems in patients with Alzheimer disease and its association with caregiver distress. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 4:S35-8.
11. Ulstein I. Commenting on the care of carers. *Nurs Older People* 2007;19(8):6.
12. Wimo A, Ljunggren G, Winblad B. Costs of dementia and dementia care: a review. *Int.J.Geriatr.Psychiatry* 1997;12(8):841-856.
13. Selbaek G, Kirkevold O, Engedal K. The prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes. *Int.J.Geriatr.Psychiatry* 2007;22(9):843-849.
14. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 2002;288(12):1475-83.
15. Finkel S. Introduction to behavioural and psychological symptoms of dementia (BPSD). *Int J Geriatr Psychiatry* 2000;15 Suppl 1:S2-4.
16. Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Neuropsychiatric symptoms in nursing home patients: factor structure invariance of the Dutch nursing home version of the neuropsychiatric inventory in different stages of dementia. *Dement Geriatr Cogn Disord* 2007;24(3):169-76.
17. Piccininni M, Di Carlo A, Baldereschi M, Zaccara G, Inzitari D. Behavioral and psychological symptoms in Alzheimer's disease: frequency and relationship with

duration and severity of the disease. *Dement Geriatr Cogn Disord* 2005;19(5-6):276-81.
18. Brodaty H, Draper B, Saab D, Low LF, Richards V, Paton H, et al. Psychosis, depression and behavioural disturbances in Sydney nursing home residents: prevalence and predictors. *Int.J.Geriatr.Psychiatry* 2001;16(5):504-512.
19. Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Agitation in Dutch institutionalized patients with dementia: factor analysis of the Dutch version of the Cohen-Mansfield Agitation Inventory. *Dement Geriatr Cogn Disord* 2007;23(1):35-41.
20. Cohen-Mansfield J. Assessment of disruptive behavior/agitation in the elderly: function, methods, and difficulties. *J.Geriatr.Psychiatry Neurol.* 1995;8(1):52-60.
21. Cohen-Mansfield J. Agitated behaviors in the elderly. II. Preliminary results in the cognitively deteriorated. *J.Am.Geriatr.Soc.* 1986;34(10):722-727.
22. Hebert R, Dubois MF, Wolfson C, Chambers L, Cohen C. Factors associated with long-term institutionalization of older people with dementia: data from the Canadian Study of Health and Aging. *J Gerontol A Biol Sci Med Sci* 2001;56(11):M693-9.
23. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology* 1996;46(1):130-135.
24. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *J Gerontol* 1989;44(3):M77-84.
25. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J.Clin.Psychiatry* 1987;48 Suppl:9-15.
26. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44(12):2308-2314.
27. Kirkevold O, Engedal K. Concealment of drugs in food and beverages in nursing homes: cross sectional study. *BMJ* 2005;330(7481):20.
28. Nygaard HA, Ruths S, Straand J, Naik M. Not less but different: psychotropic drug utilization trends in Norwegian nursing homes during a 12-year period. The Bergen District Nursing Home (BEDNURS) Study. *Aging Clin Exp Res* 2004;16(4):277-82.
29. Ruths S, Straand J, Nygaard HA. Psychotropic drug use in nursing homes--diagnostic indications and variations between institutions. *Eur J Clin Pharmacol* 2001;57(6-7):523-8.
30. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* 2006;14(3):191-210.
31. Ballard C, Corbett A, Chitramohan R, Aarsland D. Management of agitation and aggression associated with Alzheimer's disease: controversies and possible solutions. *Curr Opin Psychiatry* 2009;22(6):532-40.
32. Ballard C, Howard R. Neuroleptic drugs in dementia: benefits and harm. *Nat Rev Neurosci* 2006;7(6):492-500.
33. Lanctot KL, Best TS, Mittmann N, Liu BA, Oh PI, Einarson TR, et al. Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. *J Clin Psychiatry* 1998;59(10):550-61; quiz 562-3.
34. Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. *Cochrane Database Syst Rev* 2002(2):CD002852.
35. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA* 2005;293(5):596-608.

36. Tariot PN, Erb R, Podgorski CA, Cox C, Patel S, Jakimovich L, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am.J.Psychiatry* 1998;155(1):54-61.
37. Olin JT, Fox LS, Pawluczyk S, Taggart NA, Schneider LS. A pilot randomized trial of carbamazepine for behavioral symptoms in treatment-resistant outpatients with Alzheimer disease. *Am J Geriatr Psychiatry* 2001;9(4):400-5.
38. Herrmann N. Valproic acid treatment of agitation in dementia. *Can J Psychiatry* 1998;43(1):69-72.
39. Herrmann N, Lanctot KL, Rothenburg LS, Eryavec G. A placebo-controlled trial of valproate for agitation and aggression in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2007;23(2):116-9.
40. Porsteinsson AP, Tariot PN, Erb R, Cox C, Smith E, Jakimovich L, et al. Placebo-controlled study of divalproex sodium for agitation in dementia. *Am.J.Geriatr.Psychiatry* 2001;9(1):58-66.
41. Sival RC, Haffmans PM, Jansen PA, Duursma SA, Eikelenboom P. Sodium valproate in the treatment of aggressive behavior in patients with dementia--a randomized placebo controlled clinical trial. *Int J Geriatr Psychiatry* 2002;17(6):579-85.
42. Tariot PN, Raman R, Jakimovich L, Schneider L, Porsteinsson A, Thomas R, et al. Divalproex sodium in nursing home residents with possible or probable Alzheimer Disease complicated by agitation: a randomized, controlled trial. *Am.J.Geriatr.Psychiatry* 2005;13(11):942-949.
43. Hofman A, Rocca WA, Brayne C, Breteler MM, Clarke M, Cooper B, et al. The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. Eurodem Prevalence Research Group. *Int J Epidemiol* 1991;20(3):736-48.
44. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;54(11 Suppl 5):S4-9.
45. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *J Neurol Neurosurg Psychiatry* 2003;74(9):1206-9.
46. Ott A, Breteler MM, van Harskamp F, Claus JJ, van der Cammen TJ, Grobbee DE, et al. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. *BMJ* 1995;310(6985):970-3.
47. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. *Am J Epidemiol* 1998;147(6):574-80.
48. Engedal K, Gilje K, Laake K. Prevalence of dementia in a Norwegian sample aged 75 years and over and living at home. *Compr Gerontol A* 1988;2(3):102-6.
49. Engedal K, Haugen PK. The prevalence of dementia in a sample of elderly in Norwegia. *International Journal of Geriatric Psychiatry* 1993(8):565-570.
50. Rocca WA, Cha RH, Waring SC, Kokmen E. Incidence of dementia and Alzheimer's disease: a reanalysis of data from Rochester, Minnesota, 1975-1984. *Am J Epidemiol* 1998;148(1):51-62.
51. Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol* 2002;59(11):1737-46.
52. Wimo A, Winblad B, Aguero-Torres H, von Strauss E. The magnitude of dementia occurrence in the world. *Alzheimer Dis Assoc Disord* 2003;17(2):63-7.
53. Wancata J, Musalek M, Alexandrowicz R, Krautgartner M. Number of dementia sufferers in Europe between the years 2000 and 2050. *Eur Psychiatry* 2003;18(6):306-13.

54. Xie J, Brayne C, Matthews FE. Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up. *BMJ* 2008;336(7638):258-62.
55. Fitzpatrick AL, Kuller LH, Lopez OL, Kawas CH, Jagust W. Survival following dementia onset: Alzheimer's disease and vascular dementia. *J Neurol Sci* 2005;229-230:43-9.
56. Lopez OL, Jagust WJ, DeKosky ST, Becker JT, Fitzpatrick A, Dulberg C, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. *Arch Neurol* 2003;60(10):1385-9.
57. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry* 1998;55(9):809-15.
58. Blansjaar BA, Thomassen R, Van Schaick HW. Prevalence of dementia in centenarians. *Int J Geriatr Psychiatry* 2000;15(3):219-25.
59. Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA. Is the risk of developing Alzheimer's disease greater for women than for men? *Am J Epidemiol* 2001;153(2):132-6.
60. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology* 1998;51(3):728-33.
61. Kalmijn S, Foley D, White L, Burchfiel CM, Curb JD, Petrovitch H, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. *Arterioscler Thromb Vasc Biol* 2000;20(10):2255-60.
62. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging* 2000;21(1):49-55.
63. Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. *Neurobiol Aging* 2000;21(1):57-62.
64. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996;347(9009):1141-5.
65. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001;322(7300):1447-51.
66. Peters R, Poulter R, Warner J, Beckett N, Burch L, Bulpitt C. Smoking, dementia and cognitive decline in the elderly, a systematic review. *BMC Geriatr* 2008;8:36.
67. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, et al. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke* 2006;37(2):345-50.
68. Schneider JA, Boyle PA, Arvanitakis Z, Bienias JL, Bennett DA. Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. *Ann Neurol* 2007;62(1):59-66.
69. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 2007;69(24):2197-204.
70. Knopman DS, Mosley TH, Catellier DJ, Coker LH. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimers Dement* 2009;5(3):207-14.
71. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005;64(2):277-81.
72. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife Serum Cholesterol and Increased Risk of Alzheimer's and Vascular Dementia Three Decades Later. *Dement Geriatr Cogn Disord* 2009;28(1):75-80.

73. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999;53(9):1937-42.
74. Kopf D, Frolich L. Risk of incident Alzheimer's disease in diabetic patients: a systematic review of prospective trials. *J Alzheimers Dis* 2009;16(4):677-85.
75. Hooper C, Killick R, Lovestone S. The GSK3 hypothesis of Alzheimer's disease. *J Neurochem* 2008;104(6):1433-9.
76. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* 2005;62(10):1556-60.
77. Peters R, Beckett N, Geneva M, Tzekova M, Lu FH, Poulter R, et al. Sociodemographic and lifestyle risk factors for incident dementia and cognitive decline in the HYVET. *Age Ageing* 2009;38(5):521-7.
78. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* 2005;65(4):545-51.
79. Diaz-Arrastia R. Hyperhomocysteinemia: a new risk factor for Alzheimer disease? *Arch Neurol* 1998;55(11):1407-8.
80. Oulhaj A, Refsum H, Beaumont H, Williams J, King E, Jacoby R, et al. Homocysteine as a predictor of cognitive decline in Alzheimer's disease. *Int J Geriatr Psychiatry* 2009.
81. Seshadri S. Elevated plasma homocysteine levels: risk factor or risk marker for the development of dementia and Alzheimer's disease? *J Alzheimers Dis* 2006;9(4):393-8.
82. Coley N, Andrieu S, Gardette V, Gillette-Guyonnet S, Sanz C, Vellas B, et al. Dementia prevention: methodological explanations for inconsistent results. *Epidemiol Rev* 2008;30:35-66.
83. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol* 2006;5(9):735-41.
84. Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, Ginsberg H, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. *Neurology* 1995;45(3 Pt 1):555-7.
85. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261(5123):921-3.
86. Bergem AL, Engedal K, Kringlen E. The role of heredity in late-onset Alzheimer disease and vascular dementia. A twin study. *Arch.Gen.Psychiatry* 1997;54(3):264-270.
87. Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, et al. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. *N Engl J Med* 2009;361(3):255-63.
88. Kok E, Haikonen S, Luoto T, Huhtala H, Goebeler S, Haapasalo H, et al. Apolipoprotein E-dependent accumulation of Alzheimer disease-related lesions begins in middle age. *Ann Neurol* 2009;65(6):650-7.
89. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 1997;278(16):1349-56.
90. Henderson AS, Easteal S, Jorm AF, Mackinnon AJ, Korten AE, Christensen H, et al. Apolipoprotein E allele epsilon 4, dementia, and cognitive decline in a population sample. *Lancet* 1995;346(8987):1387-90.

91. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet* 2009.
92. Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* 2009.
93. Qiu C, Kivipelto M, Aguero-Torres H, Winblad B, Fratiglioni L. Risk and protective effects of the APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex. *J Neurol Neurosurg Psychiatry* 2004;75(6):828-33.
94. Karp A, Andel R, Parker MG, Wang HX, Winblad B, Fratiglioni L. Mentally stimulating activities at work during midlife and dementia risk after age 75: follow-up study from the Kungsholmen Project. *Am J Geriatr Psychiatry* 2009;17(3):227-36.
95. Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA* 2002;287(6):742-8.
96. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol* 2004;3(6):343-53.
97. Ngandu T, von Strauss E, Helkala EL, Winblad B, Nissinen A, Tuomilehto J, et al. Education and dementia: what lies behind the association? *Neurology* 2007;69(14):1442-50.
98. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA* 2002;288(18):2271-81.
99. Karp A, Paillard-Borg S, Wang HX, Silverstein M, Winblad B, Fratiglioni L. Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dement Geriatr Cogn Disord* 2006;21(2):65-73.
100. Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology* 2001;57(12):2236-42.
101. Verghese J, LeValley A, Derby C, Kuslansky G, Katz M, Hall C, et al. Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. *Neurology* 2006;66(6):821-7.
102. Rovio S, Kareholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol* 2005;4(11):705-11.
103. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. *Arch Neurol* 2006;63(11):1545-50.
104. Kivipelto M, Solomon A. Alzheimer's disease - the ways of prevention. *J Nutr Health Aging* 2008;12(1):89S-94S.
105. Kivipelto M, Solomon A. Preventive neurology: on the way from knowledge to action. *Neurology* 2009;73(3):168-9.
106. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med* 2006;144(2):73-81.
107. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 2008;300(9):1027-37.
108. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, et al. Ageing, fitness and neurocognitive function. *Nature* 1999;400(6743):418-9.

109. Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus* 2009.
110. Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, Koepke KM, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA* 2006;296(23):2805-14.
111. Laitinen MH, Ngandu T, Rovio S, Helkala EL, Uusitalo U, Viitanen M, et al. Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study. *Dement Geriatr Cogn Disord* 2006;22(1):99-107.
112. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, et al. Dietary fats and the risk of incident Alzheimer disease. *Arch Neurol* 2003;60(2):194-200.
113. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS, Aggarwal NT, et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. *Am J Clin Nutr* 2005;81(2):508-14.
114. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. *Arch Neurol* 2009;66(2):216-25.
115. Andrieu S, Coley N, Aisen P, Carrillo MC, DeKosky S, Durga J, et al. Methodological issues in primary prevention trials for neurodegenerative dementia. *J Alzheimers Dis* 2009;16(2):235-70.
116. Wang HX, Karp A, Herlitz A, Crowe M, Kareholt I, Winblad B, et al. Personality and lifestyle in relation to dementia incidence. *Neurology* 2009;72(3):253-9.
117. Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. *J Neurol Neurosurg Psychiatry* 2009;80(1):13-7.
118. Haag MD, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Duration of antihypertensive drug use and risk of dementia: A prospective cohort study. *Neurology* 2009;72(20):1727-34.
119. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;54(11 Suppl 5):S10-5.
120. Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* 1997;349(9046):151-4.
121. Kalaria RN. Cerebrovascular degeneration is related to amyloid-beta protein deposition in Alzheimer's disease. *Ann N Y Acad Sci* 1997;826:263-71.
122. Premkumar DR, Cohen DL, Hedera P, Friedland RP, Kalaria RN. Apolipoprotein E-epsilon4 alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. *Am J Pathol* 1996;148(6):2083-95.
123. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA* 1997;277(10):813-7.
124. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996;47(5):1113-24.
125. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol* 2003;60(3):387-92.

126. Fox NC, Rossor MN. Diagnosis of early Alzheimer's disease. *Rev Neurol (Paris)* 1999;155 Suppl 4:S33-7.
127. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *JAMA* 1996;275(7):528-32.
128. Skoog I. Detection of preclinical Alzheimer's disease. *N Engl J Med* 2000;343(7):502-3.
129. Levy R. Aging-associated cognitive decline. Working Party of the International Psychogeriatric Association in collaboration with the World Health Organization. *Int Psychogeriatr* 1994;6(1):63-8.
130. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56(3):303-8.
131. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256(3):183-94.
132. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004;256(3):240-6.
133. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. *Lancet* 2006;367(9518):1262-70.
134. WHO. *The ICD-10 Classification of Mental Health and Behavioural Disorders. Clinical descriptions and diagnostic guidelines.* Tenth revision ed, 1992.
135. WHO, editor. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic criteria for research.*, 1993.
136. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res* 2009;43(4):411-31.
137. APA, editor. *DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition - Text Revision)*, 2000.
138. Scheltens P. Imaging in Alzheimer's disease. *Dialogues Clin Neurosci* 2009;11(2):191-9.
139. Scheltens P, Weinstein HC, Leys D. Neuro-imaging in the diagnosis of Alzheimer's disease. I. Computer tomography and magnetic resonance imaging. *Clin Neurol Neurosurg* 1992;94(4):277-89.
140. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007;6(8):734-46.
141. Sunderland T, Jeste D, Baiyewu O, Sirovatka PJ, Regier DA, editors. *Diagnostic Issues in Dementia. Advancing the Research Agenda for DSM-V*: American Psychiatric Association, Arlington, Virginia, 2007.
142. Wiederkehr S, Simard M, Fortin C, van Reekum R. Validity of the clinical diagnostic criteria for vascular dementia: a critical review. Part II. *J Neuropsychiatry Clin Neurosci* 2008;20(2):162-77.
143. Wiederkehr S, Simard M, Fortin C, van Reekum R. Comparability of the clinical diagnostic criteria for vascular dementia: a critical review. Part I. *J Neuropsychiatry Clin Neurosci* 2008;20(2):150-61.
144. Wetterling T, Kanitz RD, Borgis KJ. Comparison of different diagnostic criteria for vascular dementia (ADDTC, DSM-IV, ICD-10, NINDS-AIREN). *Stroke* 1996;27(1):30-6.
145. Gold G, Bouras C, Canuto A, Bergallo MF, Herrmann FR, Hof PR, et al. Clinicopathological validation study of four sets of clinical criteria for vascular dementia. *Am J Psychiatry* 2002;159(1):82-7.

146. Bond J, Stave C, Sganga A, O'Connell B, Stanley RL. Inequalities in dementia care across Europe: key findings of the Facing Dementia Survey. *Int J Clin Pract Suppl* 2005(146):8-14.
147. Rimmer E, Stave C, Sganga A, O'Connell B. Implications of the Facing Dementia Survey for policy makers and third-party organisations across Europe. *Int J Clin Pract Suppl* 2005(146):34-8.
148. Waldemar G, Phung KT, Burns A, Georges J, Hansen FR, Iliffe S, et al. Access to diagnostic evaluation and treatment for dementia in Europe. *Int J Geriatr Psychiatry* 2007;22(1):47-54.
149. Green RC, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. *N Engl J Med* 2009;361(3):245-54.
150. Ettema TP, Droes RM, de Lange J, Mellenbergh GJ, Ribbe MW. A review of quality of life instruments used in dementia. *Qual Life Res* 2005;14(3):675-86.
151. Gwyther LP. The perspective of the person with Alzheimer disease: which outcomes matter in early to middle stages of dementia? *Alzheimer Dis Assoc Disord* 1997;11 Suppl 6:18-24.
152. Jennings B. A life greater than the sum of its sensations: ethics, dementia, and the quality of life. *J Ment Health Aging* 1999;5(1):95-106.
153. Rabins PV, Black BS. Measuring quality of life in dementia: purposes, goals, challenges and progress. *Int Psychogeriatr* 2007;19(3):401-7.
154. Rabins PV, Kasper JD. Measuring quality of life in dementia: conceptual and practical issues. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 6:100-4.
155. Ready RE, Ott BR. Quality of Life measures for dementia. *Health Qual Life Outcomes* 2003;1:11.
156. Lawton MP. Quality of life in Alzheimer disease. *Alzheimer Dis Assoc Disord* 1994;8 Suppl 3:138-50.
157. Lawton MP. Assessing quality of life in Alzheimer disease research. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 6:91-9.
158. Lawton MP. Observed affect and quality of life in dementia: Further affirmations and problems. *J Ment Health Aging* 1999;5(1).
159. Sloane PD, Zimmerman S, Williams CS, Reed PS, Gill KS, Preisser JS. Evaluating the quality of life of long-term care residents with dementia. *Gerontologist* 2005;45 Spec No 1(1):37-49.
160. Whitehouse PJ, Rabins PV. Quality of life and dementia. *Alzheimer Dis Assoc Disord* 1992;6(3):135-7.
161. McCallion P, McCarron M. Perspective on quality of life in dementia care. *Intellect Dev Disabil* 2007;45(1):56-9.
162. Kane RA. Long-term care and a good quality of life: bringing them closer together. *Gerontologist* 2001;41(3):293-304.
163. Whitehouse PJ, Orgogozo JM, Becker RE, Gauthier S, Pontecorvo M, Erzigkeit H, et al. Quality-of-life assessment in dementia drug development. Position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 3:56-60.
164. Bergland A, Kirkevold M. Thriving--a useful theoretical perspective to capture the experience of well-being among frail elderly in nursing homes? *J Adv Nurs* 2001;36(3):426-32.
165. Gonzalez-Salvador T, Lyketsos CG, Baker A, Hovanec L, Roques C, Brandt J, et al. Quality of life in dementia patients in long-term care. *Int J Geriatr Psychiatry* 2000;15(2):181-9.

166. Hancock GA, Woods B, Challis D, Orrell M. The needs of older people with dementia in residential care. *Int J Geriatr Psychiatry* 2006;21(1):43-9.
167. Samus QM, Rosenblatt A, Steele C, Baker A, Harper M, Brandt J, et al. The association of neuropsychiatric symptoms and environment with quality of life in assisted living residents with dementia. *Gerontologist* 2005;45 Spec No 1(1):19-26.
168. Rabins PV, Kasper JD, Kleinman L, Black BS, Patrick DL. Concepts and methods in the development of the ADRQL: An instrument for assessing health related quality of life in persons with Alzheimer's disease. *J Ment Health Aging* 1999;5(1):33-48.
169. Cummings JL, Hegarty A. Neurology, psychiatry, and neuropsychiatry. *Neurology* 1994;44(2):209-213.
170. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde". *Clin Anat* 1995;8(6):429-31.
171. Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. *Int Psychogeriatr* 1996;8 Suppl 3:497-500.
172. Graeber MB, Kosel S, Egensperger R, Banati RB, Muller U, Bise K, et al. Rediscovery of the case described by Alois Alzheimer in 1911: historical, histological and molecular genetic analysis. *Neurogenetics* 1997;1(1):73-80.
173. Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. *Am J Geriatr Psychiatry* 2000;8(1):29-34.
174. Raskind MA. Geriatric psychopharmacology. Management of late-life depression and the noncognitive behavioral disturbances of Alzheimer's disease. *Psychiatr Clin North Am* 1993;16(4):815-27.
175. Sclan SG, Saillon A, Franssen E, HugonotDiener L, Reisberg B. The behavior pathology in Alzheimer's disease rating scale (BEHAVE-AD): Reliability and analysis of symptom category scores. 1996.
176. Cohen-Mansfield J, Billig N. Agitated behaviors in the elderly. I. A conceptual review. *J.Am.Geriatr.Soc.* 1986;34(10):711-721.
177. Cohen CA, Gold DP, Shulman KI, Wortley JT, McDonald G, Wargon M. Factors determining the decision to institutionalize dementing individuals: a prospective study. *Gerontologist* 1993;33(6):714-20.
178. Burns A, Folstein S, Brandt J, Folstein M. Clinical assessment of irritability, aggression, and apathy in Huntington and Alzheimer disease. *J Nerv Ment Dis* 1990;178(1):20-6.
179. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. IV: Disorders of behaviour. *Br J Psychiatry* 1990;157:86-94.
180. Cohen-Mansfield J, Marx MS, Werner P. Observational data on time use and behavior problems in the nursing home. *J.Appl.Gerontol.* 1992;11(1):111-121.
181. Cummings JL, Diaz C, Levy M, Binetti G, Litvan II. Neuropsychiatric Syndromes in Neurodegenerative Disease: Frequency and Signficance. *Semin Clin Neuropsychiatry* 1996;1(4):241-247.
182. Drevets WC, Rubin EH. Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. *Biol Psychiatry* 1989;25(1):39-48.
183. Lerner AJ, Koss E, Patterson MB, Ownby RL, Hedera P, Friedland RP, et al. Concomitants of visual hallucinations in Alzheimer's disease. *Neurology* 1994;44(3 Pt 1):523-7.
184. Levy ML, Cummings JL, Fairbanks LA, Bravi D, Calvani M, Carta A. Longitudinal assessment of symptoms of depression, agitation, and psychosis in 181 patients with Alzheimer's disease. *Am J Psychiatry* 1996;153(11):1438-43.

185. Oppenheim G. The earliest signs of Alzheimer's disease. *J Geriatr Psychiatry Neurol* 1994;7(2):116-20.
186. Reisberg B, Ferris SH, de Leon MJ, Kluger A, Franssen E, Borenstein J, et al. The stage specific temporal course of Alzheimer's disease: functional and behavioral concomitants based upon cross-sectional and longitudinal observation. *Prog Clin Biol Res* 1989;317:23-41.
187. Rosen J, Zubenko GS. Emergence of psychosis and depression in the longitudinal evaluation of Alzheimer's disease. *Biol Psychiatry* 1991;29(3):224-32.
188. Rubin EH, Kinscherf DA. Psychopathology of very mild dementia of the Alzheimer type. *Am J Psychiatry* 1989;146(8):1017-21.
189. Teri L, Larson EB, Reifler BV. Behavioral disturbance in dementia of the Alzheimer's type. *J Am Geriatr Soc* 1988;36(1):1-6.
190. Weiner MF, Williams B, Risser RC. Assessment of behavioral symptoms in community-dwelling dementia patients. *Am J Geriatr Psychiatry* 1997;5(1):26-30.
191. Wragg RE, Jeste DV. Overview of depression and psychosis in Alzheimer's disease. *Am J Psychiatry* 1989;146(5):577-87.
192. Robert PH, Verhey FR, Byrne EJ, Hurt C, De Deyn PP, Nobili F, et al. Grouping for behavioral and psychological symptoms in dementia: clinical and biological aspects. Consensus paper of the European Alzheimer disease consortium. *Eur Psychiatry* 2005;20(7):490-6.
193. Kunik ME, Snow-Turek AL, Iqbal N, Molinari VA, Orengo CA, Workman RH, et al. Contribution of psychosis and depression to behavioral disturbances in geropsychiatric inpatients with dementia. *J Gerontol A Biol Sci Med Sci* 1999;54(3):M157-61.
194. Lyketsos CG. Neuropsychiatric symptoms (behavioral and psychological symptoms of dementia) and the development of dementia treatments. *Int Psychogeriatr* 2007;19(3):409-20.
195. Jack CR, Jr., Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J Magn Reson Imaging* 2008;27(4):685-91.
196. De Jager CA, Hogervorst E, Combrinck M, Budge MM. Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's disease. *Psychol Med* 2003;33(6):1039-50.
197. Cummings JL. Theories behind existing scales for rating behavior in dementia. *Int Psychogeriatr* 1996;8 Suppl 3:293-300.
198. Cummings JL. Behavior as an efficacy outcome. *Alzheimer Dis.Assoc.Disord.* 1997;11 Suppl 4:v-vi.
199. Cummings JL, Masterman DL. Assessment of treatment-associated changes in behavior and cholinergic therapy of neuropsychiatric symptoms in Alzheimer's disease. *J Clin Psychiatry* 1998;59 Suppl 13:23-30.
200. Wood S, Cummings JL, Hsu MA, Barclay T, Wheatley MV, Yarema KT, et al. The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. *Am.J.Geriatr.Psychiatry* 2000;8(1):75-83.
201. Tariot PN, Mack JL, Patterson MB, Edland SD, Weiner MF, Fillenbaum G, et al. The Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease. The Behavioral Pathology Committee of the Consortium to Establish a Registry for Alzheimer's Disease. *Am.J.Psychiatry* 1995;152(9):1349-1357.
202. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* 2000;12(2):233-9.

203. Kang SJ, Choi SH, Lee BH, Jeong Y, Hahm DS, Han IW, et al. Caregiver-Administered Neuropsychiatric Inventory (CGA-NPI). *J.Geriatr.Psychiatry Neurol.* 2004;17(1):32-35.
204. Brodaty H, Corey-Bloom J, Potocnik FC, Truyen L, Gold M, Damaraju CR. Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer's disease. *Dement Geriatr Cogn Disord* 2005;20(2-3):120-32.
205. Forester B, Vanelli M, Hyde J, Perez R, Ahokpossi C, Sribney W, et al. Report on an open-label prospective study of divalproex sodium for the behavioral and psychological symptoms of dementia as monotherapy and in combination with second-generation antipsychotic medication. *Am J Geriatr Pharmacother* 2007;5(3):209-17.
206. Herrmann N, Gill SS, Bell CM, Anderson GM, Bronskill SE, Shulman KI, et al. A population-based study of cholinesterase inhibitor use for dementia. *J Am Geriatr Soc* 2007;55(10):1517-23.
207. Lyketsos CG, Sheppard JM, Steele CD, Kopunek S, Steinberg M, Baker AS, et al. Randomized, placebo-controlled, double-blind clinical trial of sertraline in the treatment of depression complicating Alzheimer's disease: initial results from the Depression in Alzheimer's Disease study. *Am J Psychiatry* 2000;157(10):1686-9.
208. Peskind ER, Tsuang DW, Bonner LT, Pascualy M, Riekse RG, Snowden MB, et al. Propranolol for disruptive behaviors in nursing home residents with probable or possible Alzheimer disease: a placebo-controlled study. *Alzheimer Dis Assoc Disord* 2005;19(1):23-8.
209. Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. *J Neurol Neurosurg Psychiatry* 2001;71(5):589-95.
210. Sommer OH, Aga O, Cvancarova M, Olsen IC, Selbaek G, Engedal K. Effect of oxcarbazepine in the treatment of agitation and aggression in severe dementia. *Dement Geriatr Cogn Disord* 2009;27(2):155-63.
211. Tariot PN, Cummings JL, Katz IR, Mintzer J, Perdomo CA, Schwam EM, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *J.Am.Geriatr.Soc.* 2001;49(12):1590-1599.
212. Winblad B, Jones RW, Wirth Y, Stoffler A, Mobius HJ. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. *Dement Geriatr Cogn Disord* 2007;24(1):20-7.
213. Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. *Dement Geriatr Cogn Disord* 2006;21(5-6):353-63.
214. Baiyewu O, Smith-Gamble V, Akinbiyi A, Lane KA, Hall KS, Ogunniyi A, et al. Behavioral and caregiver reaction of dementia as measured by the neuropsychiatric inventory in Nigerian community residents. *Int Psychogeriatr* 2003;15(4):399-409.
215. Bidzan L, Bidzan M. [Reliability of the Neuropsychiatric Inventory-Nursing Homes Polish version]. *Psychiatr Pol* 2005;39(6):1219-29.
216. Binetti G, Mega MS, Magni E, Padovani A, Rozzini L, Bianchetti A, et al. Behavioral disorders in Alzheimer disease: a transcultural perspective. *Arch Neurol* 1998;55(4):539-44.
217. Boada M, Tarraga L, Modinos G, Lopez OL, Cummings JL. [Neuropsychiatric Inventory-Nursing Home version (NPI-NH): Spanish validation]. *Neurologia* 2005;20(10):665-73.

218. Choi SH, Na DL, Kwon HM, Yoon SJ, Jeong JH, Ha CK. The Korean version of the neuropsychiatric inventory: a scoring tool for neuropsychiatric disturbance in dementia patients. *J Korean Med Sci* 2000;15(6):609-15.
219. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001;57(4):613-20.
220. Fuh JL, Liu CK, Mega MS, Wang SJ, Cummings JL. Behavioral disorders and caregivers' reaction in Taiwanese patients with Alzheimer's disease. *Int Psychogeriatr* 2001;13(1):121-8.
221. Gauthier S, Feldman H, Hecker J, Vellas B, Ames D, Subbiah P, et al. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *Int Psychogeriatr* 2002;14(4):389-404.
222. Hirono N, Mori E, Ikejiri Y, Imamura T, Shimomura T, Hashimoto M, et al. [Japanese version of the Neuropsychiatric Inventory--a scoring system for neuropsychiatric disturbance in dementia patients]. *No To Shinkei* 1997;49(3):266-71.
223. Kat MG, de Jonghe JF, Aalten P, Kalisvaart CJ, Droes RM, Verhey FR. [Neuropsychiatric symptoms of dementia: psychometric aspects of the Dutch Neuropsychiatric Inventory (NPI)]. *Tijdschr Gerontol Geriatr* 2002;33(4):150-5.
224. Lange RT, Hopp GA, Kang N. Psychometric properties and factor structure of the Neuropsychiatric Inventory Nursing Home version in an elderly neuropsychiatric population. *Int.J.Geriatr.Psychiatry* 2004;19(5):440-448.
225. Leung VP, Lam LC, Chiu HF, Cummings JL, Chen QL. Validation study of the Chinese version of the neuropsychiatric inventory (CNPI). *Int J Geriatr Psychiatry* 2001;16(8):789-93.
226. Politis AM, Mayer LS, Passa M, Maillis A, Lyketsos CG. Validity and reliability of the newly translated Hellenic Neuropsychiatric Inventory (H-NPI) applied to Greek outpatients with Alzheimer's disease: a study of disturbing behaviors among referrals to a memory clinic. *Int J Geriatr Psychiatry* 2004;19(3):203-8.
227. Selbaek G, Kirkevold O, Sommer OH, Engedal K. The reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, nursing home version (NPI-NH). *Int.Psychogeriatr.* 2008;20(2):375-382.
228. Reisberg B, Borenstein J, Franssen E, Shulman E, Steinberg G, Ferris SH. Remediable behavioral symptomatology in Alzheimer's disease. *Hosp.Community Psychiatry* 1986;37(12):1199-1201.
229. Patterson MB, Schnell AH, Martin RJ, Mendez MF, Smyth KA, Whitehouse PJ. Assessment of behavioral and affective symptoms in Alzheimer's disease. *J Geriatr Psychiatry Neurol* 1990;3(1):21-30.
230. Finkel SI, Lyons JS, Anderson RL. A brief agitation rating scale (BARS) for nursing home elderly. *J.Am.Geriatr.Soc.* 1993;41(1):50-52.
231. Monteiro IM, Boksay I, Auer SR, Torossian C, Ferris SH, Reisberg B. Addition of a frequency-weighted score to the Behavioral Pathology in Alzheimer's Disease Rating Scale: the BEHAVE-AD-FW: methodology and reliability. *Eur Psychiatry* 2001;16 Suppl 1:5s-24s.
232. Monteiro IM, Boksay I, Auer SR, Torossian C, Sinaiko E, Reisberg B. Reliability of routine clinical instruments for the assessment of Alzheimer's disease administered by telephone. *J Geriatr Psychiatry Neurol* 1998;11(1):18-24.
233. Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. *J Clin Psychiatry* 1999;60(2):107-15.

234. Reisberg B, Ferris SH, Torossian C, Kluger A, Monteiro I. Pharmacologic treatment of Alzheimer's disease: a methodologic critique based upon current knowledge of symptomatology and relevance for drug trials. *Int Psychogeriatr* 1992;4 Suppl 1:9-42.
235. Brodaty H, Green A, Koschera A. Meta-analysis of psychosocial interventions for caregivers of people with dementia. *J.Am.Geriatr.Soc.* 2003;51(5):657-664.
236. Mack JL, Patterson MB, Tariot PN. Behavior Rating Scale for Dementia: development of test scales and presentation of data for 555 individuals with Alzheimer's disease. *J Geriatr Psychiatry Neurol* 1999;12(4):211-23.
237. Devanand DP, Miller L, Richards M, Marder K, Bell K, Mayeux R, et al. The Columbia University Scale for Psychopathology in Alzheimer's disease. *Arch Neurol* 1992;49(4):371-6.
238. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. *Biol.Psychiatry* 1988;23(3):271-284.
239. Patterson MB, Mack JL, Mackell JA, Thomas R, Tariot P, Weiner M, et al. A longitudinal study of behavioral pathology across five levels of dementia severity in Alzheimer's disease: the CERAD Behavior Rating Scale for Dementia. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 2:S40-4.
240. Weiner MF, Koss E, Patterson M, Jin S, Teri L, Thomas R, et al. A comparison of the Cohen-Mansfield agitation inventory with the CERAD behavioral rating scale for dementia in community-dwelling persons with Alzheimer's disease. *J Psychiatr Res* 1998;32(6):347-51.
241. Mohs RC, Cohen L. Alzheimer's Disease Assessment Scale (ADAS). *Psychopharmacol Bull* 1988;24(4):627-8.
242. Bucht G, Adolfsson R. The Comprehensive Psychopathological Rating Scale in patients with dementia of Alzheimer type and multiinfarct dementia. *Acta Psychiatr Scand* 1983;68(4):263-70.
243. Hwang TJ, Masterman DL, Ortiz F, Fairbanks LA, Cummings JL. Mild cognitive impairment is associated with characteristic neuropsychiatric symptoms. *Alzheimer Dis Assoc Disord* 2004;18(1):17-21.
244. Fuh JL, Wang SJ, Cummings JL. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. *J Neurol Neurosurg Psychiatry* 2005;76(10):1337-41.
245. Liu W, Miller BL, Kramer JH, Rankin K, Wyss-Coray C, Gearhart R, et al. Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. *Neurology* 2004;62(5):742-8.
246. Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2006;77(1):4-7.
247. Ritchie K. Behavioral disturbances of dementia in ambulatory care settings. *Int Psychogeriatr* 1996;8 Suppl 3:439-42.
248. Holtzer R, Tang MX, Devanand DP, Albert SM, Wegesin DJ, Marder K, et al. Psychopathological features in Alzheimer's disease: course and relationship with cognitive status. *J Am Geriatr Soc* 2003;51(7):953-60.
249. Ballard CG, O'Brien JT, Coope B, Wilcock G. Psychotic symptoms in dementia and the rate of cognitive decline. *J Am Geriatr Soc* 1997;45(8):1031-2.
250. Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Behavioral symptoms and the administration of psychotropic drugs to aged patients with dementia in nursing homes and in acute geriatric wards. *Int Psychogeriatr* 2004;16(1):61-74.
251. Schneider LS, Dagerman KS. Psychosis of Alzheimer's disease: clinical characteristics and history. *J Psychiatr Res* 2004;38(1):105-11.

252. Zuidema SU, Derksen E, Verhey FR, Koopmans RT. Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. *Int J Geriatr Psychiatry* 2007;22(7):632-8.
253. Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Predictors of neuropsychiatric symptoms in nursing home patients: influence of gender and dementia severity. *Int J Geriatr Psychiatry* 2009.
254. Gruber-Baldini AL, Boustani M, Sloane PD, Zimmerman S. Behavioral symptoms in residential care/assisted living facilities: prevalence, risk factors, and medication management. *J Am Geriatr Soc* 2004;52(10):1610-7.
255. Robert PH, Berr C, Volteau M, Bertogliati C, Benoit M, Sarazin M, et al. Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: a one-year follow-up study. *Clin Neurol Neurosurg* 2006;108(8):733-6.
256. Savva GM, Zaccai J, Matthews FE, Davidson JE, McKeith I, Brayne C. Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *Br J Psychiatry* 2009;194(3):212-9.
257. Aalten P, Verhey FR, Boziki M, Bullock R, Byrne EJ, Camus V, et al. Neuropsychiatric syndromes in dementia. Results from the European Alzheimer Disease Consortium: part I. *Dement Geriatr Cogn Disord* 2007;24(6):457-63.
258. Aalten P, Verhey FR, Boziki M, Brugnolo A, Bullock R, Byrne EJ, et al. Consistency of neuropsychiatric syndromes across dementias: results from the European Alzheimer Disease Consortium. Part II. *Dement Geriatr Cogn Disord* 2008;25(1):1-8.
259. Lyketsos CG, Sheppard JM, Steinberg M, Tschanz JA, Norton MC, Steffens DC, et al. Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. *Int J Geriatr Psychiatry* 2001;16(11):1043-53.
260. Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry* 2008;23(2):170-7.
261. Selbaek G, Kirkevold O, Engedal K. The course of psychiatric and behavioral symptoms and the use of psychotropic medication in patients with dementia in Norwegian nursing homes--a 12-month follow-up study. *Am.J.Geriatr.Psychiatry* 2008;16(7):528-536.
262. Ryu SH, Katona C, Rive B, Livingston G. Persistence of and changes in neuropsychiatric symptoms in Alzheimer disease over 6 months: the LASER-AD study. *Am J Geriatr Psychiatry* 2005;13(11):976-83.
263. Stern Y, Mayeux R, Sano M, Hauser WA, Bush T. Predictors of disease course in patients with probable Alzheimer's disease. *Neurology* 1987;37(10):1649-1653.
264. Smith GE, Kokmen E, O'Brien PC. Risk factors for nursing home placement in a population-based dementia cohort. *J.Am.Geriatr.Soc.* 2000;48(5):519-525.
265. Wimo A, Gustafsson L, Mattson B. Predictive validity of factors influencing the institutionalization of elderly people with psycho-geriatric disorders. *Scand.J.Prim.Health Care* 1992;10(3):185-191.
266. Yaffe K, Fox P, Newcomer R, Sands L, Lindquist K, Dane K, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* 2002;287(16):2090-7.
267. Cummings JL, Mackell J, Kaufer D. Behavioral effects of current Alzheimer's disease treatments: a descriptive review. *Alzheimers Dement* 2008;4(1):49-60.
268. Donaldson C, Tarrier N, Burns A. The impact of the symptoms of dementia on caregivers. *Br J Psychiatry* 1997;170:62-8.

269. Aud MA. Dangerous wandering: elopements of older adults with dementia from long-term care facilities. *Am J Alzheimers Dis Other Demen* 2004;19(6):361-8.
270. Hawes C, Phillips CD, Rose M, Holan S, Sherman M. A national survey of assisted living facilities. *Gerontologist* 2003;43(6):875-82.
271. Cuijpers P. Depressive disorders in caregivers of dementia patients: a systematic review. *Aging Ment Health* 2005;9(4):325-30.
272. Haley WE, Levine EG, Brown SL, Berry JW, Hughes GH. Psychological, social, and health consequences of caring for a relative with senile dementia. *J Am Geriatr Soc* 1987;35(5):405-11.
273. Ulstein ID, Sandvik L, Wyller TB, Engedal K. A one-year randomized controlled psychosocial intervention study among family carers of dementia patients--effects on patients and carers. *Dement Geriatr Cogn Disord* 2007;24(6):469-75.
274. Brodaty H, Green A, Low LF. Family carers for people with dementia. In: O'Brien J, Ames D, Burns A, editors. *Dementia*. 3rd ed: Arnold, London, 2005:118-1.
275. Ulstein I, Wyller TB, Engedal K. Correlates of intrusion and avoidance as stress response symptoms in family carers of patients suffering from dementia. *Int J Geriatr Psychiatry* 2008;23(10):1051-7.
276. Gaugler JE, Yu F, Krichbaum K, Wyman JF. Predictors of nursing home admission for persons with dementia. *Med Care* 2009;47(2):191-8.
277. Ulstein I, Bruun Wyller T, Engedal K. The relative stress scale, a useful instrument to identify various aspects of carer burden in dementia? *Int J Geriatr Psychiatry* 2007;22(1):61-7.
278. Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc* 1998;46(2):210-5.
279. Sink KM, Covinsky KE, Barnes DE, Newcomer RJ, Yaffe K. Caregiver characteristics are associated with neuropsychiatric symptoms of dementia. *J Am Geriatr Soc* 2006;54(5):796-803.
280. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56(9):1154-1166.
281. Mittelman MS, Brodaty H, Wallen AS, Burns A. A three-country randomized controlled trial of a psychosocial intervention for caregivers combined with pharmacological treatment for patients with Alzheimer disease: effects on caregiver depression. *Am J Geriatr Psychiatry* 2008;16(11):893-904.
282. Mittelman MS, Ferris SH, Shulman E, Steinberg G, Levin B. A family intervention to delay nursing home placement of patients with Alzheimer disease. A randomized controlled trial. *JAMA* 1996;276(21):1725-1731.
283. Anderson RA, Issel LM, McDaniel Jr RR. Nursing homes as complex adaptive systems: relationship between management practice and resident outcomes. *Nurs Res* 2003;52(1):12-21.
284. Waaler HM. [Nursing needs among recipients of community health care]. *Tidsskr Nor Laegeforen* 2005;125(8):1012-4.
285. Mollica R. The evolution of assisted living. A view from the states. *Caring* 2001;20(8):24-6.
286. Burgio LD, Park NS, Hardin JM, Sun F. A longitudinal examination of agitation and resident characteristics in the nursing home. *Gerontologist* 2007;47(5):642-9.

287. Saarela TM, Finne-Soveri H, Liedenpohja AM, Noro A. Comparing psychogeriatric units to ordinary long-term care units - are there differences in case-mix or clinical symptoms? *Nord J Psychiatry* 2008;62(1):32-8.
288. Buckwalter KC, Maas M, Reed D. Assessing family and staff caregiver outcomes in Alzheimer disease research. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 6:105-16.
289. McAiney CA. The development of the empowered aide model. An intervention for long-term care staff who care for Alzheimer's residents. *J Gerontol Nurs* 1998;24(1):17-22; quiz 60.
290. Karner TX, Montgomery RJ, Dobbs D, Wittmaier C. Increasing staff satisfaction. The impact of SCUs and family involvement. *J Gerontol Nurs* 1998;24(2):39-44.
291. Montgomery RJ. The family role in the context of long-term care. *J Aging Health* 1999;11(3):383-416.
292. Kirkevold O, Engedal K. The quality of care in Norwegian nursing homes. *Scand J Caring Sci* 2006;20(2):177-83.
293. Edvardsson D, Sandman PO, Nay R, Karlsson S. Associations between the working characteristics of nursing staff and the prevalence of behavioral symptoms in people with dementia in residential care. *Int Psychogeriatr* 2008;20(4):764-76.
294. Edvardsson D, Sandman PO, Nay R, Karlsson S. Predictors of job strain in residential dementia care nursing staff. *J Nurs Manag* 2009;17(1):59-65.
295. Cohen-Mansfield J, Parpura-Gill A. Practice style in the nursing home: dimensions for assessment and quality improvement. *Int J Geriatr Psychiatry* 2008;23(4):376-86.
296. Haggstrom E, Skovdahl K, Flackman B, Kihlgren AL, Kihlgren M. Work satisfaction and dissatisfaction--caregivers' experiences after a two-year intervention in a newly opened nursing home. *J Clin Nurs* 2005;14(1):9-19.
297. Laine J, Noro A, Finne-Soveri H, Hakkinen U. Patient- and ward-level determinants of nursing time in nursing facilities. *J Health Serv Res Policy* 2005;10(4):226-31.
298. Pekkarinen L, Elovainio M, Sinervo T, Finne-Soveri H, Noro A. Nursing working conditions in relation to restraint practices in long-term care units. *Med Care* 2006;44(12):1114-20.
299. Pekkarinen L, Sinervo T, Elovainio M, Noro A, Finne-Soveri H. Drug use and pressure ulcers in long-term care units: do nurse time pressure and unfair management increase the prevalence? *J Clin Nurs* 2008;17(22):3067-73.
300. Cohen-Mansfield J. Nonpharmacologic interventions for inappropriate behaviors in dementia: a review, summary, and critique. *Am.J.Geriatr.Psychiatry* 2001;9(4):361-381.
301. Ragsdale V, McDougall GJ, Jr. The changing face of long-term care: looking at the past decade. *Issues Ment Health Nurs* 2008;29(9):992-1001.
302. Hemels ME, Lanctot KL, Iskedjian M, Einarson TR. Clinical and economic factors in the treatment of behavioural and psychological symptoms of dementia. *Drugs Aging* 2001;18(7):527-50.
303. Vuori H. Health for all through research on primary care. *Scand J Prim Health Care* 1992;10(1):3-6.
304. Belden, Russonello, Steward. Caring for Persons with Alzheimer's: 2004 National Survey. In: Caregiving AsAaNAf, editor, 2004.
305. Enright RB, Jr. Time spent caregiving and help received by spouses and adult children of brain-impaired adults. *Gerontologist* 1991;31(3):375-83.
306. Horowitz A. Sons and daughters as caregivers to older parents: differences in role performance and consequences. *Gerontologist* 1985;25(6):612-7.
307. Horowitz A. Family caregiving to the frail elderly. *Annu Rev Gerontol Geriatr* 1985;5:194-246.

308. Rice DP, Fox PJ, Max W, Webber PA, Lindeman DA, Hauck WW, et al. The economic burden of Alzheimer's disease care. *Health Aff (Millwood)* 1993;12(2):164-76.
309. Langa KM, Chernew ME, Kabeto MU, Herzog AR, Ofstedal MB, Willis RJ, et al. National estimates of the quantity and cost of informal caregiving for the elderly with dementia. *J Gen Intern Med* 2001;16(11):770-8.
310. Greene VL, Ondrich JI. Risk factors for nursing home admissions and exits: a discrete-time hazard function approach. *J Gerontol* 1990;45(6):S250-8.
311. Webber PA, Fox P, Burnette D. Living alone with Alzheimer's disease: effects on health and social service utilization patterns. *Gerontologist* 1994;34(1):8-14.
312. Fox PJ. Service use and cost outcomes for persons with Alzheimer disease. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 6:125-34.
313. Comas-Herrera A, Wittenberg R, Pickard L, Knapp M. Cognitive impairment in older people: future demand for long-term care services and the associated costs. *Int J Geriatr Psychiatry* 2007;22(10):1037-45.
314. Max W. The cost of Alzheimer's disease. Will drug treatment ease the burden? *Pharmacoeconomics* 1996;9(1):5-10.
315. Wimo A, Karlsson G, Sandman PO, Winblad B. [Care of patients with dementia--a ticking cost bomb?]. *Nord Med* 1995;110(4):123-6.
316. Ernst RL, Hay JW, Fenn C, Tinklenberg J, Yesavage JA. Cognitive function and the costs of Alzheimer disease. An exploratory study. *Arch Neurol* 1997;54(6):687-93.
317. Jonsson L, Eriksdotter Jonhagen M, Kilander L, Soininen H, Hallikainen M, Waldemar G, et al. Determinants of costs of care for patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2006;21(5):449-59.
318. Cohen-Mansfield J, Werner P, Marx MS. An observational study of agitation in agitated nursing home residents. *Int.Psychogeriatr.* 1989;1(2):153-165.
319. Cohen-Mansfield J. Agitated behaviour and cognitive functioning in nursing home residents: Preliminary results. *Clin. Gerontol.* 1988;7:11-22.
320. Finkel SJ, Lyons JS, Anderson RL. Reliability and validity of the Cohen Mansfield Agitation Inventory in institutionalized elderly. *Int J Geriatr Psychiatry* 1992;7:487-490.
321. Cohen-Mansfield J. Assessment of agitation. *Int.Psychogeriatr.* 1996;8(2):233-245.
322. Cohen-Mansfield J. Conceptualization of agitation: results based on the Cohen-Mansfield Agitation Inventory and the Agitation Behavior Mapping Instrument. *Int Psychogeriatr* 1996;8 Suppl 3:309-15; discussion 351-4.
323. Taft LB. Conceptual analysis of agitation in the confused elderly. *Arch Psychiatr Nurs* 1989;3(2):102-7.
324. Ellis JL. Factors associated with behavioral symptoms in persons with dementia residing in assisted living. University of Wisconsin-Milwaukee, 2006.
325. Cipher DJ, Clifford PA, Roper KD. Behavioral manifestations of pain in the demented elderly. *J Am Med Dir Assoc* 2006;7(6):355-65.
326. Raskind MA. Evaluation and management of aggressive behavior in the elderly demented patient. *J Clin Psychiatry* 1999;60 Suppl 15:45-9.
327. Devanand DP, Brockington CD, Moody BJ, Brown RP, Mayeux R, Endicott J, et al. Behavioral syndromes in Alzheimer's disease. *Int Psychogeriatr* 1992;4 Suppl 2:161-84.
328. Ryden MB. Aggressive behavior in persons with dementia who live in the community. *Alzheimer Dis Assoc Disord* 1988;2(4):342-55.
329. Zimmer JG, Watson N, Treat A. Behavioral problems among patients in skilled nursing facilities. *Am J Public Health* 1984;74(10):1118-21.

330. Winger J, Schirm V, Stewart D. Aggressive behavior in long-term care. *J Psychosoc Nurs Ment Health Serv* 1987;25(4):28-33.
331. Patel V, Hope RA. Aggressive behaviour in elderly psychiatric inpatients. *Acta Psychiatr.Scand.* 1992;85(2):131-135.
332. Patel V, Hope RA. A rating scale for aggressive behaviour in the elderly--the RAGE. *Psychol.Med.* 1992;22(1):211-221.
333. Lesser JM, Hughes S. Psychosis-related disturbances. Psychosis, agitation, and disinhibition in Alzheimer's disease: definitions and treatment options. *Geriatrics* 2006;61(12):14-20.
334. Rabinowitz J, Davidson M, De Deyn PP, Katz I, Brodaty H, Cohen-Mansfield J. Factor analysis of the Cohen-Mansfield Agitation Inventory in three large samples of nursing home patients with dementia and behavioral disturbance. *Am.J.Geriatr.Psychiatry* 2005;13(11):991-998.
335. Poole J, Mott S. Agitated older patients: nurses' perceptions and reality. *Int J Nurs Pract* 2003;9(5):306-12.
336. Engedal K, Haugen PK. *Demens - fakta og utfordringer*. 3.utg., rev. og utvidet edn ed. Sem, Norway: Nasjonalt kompetansesenter for aldersdemens, 2004.
337. Cohen-Mansfield J, Jensen B. Nursing home physicians' knowledge of and attitudes toward nonpharmacological interventions for treatment of behavioral disturbances associated with dementia. *J Am Med Dir Assoc* 2008;9(7):491-8.
338. Gerdner LA, Buckwalter KC. A nursing challenge: Assessment and management of agitation in Alzheimer's patients. *J Gerontol Nurs* 1994;20(4):11-20.
339. Choy CN, Lam LC, Chan WC, Li SW, Chiu HF. Agitation in Chinese elderly: validation of the Chinese version of the Cohen-Mansfield Agitation Inventory. *Int Psychogeriatr* 2001;13(3):325-35.
340. de Jonghe JF, Kat MG. Factor structure and validity of the Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI-D). *J.Am.Geriatr.Soc.* 1996;44(7):888-889.
341. Miller RJ, Snowdon J, Vaughan R. The use of the Cohen-Mansfield Agitation Inventory in the assessment of behavioral disorders in nursing homes. *J Am Geriatr Soc* 1995;43(5):546-9.
342. Schreiner AS, Yamamoto E, Shiotani H. Agitated behavior in elderly nursing home residents with dementia in Japan. *J Gerontol B Psychol Sci Soc Sci* 2000;55(3):P180-6.
343. Suh GH. Agitated behaviours among the institutionalized elderly with dementia: validation of the Korean version of the Cohen-Mansfield Agitation Inventory. *Int J Geriatr Psychiatry* 2004;19(4):378-85.
344. Vespa A, Gori S, Bonaiuto S, Cruciani G, Spazzafumo L. Validation of the Cohen-Mansfield agitation inventory (CMAI-long form) on a sample of Italian demented patients. *Arch.Gerontol.Geriatr.Suppl* 2002;8:377-383.
345. Weiner MF, Tractenberg RE, Jin S, Gamst A, Thomas RG, Koss E, et al. Assessing Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory: scoring and clinical implications. *J Psychiatr Res* 2002;36(1):19-25.
346. Chrisman M, Tabar D, Whall AL, Booth DE. Agitated behavior in the cognitively impaired elderly. *J Gerontol Nurs* 1991;17(12):9-13.
347. Boustani M, Zimmerman S, Williams CS, Gruber-Baldini AL, Watson L, Reed PS, et al. Characteristics associated with behavioral symptoms related to dementia in long-term care residents. *Gerontologist* 2005;45 Spec No 1(1):56-61.
348. Cakir S, Kulaksizoglu IB. The efficacy of mirtazapine in agitated patients with Alzheimer's disease: A 12-week open-label pilot study. *Neuropsychiatr Dis Treat* 2008;4(5):963-6.

349. Porsteinsson AP, Tariot PN, Erb R, Cox C, Smith E, Jakimovich L, et al. Placebo-controlled study of divalproex sodium for agitation in dementia. *Am J Geriatr Psychiatry* 2001;9(1):58-66.
350. Lam LCW, Chiu HFK, Ng J. Aggressive behaviour in the Chinese elderly - validation of the Chinese version of the Rating Scale for Aggressive Behaviour in the Elderly (RAGE) in hospital and nursing home settings. *Int.J.Geriatr.Psychiatry* 1997;12:678-681.
351. Shah AK, Chiu E, Ames D. The relationship between two aggression scales used in nursing homes for the elderly. *Int.J.Geriatr.Psychiatry* 1997;12:628-631.
352. Snowdon J, Miller R, Vaughan R. Behavioural problems in Sydney nursing homes. *Int. J. Geriatr. Psychiatry* 1996;11:535-541.
353. Rosen J, Burgio L, Kollar M, et al. The Pittsburgh Agitation Scale; a user-friendly instrument for rating agitation in dementia patients. *Am.J.Geriatr.Psychiatry* 1994;2:60-74.
354. Holmes C, Hopkins V, Hensford C, MacLaughlin V, Wilkinson D, Rosenvinge H. Lavender oil as a treatment for agitated behaviour in severe dementia: a placebo controlled study. *Int J Geriatr Psychiatry* 2002;17(4):305-8.
355. Palmsteirna T, Wistedt B. Staff observation aggression scale, SOAS: presentation and evaluation. *Acta Psychiatr Scand* 1987;76(6):657-63.
356. Nijman H, Palmstierna T. Measuring aggression with the staff observation aggression scale--revised. *Acta Psychiatr Scand Suppl* 2002(412):101-2.
357. Nijman HL, Palmstierna T, Almvik R, Stolker JJ. Fifteen years of research with the Staff Observation Aggression Scale: a review. *Acta Psychiatr Scand* 2005;111(1):12-21.
358. Lambert MJ, Hill CE, editors. *Assessing psychotherapy outcomes and processes*. 4th edition ed. New York: Wiley and Sons, 1994.
359. Shah AK, Fineberg NA, James DV. Violence among psychiatric inpatients. *Acta Psychiatr Scand* 1991;84(4):305-9.
360. Shah A. Some methodological issues in using aggression rating scales in intervention studies among institutionalized elderly. *Int Psychogeriatr* 1999;11(4):439-44.
361. Lanza ML. Origins of aggression. *J Psychosoc Nurs Ment Health Serv* 1983;21(6):11-6.
362. Shah A, Evans H, Parkash N. Evaluation of three aggression/agitation behaviour rating scales for use on an acute admission and assessment psychogeriatric ward. *Int J Geriatr Psychiatry* 1998;13(6):415-20.
363. Kirkevold O, Sandvik L, Engedal K. Use of constraints and their correlates in Norwegian nursing homes. *Int.J.Geriatr.Psychiatry* 2004;19(10):980.
364. Testad I, Aasland AM, Aarsland D. The effect of staff training on the use of restraint in dementia: a single-blind randomised controlled trial. *Int.J.Geriatr.Psychiatry* 2005;20(6):587-590.
365. Lackner TE, Wyman JF, McCarthy TC, Monigold M, Davey C. Randomized, Placebo-Controlled Trial of the Cognitive Effect, Safety, and Tolerability of Oral Extended-Release Oxybutynin in Cognitively Impaired Nursing Home Residents with Urge Urinary Incontinence. *Journal of the American Geriatrics Society* 2009;17(5):40-42.
366. Lee HB, Hanner JA, Yokley JL, Appleby B, Hurowitz L, Lyketsos CG. Clozapine for treatment-resistant agitation in dementia. *J Geriatr Psychiatry Neurol* 2007;20(3):178-82.
367. Spear J, Chawla S, O'Reilly M, Rock D. Does the HoNOS 65+ meet the criteria for a clinical outcome indicator for mental health services for older people? *Int.J.Geriatr.Psychiatry* 2002;17(3):226-230.
368. Tsolaki M. Evaluation of tiapride in agitated elderly outpatients: an open study. *Hum Psychopharmacol* 2001;16(5):417-422.

369. Wiener PK, Kiosses DN, Klimstra S, Murphy C, Alexopoulos GS. A short-term inpatient program for agitated demented nursing home residents. *Int.J.Geriatr.Psychiatry* 2001;16(9):866-872.
370. Devanand DP, Jacobs DM, Tang MX, Del Castillo-Castaneda C, Sano M, Marder K, et al. The course of psychopathologic features in mild to moderate Alzheimer disease. *Arch Gen Psychiatry* 1997;54(3):257-63.
371. Senanarong V, Cummings JL, Fairbanks L, Mega M, Masterman DM, O'Connor SM, et al. Agitation in Alzheimer's disease is a manifestation of frontal lobe dysfunction. *Dement.Geriatr.Cogn Disord.* 2004;17(1-2):14-20.
372. McShane R, Keene J, Fairburn C, Jacoby R, Hope T. Psychiatric symptoms in patients with dementia predict the later development of behavioural abnormalities. *Psychol.Med.* 1998;28(5):1119-1127.
373. Aarsland D, Cummings JL, Yenner G, Miller B. Relationship of aggressive behavior to other neuropsychiatric symptoms in patients with Alzheimer's disease. *Am J Psychiatry* 1996;153(2):243-7.
374. Gilley DW, Wilson RS, Beckett LA, Evans DA. Psychotic symptoms and physically aggressive behavior in Alzheimer's disease. *J Am Geriatr Soc* 1997;45(9):1074-9.
375. Cohen-Mansfield J. Agitated behavior in persons with dementia: the relationship between type of behavior, its frequency, and its disruptiveness. *J Psychiatr Res* 2008;43(1):64-9.
376. Engelborghs S, Maertens K, Nagels G, Vloeberghs E, Marien P, Symons A, et al. Neuropsychiatric symptoms of dementia: cross-sectional analysis from a prospective, longitudinal Belgian study. *Int J Geriatr Psychiatry* 2005;20(11):1028-37.
377. Rosen HJ, Hartikainen KM, Jagust W, Kramer JH, Reed BR, Cummings JL, et al. Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. *Neurology* 2002;58(11):1608-15.
378. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;51(6):1546-54.
379. Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Predictors of neuropsychiatric symptoms in nursing home patients: influence of gender and dementia severity. *Int J Geriatr Psychiatry* 2009;24(10):1079-1086.
380. Forstl H, Burns A, Levy R, Cairns N. Neuropathological correlates of psychotic phenomena in confirmed Alzheimer's disease. *Br J Psychiatry* 1994;165(2):53-9.
381. Minger SL, Esiri MM, McDonald B, Keene J, Carter J, Hope T, et al. Cholinergic deficits contribute to behavioral disturbance in patients with dementia. *Neurology* 2000;55(10):1460-7.
382. Russo-Neustadt A, Cotman CW. Adrenergic receptors in Alzheimer's disease brain: selective increases in the cerebella of aggressive patients. *J Neurosci* 1997;17(14):5573-80.
383. Sharp SI, Ballard CG, Chen CP, Francis PT. Aggressive behavior and neuroleptic medication are associated with increased number of alpha1-adrenoceptors in patients with Alzheimer disease. *Am J Geriatr Psychiatry* 2007;15(5):435-7.
384. Lehninger FW, Ravindran VL, Stewart JT. Management strategies for problem behaviors in the patient with dementia. *Geriatrics* 1998;53(4):55-6, 66-8, 71-5.
385. Lindenmayer JP. The pathophysiology of agitation. *J Clin Psychiatry* 2000;61 Suppl 14:5-10.
386. Siegel A, Victoroff J. Understanding human aggression: New insights from neuroscience. *Int J Law Psychiatry* 2009;32(4):209-15.

387. Siever LJ. Neurobiology of aggression and violence. *Am J Psychiatry* 2008;165(4):429-42.
388. Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat Neurosci* 1999;2(11):1032-7.
389. Soloff PH, Meltzer CC, Becker C, Greer PJ, Kelly TM, Constantine D. Impulsivity and prefrontal hypometabolism in borderline personality disorder. *Psychiatry Res* 2003;123(3):153-63.
390. Volkow ND, Tancredi LR, Grant C, Gillespie H, Valentine A, Mullani N, et al. Brain glucose metabolism in violent psychiatric patients: a preliminary study. *Psychiatry Res* 1995;61(4):243-53.
391. Lai MK, Tsang SW, Francis PT, Esiri MM, Keene J, Hope T, et al. Reduced serotonin 5-HT1A receptor binding in the temporal cortex correlates with aggressive behavior in Alzheimer disease. *Brain Res* 2003;974(1-2):82-7.
392. Garcia-Alloza M, Gil-Bea FJ, Diez-Ariza M, Chen CP, Francis PT, Lasheras B, et al. Cholinergic-serotonergic imbalance contributes to cognitive and behavioral symptoms in Alzheimer's disease. *Neuropsychologia* 2005;43(3):442-9.
393. Garcia-Alloza M, Tsang SW, Gil-Bea FJ, Francis PT, Lai MK, Marcos B, et al. Involvement of the GABAergic system in depressive symptoms of Alzheimer's disease. *Neurobiol Aging* 2006;27(8):1110-7.
394. Tekin S, Mega MS, Masterman DM, Chow T, Garakian J, Vinters HV, et al. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. *Ann Neurol* 2001;49(3):355-61.
395. Sultzer DL, Mahler ME, Mandelkern MA, Cummings JL, Van Gorp WG, Hinkin CH, et al. The relationship between psychiatric symptoms and regional cortical metabolism in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 1995;7(4):476-84.
396. Hirono N, Mega MS, Dinov ID, Mishkin F, Cummings JL. Left frontotemporal hypoperfusion is associated with aggression in patients with dementia. *Arch Neurol* 2000;57(6):861-6.
397. Herrmann N, Lanctot KL, Khan LR. The role of norepinephrine in the behavioral and psychological symptoms of dementia. *J Neuropsychiatry Clin Neurosci* 2004;16(3):261-76.
398. Sukonick DL, Pollock BG, Sweet RA, Mulsant BH, Rosen J, Klunk WE, et al. The 5-HTTPR*S/*L polymorphism and aggressive behavior in Alzheimer disease. *Arch Neurol* 2001;58(9):1425-8.
399. Gormley N, Rizwan MR, Lovestone S. Clinical predictors of aggressive behaviour in Alzheimer's disease. *Int J Geriatr Psychiatry* 1998;13(2):109-15.
400. Pelletier IC, Landreville P. Discomfort and agitation in older adults with dementia. *BMC Geriatr* 2007;7:27.
401. Algase DL, Beck C, Kolanowski A, Whall A, Berent S, Richards K, et al. Need-driven dementia-compromised behavior: An alternative view of disruptive behavior. *American Journal of Alzheimer's Disease and Other Dementias* 1996;11(Nov):10-19.
402. Deutsch LH, Rovner BW. Agitation and other noncognitive abnormalities in Alzheimer's disease. *Psychiatr.Clin.North Am.* 1991;14(2):341-351.
403. Middleton JI, Stewart NJ, Richardson JS. Caregiver distress. Related to disruptive behaviors on special care units versus traditional long-term care units. *J Gerontol Nurs* 1999;25(3):11-9.
404. Zieber CG, Hagen B, Armstrong-Esther C, Aho M. Pain and agitation in long-term care residents with dementia: use of the Pittsburgh Agitation Scale. *Int J Palliat Nurs* 2005;11(2):71-8.

405. Kelley LS, Buckwalter KC, Maas ML. Access to health care resources for family caregivers of elderly persons with dementia. *Nurs Outlook* 1999;47(1):8-14.
406. Kim EJ, Buschmann MT. The effect of expressive physical touch on patients with dementia. *Int J Nurs Stud* 1999;36(3):235-43.
407. Hagberg B, Samuelsson G, Lindberg B, Dehlin O. Stability and change of personality in old age and its relation to survival. *J Gerontol* 1991;46(6):P285-91.
408. Cohen-Mansfield J, Werner P. Longitudinal predictors of non-aggressive agitated behaviors in the elderly. *Int.J.Geriatr.Psychiatry* 1999;14(10):831-844.
409. Cohen-Mansfield j. Nonpharmacological management of behavioral problems in persons with dementia: The TREA model. *Alzheimer's Care Quarterly* 2000;1(4):22-34.
410. Marengoni A, Winblad B, Karp A, Fratiglioni L. Prevalence of chronic diseases and multimorbidity among the elderly population in Sweden. *Am J Public Health* 2008;98(7):1198-200.
411. Jackson GA, Templeton GJ, Whyte J. An overview of behaviour difficulties found in long-term elderly care settings. *Int J Geriatr Psychiatry* 1999;14(6):426-30.
412. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing* 2006;35(4):350-64.
413. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. *J Am Geriatr Soc* 2002;50(10):1723-32.
414. Inouye SK. Delirium in hospitalized older patients: recognition and risk factors. *J Geriatr Psychiatry Neurol* 1998;11(3):118-25; discussion 157-8.
415. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. *J Gen Intern Med* 1998;13(4):234-42.
416. O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *J Am Geriatr Soc* 1997;45(2):174-8.
417. Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. *Age Ageing* 1999;28(6):551-6.
418. Levkoff SE, Evans DA, Liptzin B, Cleary PD, Lipsitz LA, Wetle TT, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med* 1992;152(2):334-40.
419. Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age Ageing* 2009;38(1):19-26.
420. Cole M, McCusker J, Dendukuri N, Han L. The prognostic significance of subsyndromal delirium in elderly medical inpatients. *J Am Geriatr Soc* 2003;51(6):754-60.
421. Edlund A, Lundstrom M, Sandberg O, Bucht G, Brannstrom B, Gustafson Y. Symptom profile of delirium in older people with and without dementia. *J Geriatr Psychiatry Neurol* 2007;20(3):166-71.
422. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry* 2006;63(5):530-8.
423. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? *J Neurol Neurosurg Psychiatry* 2004;75(12):1662-6.
424. Verhey FR, Ponds RW, Rozendaal N, Jolles J. Depression, insight, and personality changes in Alzheimer's disease and vascular dementia. *J Geriatr Psychiatry Neurol* 1995;8(1):23-7.
425. Harwood DG, Sultzer DL. "Life is not worth living": hopelessness in Alzheimer's disease. *J Geriatr Psychiatry Neurol* 2002;15(1):38-43.

426. Harwood DG, Sultzer DL, Wheatley MV. Impaired insight in Alzheimer disease: association with cognitive deficits, psychiatric symptoms, and behavioral disturbances. *Neuropsychiatry Neuropsychol Behav Neurol* 2000;13(2):83-8.
427. Hirono N, Mori E, Ishii K, Ikejiri Y, Imamura T, Shimomura T, et al. Frontal lobe hypometabolism and depression in Alzheimer's disease. *Neurology* 1998;50(2):380-3.
428. O'Brien J, Perry R, Barber R, Gholkar A, Thomas A. The association between white matter lesions on magnetic resonance imaging and noncognitive symptoms. *Ann N Y Acad Sci* 2000;903:482-9.
429. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry* 2003;54(3):338-52.
430. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci U S A* 1996;93(9):3908-13.
431. Gilley DW, Bienias JL, Wilson RS, Bennett DA, Beck TL, Evans DA. Influence of behavioral symptoms on rates of institutionalization for persons with Alzheimer's disease. *Psychol Med* 2004;34(6):1129-35.
432. Lee HB, Lyketsos CG. Depression in Alzheimer's disease: heterogeneity and related issues. *Biol Psychiatry* 2003;54(3):353-62.
433. Janzing JG, Hooijer C, van 't Hof MA, Zitman FG. Depression in subjects with and without dementia: a comparison using GMS-AGECAT. *Int J Geriatr Psychiatry* 2002;17(1):1-5.
434. Li YS, Meyer JS, Thornby J. Longitudinal follow-up of depressive symptoms among normal versus cognitively impaired elderly. *Int J Geriatr Psychiatry* 2001;16(7):718-27.
435. Bassiony MM, Warren A, Rosenblatt A, Baker A, Steinberg M, Steele CD, et al. The relationship between delusions and depression in Alzheimer's disease. *Int J Geriatr Psychiatry* 2002;17(6):549-56.
436. Tractenberg RE, Weiner MF, Patterson MB, Teri L, Thal LJ. Comorbidity of psychopathological domains in community-dwelling persons with Alzheimer's disease. *J Geriatr Psychiatry Neurol* 2003;16(2):94-9.
437. Zubenko GS, Zubenko WN, McPherson S, Spoor E, Marin DB, Farlow MR, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. *Am J Psychiatry* 2003;160(5):857-66.
438. Ballard C, Holmes C, McKeith I, Neill D, O'Brien J, Cairns N, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. *Am J Psychiatry* 1999;156(7):1039-45.
439. Klatka LA, Louis ED, Schiffer RB. Psychiatric features in diffuse Lewy body disease: a clinicopathologic study using Alzheimer's disease and Parkinson's disease comparison groups. *Neurology* 1996;47(5):1148-52.
440. Aarsland D, Ballard C, Larsen JP, McKeith I. A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. *Int J Geriatr Psychiatry* 2001;16(5):528-36.
441. Lyketsos CG, Steele C, Galik E, Rosenblatt A, Steinberg M, Warren A, et al. Physical aggression in dementia patients and its relationship to depression. *Am J Psychiatry* 1999;156(1):66-71.
442. Lyketsos CG, Steele C, Baker L, Galik E, Kopunek S, Steinberg M, et al. Major and minor depression in Alzheimer's disease: prevalence and impact. *J Neuropsychiatry Clin Neurosci* 1997;9(4):556-61.
443. Olin JT, Katz IR, Meyers BS, Schneider LS, Lebowitz BD. Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. *Am J Geriatr Psychiatry* 2002;10(2):129-41.

444. Olin JT, Schneider LS, Katz IR, Meyers BS, Alexopoulos GS, Breitner JC, et al. Provisional diagnostic criteria for depression of Alzheimer disease. *Am J Geriatr Psychiatry* 2002;10(2):125-8.
445. Shankar KK, Orrell MW. Detecting and managing depression and anxiety in people with dementia. *Current Opinion in Psychiatry* 2000;13:55-59.
446. Chemerinski E, Petracca G, Manes F, Leiguarda R, Starkstein SE. Prevalence and correlates of anxiety in Alzheimer's disease. *Depress Anxiety* 1998;7(4):166-70.
447. Ferretti L, McCurry SM, Logsdon R, Gibbons L, Teri L. Anxiety and Alzheimer's disease. *J Geriatr Psychiatry Neurol* 2001;14(1):52-8.
448. Forsell Y, Winblad B. Anxiety disorders in non-demented and demented elderly patients: prevalence and correlates. *J Neurol Neurosurg Psychiatry* 1997;62(3):294-5.
449. Ballard C, Neill D, O'Brien J, McKeith IG, Ince P, Perry R. Anxiety, depression and psychosis in vascular dementia: prevalence and associations. *J Affect Disord* 2000;59(2):97-106.
450. Starkstein SE, Jorge R, Petracca G, Robinson RG. The construct of generalized anxiety disorder in Alzheimer disease. *Am J Geriatr Psychiatry* 2007;15(1):42-9.
451. Cohen GD. Anxiety in Alzheimer's disease. Confusion and denial. *Am J Geriatr Psychiatry* 1998;6(1):1-4.
452. Yesavage JA, Taylor B, editors. *Anxiety and Dementia*. New York: Springer Publishing Co, 1991.
453. Mintzer JE, Brawman-Mintzer O. Agitation as a possible expression of generalized anxiety disorder in demented elderly patients: toward a treatment approach. *J.Clin.Psychiatry* 1996;57 Suppl 7:55-63.
454. Seignourel PJ, Kunik ME, Snow L, Wilson N, Stanley M. Anxiety in dementia: a critical review. *Clin Psychol Rev* 2008;28(7):1071-82.
455. Guadagnoli E, Velicer WF. Relation of sample size to the stability of component patterns. *Psychol Bull* 1988;103(2):265-75.
456. Harwood DG, Ownby RL, Barker WW, Duara R. The behavioral pathology in Alzheimer's Disease Scale (BEHAVE-AD): factor structure among community-dwelling Alzheimer's disease patients. *Int J Geriatr Psychiatry* 1998;13(11):793-800.
457. Mirakhur A, Craig D, Hart DJ, McLlroy SP, Passmore AP. Behavioural and psychological syndromes in Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19(11):1035-9.
458. Aalten P, de Vugt ME, Lousberg R, Korten E, Jaspers N, Senden B, et al. Behavioral problems in dementia: a factor analysis of the neuropsychiatric inventory. *Dement Geriatr Cogn Disord* 2003;15(2):99-105.
459. Frisoni GB, Rozzini L, Gozzetti A, Binetti G, Zanetti O, Bianchetti A, et al. Behavioral syndromes in Alzheimer's disease: description and correlates. *Dement Geriatr Cogn Disord* 1999;10(2):130-8.
460. Cummings JL, McRae T, Zhang R. Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. *Am J Geriatr Psychiatry* 2006;14(7):605-12.
461. Twelftree H, Qazi A. Relationship between anxiety and agitation in dementia. *Aging Ment Health* 2006;10(4):362-7.
462. Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* 2000;157(5):708-14.
463. Margallo-Lana M, Swann A, O'Brien J, Fairbairn A, Reichelt K, Potkins D, et al. Prevalence and pharmacological management of behavioural and psychological

symptoms amongst dementia sufferers living in care environments. *Int J Geriatr Psychiatry* 2001;16(1):39-44.
464. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am J Psychiatry* 2005;162(11):2022-30.
465. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005;65(12):1863-72.
466. Hirono N, Mori E, Yasuda M, Ikejiri Y, Imamura T, Shimomura T, et al. Factors associated with psychotic symptoms in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1998;64(5):648-52.
467. Ballard C, Piggott M, Johnson M, Cairns N, Perry R, McKeith I, et al. Delusions associated with elevated muscarinic binding in dementia with Lewy bodies. *Ann Neurol* 2000;48(6):868-76.
468. Teaktong T, Piggott MA, McKeith IG, Perry RH, Ballard CG, Perry EK. Muscarinic M2 and M4 receptors in anterior cingulate cortex: relation to neuropsychiatric symptoms in dementia with Lewy bodies. *Behav Brain Res* 2005;161(2):299-305.
469. Lai MK, Lai OF, Keene J, Esiri MM, Francis PT, Hope T, et al. Psychosis of Alzheimer's disease is associated with elevated muscarinic M2 binding in the cortex. *Neurology* 2001;57(5):805-11.
470. Farber NB, Rubin EH, Newcomer JW, Kinscherf DA, Miller JP, Morris JC, et al. Increased neocortical neurofibrillary tangle density in subjects with Alzheimer disease and psychosis. *Arch Gen Psychiatry* 2000;57(12):1165-73.
471. Perry EK, Marshall E, Kerwin J, Smith CJ, Jabeen S, Cheng AV, et al. Evidence of a monoaminergic-cholinergic imbalance related to visual hallucinations in Lewy body dementia. *J Neurochem* 1990;55(4):1454-6.
472. Tariot PN. Treatment strategies for agitation and psychosis in dementia. *J.Clin.Psychiatry* 1996;57 Suppl 14:21-29.
473. Kalapatapu RK, Neugroschl JA. Update on neuropsychiatric symptoms of dementia: evaluation and management. *Geriatrics* 2009;64(4):20-6.
474. Mintzer JE, Brown SA, Hoernig KS. Alzheimer's disease and managed care: challenges and strategies. *J.S.C.Med.Assoc.* 1996;92(6):255-260.
475. Salzman C, Jeste DV, Meyer RE, Cohen-Mansfield J, Cummings J, Grossberg GT, et al. Elderly patients with dementia-related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. *J Clin Psychiatry* 2008;69(6):889-98.
476. Snowdon DA. Healthy aging and dementia: findings from the Nun Study. *Ann Intern Med* 2003;139(5 Pt 2):450-4.
477. Kitwood T. A dialectical framework for dementia. In: Woods RT, editor. *Handbook of the clinical psychology of ageing.* Chichester: John Wiley & Sons Ltd, 1996.
478. Kitwood T. *Dementia reconsidered: The person comes first.* Buckingham: Open University Press., 1997.
479. Kitwood T. Toward a theory of dementia care: ethics and interaction. *J Clin Ethics* 1998;9(1):23-34.
480. Karlsson I, Brane G, Melin E, Nyth AL, Rybo E. Effects of environmental stimulation on biochemical and psychological variables in dementia. *Acta Psychiatr Scand* 1988;77(2):207-13.
481. Widerlov E, Brane G, Ekman R, Kihlgren M, Norberg A, Karlsson I. Elevated CSF somatostatin concentrations in demented patients parallel improved psychomotor functions induced by integrity-promoting care. *Acta Psychiatr Scand* 1989;79(1):41-7.

482. Edvardsson D, Winblad B, Sandman PO. Person-centred care of people with severe Alzheimer's disease: current status and ways forward. *Lancet Neurol* 2008;7(4):362-7.
483. Smith M, Buckwalter K. Behaviors associated with dementia: whether resisting care or exhibiting apathy, an older adult with dementia is attempting communication. Nurses and other caregivers must learn to 'hear' this language. *Am J Nurs* 2005;105(7):40-52; quiz 53.
484. Brooker D. *Person-centred dementia care: Making services better.* London: Jessica Kingsley Publications, 2007.
485. Chenoweth L, King MT, Jeon YH, Brodaty H, Stein-Parbury J, Norman R, et al. Caring for Aged Dementia Care Resident Study (CADRES) of person-centred care, dementia-care mapping, and usual care in dementia: a cluster-randomised trial. *Lancet Neurol* 2009;8(4):317-25.
486. Ballard C, Aarsland D. Person-centred care and care mapping in dementia. *Lancet Neurol* 2009;8(4):302-3.
487. Vink AC, Birks JS, Bruinsma MS, Scholten RJ. Music therapy for people with dementia. *Cochrane Database Syst Rev* 2004(3):CD003477.
488. Gerdner LA. Use of individualized music by trained staff and family: translating research into practice. *J Gerontol Nurs* 2005;31(6):22-30; quiz 55-6.
489. Gerdner LA, Swanson EA. Effects of individualized music on confused and agitated elderly patients. *Arch Psychiatr Nurs* 1993;7(5):284-91.
490. Sung HC, Chang AM, Abbey J. The effects of preferred music on agitation of older people with dementia in Taiwan. *Int J Geriatr Psychiatry* 2006;21(10):999-1000.
491. Hicks-Moore SL. Relaxing music at mealtime in nursing homes: effects on agitated patients with dementia. *J Gerontol Nurs* 2005;31(12):26-32.
492. Clark ME, Lipe AW, Bilbrey M. Use of music to decrease aggressive behaviors in people with dementia. *J Gerontol Nurs* 1998;24(7):10-7.
493. Garland K, Beer E, Eppingstall B, O'Connor DW. A comparison of two treatments of agitated behavior in nursing home residents with dementia: simulated family presence and preferred music. *Am J Geriatr Psychiatry* 2007;15(6):514-21.
494. Forbes D, Forbes S, Morgan DG, Markle-Reid M, Wood J, Culum I. Physical activity programs for persons with dementia. *Cochrane Database Syst Rev* 2008(3):CD006489.
495. Neal M, Briggs M. Validation therapy for dementia. *Cochrane Database Syst Rev* 2003(3):CD001394.
496. Snyder M, Egan EC, Burns KR. Interventions for decreasing agitation behaviors in persons with dementia. *J Gerontol Nurs* 1995;21(7):34-40.
497. Lin LC, Yang MH, Kao CC, Wu SC, Tang SH, Lin JG. Using acupressure and Montessori-based activities to decrease agitation for residents with dementia: a cross-over trial. *J Am Geriatr Soc* 2009;57(6):1022-9.
498. Chung JC, Lai CK, Chung PM, French HP. Snoezelen for dementia. *Cochrane Database Syst Rev* 2002(4):CD003152.
499. Baker R, Bell S, Baker E, Gibson S, Holloway J, Pearce R, et al. A randomized controlled trial of the effects of multi-sensory stimulation (MSS) for people with dementia. *Br J Clin Psychol* 2001;40(Pt 1):81-96.
500. Baker R, Holloway J, Holtkamp CC, Larsson A, Hartman LC, Pearce R, et al. Effects of multi-sensory stimulation for people with dementia. *J Adv Nurs* 2003;43(5):465-77.
501. Kragt K, Holtkamp CC, van Dongen MC, van Rossum E, Salentijn C. [The effect of sensory stimulation in the sensory stimulation room on the well-being of demented elderly. A cross-over trial in residents of the R.C. Care Center Bernardus in Amsterdam]. *Verpleegkunde* 1997;12(4):227-36.

502. van Weert JC, van Dulmen AM, Spreeuwenberg PM, Ribbe MW, Bensing JM. Behavioral and mood effects of snoezelen integrated into 24-hour dementia care. *J Am Geriatr Soc* 2005;53(1):24-33.
503. Livingston G, Johnston K, Katona C, Paton J, Lyketsos CG. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. *Am J Psychiatry* 2005;162(11):1996-2021.
504. Woods B, Spector A, Jones C, Orrell M, Davies S. Reminiscence therapy for dementia. *Cochrane Database Syst Rev* 2005(2):CD001120.
505. Forbes D, Culum I, Lischka AR, Morgan DG, Peacock S, Forbes J, et al. Light therapy for managing cognitive, sleep, functional, behavioural, or psychiatric disturbances in dementia. *Cochrane Database Syst Rev* 2009(4):CD003946.
506. Kverno KS, Black BS, Nolan MT, Rabins PV. Research on treating neuropsychiatric symptoms of advanced dementia with non-pharmacological strategies, 1998-2008: a systematic literature review. *Int Psychogeriatr* 2009;21(5):825-43.
507. O'Connor DW, Ames D, Gardner B, King M. Psychosocial treatments of psychological symptoms in dementia: a systematic review of reports meeting quality standards. *Int Psychogeriatr* 2009;21(2):241-51.
508. Owen JE, Roth DL, Stevens AB, McCarty HJ, Clay OJ, Wadley VG, et al. Association of life events and psychological distress in family caregivers of dementia patients. *Aging Ment Health* 2002;6(1):62-71.
509. Sloane PD, Mitchell CM, Preisser JS, Phillips C, Commander C, Burker E. Environmental correlates of resident agitation in Alzheimer's disease special care units. *J Am Geriatr Soc* 1998;46(7):862-9.
510. Testad I, Auer S, Mittelman M, Ballard C, Fossey J, Donabauer Y, et al. Nursing home structure and association with agitation and use of psychotropic drugs in nursing home residents in three countries: Norway, Austria and England. *Int J Geriatr Psychiatry* 2009.
511. Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Environmental correlates of neuropsychiatric symptoms in nursing home patients with dementia. *Int J Geriatr Psychiatry* 2009.
512. Graff MJ, Vernooij-Dassen MJ, Thijssen M, Dekker J, Hoefnagels WH, Rikkert MG. Community based occupational therapy for patients with dementia and their care givers: randomised controlled trial. *BMJ* 2006;333(7580):1196.
513. Graff MJ, Vernooij-Dassen MJ, Thijssen M, Dekker J, Hoefnagels WH, Olderikkert MG. Effects of community occupational therapy on quality of life, mood, and health status in dementia patients and their caregivers: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci* 2007;62(9):1002-9.
514. Graff MJ, Adang EM, Vernooij-Dassen MJ, Dekker J, Jonsson L, Thijssen M, et al. Community occupational therapy for older patients with dementia and their care givers: cost effectiveness study. *BMJ* 2008;336(7636):134-8.
515. Spijker A, Verhey F, Graff M, Grol R, Adang E, Wollersheim H, et al. Systematic care for caregivers of people with dementia in the ambulatory mental health service: designing a multicentre, cluster, randomized, controlled trial. *BMC Geriatr* 2009;9:21.
516. Gitlin LN, Winter L, Vause Earland T, Adel Herge E, Chernett NL, Piersol CV, et al. The Tailored Activity Program to reduce behavioral symptoms in individuals with dementia: feasibility, acceptability, and replication potential. *Gerontologist* 2009;49(3):428-39.
517. Shah A, De T. The effect of an educational intervention package about aggressive behaviour directed at the nursing staff on a continuing care psychogeriatric ward. *Int J Geriatr Psychiatry* 1998;13(1):35-40.

518. Fossey J, Ballard C, Juszczak E, James I, Alder N, Jacoby R, et al. Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. *BMJ* 2006;332(7544):756-61.
519. Cohen-Mansfield J, Dakheel-Ali M, Marx MS. Engagement in persons with dementia: the concept and its measurement. *Am J Geriatr Psychiatry* 2009;17(4):299-307.
520. Ballard C, Powell I, James I, Reichelt K, Myint P, Potkins D, et al. Can psychiatric liaison reduce neuroleptic use and reduce health service utilization for dementia patients residing in care facilities. *Int J Geriatr Psychiatry* 2002;17(2):140-5.
521. Kuske B, Hanns S, Luck T, Angermeyer MC, Behrens J, Riedel-Heller SG. Nursing home staff training in dementia care: a systematic review of evaluated programs. *Int Psychogeriatr* 2007;19(5):818-41.
522. Vasse E, Vernooij-Dassen M, Spijker A, Rikkert MO, Koopmans R. A systematic review of communication strategies for people with dementia in residential and nursing homes. *Int Psychogeriatr* 2009:1-12.
523. Levy-Storms L. Therapeutic communication training in long-term care institutions: recommendations for future research. *Patient Educ Couns* 2008;73(1):8-21.
524. Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. *J Am Geriatr Soc* 1990;38(5):553-63.
525. De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PL, Eriksson S, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology* 1999;53(5):946-55.
526. Chan WC, Lam LC, Choy CN, Leung VP, Li SW, Chiu HF. A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioural and psychological symptoms in Chinese dementia patients. *Int J Geriatr Psychiatry* 2001;16(12):1156-62.
527. Suh GH, Son HG, Ju YS, Jcho KH, Yeon BK, Shin YM, et al. A randomized, double-blind, crossover comparison of risperidone and haloperidol in Korean dementia patients with behavioral disturbances. *Am J Geriatr Psychiatry* 2004;12(5):509-16.
528. Gareri P, Cotroneo A, Lacava R, Seminara G, Marigliano N, Loiacono A, et al. Comparison of the efficacy of new and conventional antipsychotic drugs in the treatment of behavioral and psychological symptoms of dementia (BPSD). *Arch Gerontol Geriatr Suppl* 2004(9):207-15.
529. Tariot PN, Schneider L, Katz IR, Mintzer JE, Street J, Copenhaver M, et al. Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. *Am J Geriatr Psychiatry* 2006;14(9):767-76.
530. Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007;146(11):775-86.
531. Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ* 2007;176(5):627-32.
532. Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, et al. Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID). *Health Technol Assess* 2009;13(21):iii-iv, ix-xi, 1-54.
533. Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J.Clin.Psychiatry* 2003;64(2):134-143.
534. De Deyn PP, Katz IR, Brodaty H, Lyons B, Greenspan A, Burns A. Management of agitation, aggression, and psychosis associated with dementia: a pooled analysis

including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. *Clin Neurol Neurosurg* 2005;107(6):497-508.
535. Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry* 2000;57(10):968-76.
536. Street JS, Clark WS, Kadam DL, Mitan SJ, Juliar BE, Feldman PD, et al. Long-term efficacy of olanzapine in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer's dementia. *Int J Geriatr Psychiatry* 2001;16 Suppl 1:S62-70.
537. De Deyn PP, Carrasco MM, Deberdt W, Jeandel C, Hay DP, Feldman PD, et al. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19(2):115-26.
538. Clark WS, Street JS, Feldman PD, Breier A. The effects of olanzapine in reducing the emergence of psychosis among nursing home patients with Alzheimer's disease. *J Clin Psychiatry* 2001;62(1):34-40.
539. Bigos KL, Pollock BG, Coley KC, Miller del D, Marder SR, Aravagiri M, et al. Sex, race, and smoking impact olanzapine exposure. *J Clin Pharmacol* 2008;48(2):157-65.
540. Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. *BMJ* 2005;330(7496):874.
541. Kurlan R, Cummings J, Raman R, Thal L. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. *Neurology* 2007;68(17):1356-63.
542. De Deyn P, Jeste DV, Swanink R, Kostic D, Breder C, Carson WH, et al. Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease: a randomized, placebo-controlled study. *J Clin Psychopharmacol* 2005;25(5):463-7.
543. Mintzer JE, Tune LE, Breder CD, Swanink R, Marcus RN, McQuade RD, et al. Aripiprazole for the treatment of psychoses in institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses. *Am J Geriatr Psychiatry* 2007;15(11):918-31.
544. Streim JE, Breder C, Swanink R, al. e. Flexible dose aripiprazole in psychosis of Alzheimer's dementia. *157th American Psychiatric Association Meeting.* New York, NY., 2004.
545. Madhusoodanan S, Shah P. Management of psychosis in patients with Alzheimer's disease: focus on aripiprazole. *Clin Interv Aging* 2008;3(3):491-501.
546. Fontaine CS, Hynan LS, Koch K, Martin-Cook K, Svetlik D, Weiner MF. A double-blind comparison of olanzapine versus risperidone in the acute treatment of dementia-related behavioral disturbances in extended care facilities. *J Clin Psychiatry* 2003;64(6):726-30.
547. Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006;355(15):1525-38.
548. Alanen HM, Finne-Soveri H, Noro A, Leinonen E. Use of antipsychotic medications among elderly residents in long-term institutional care: a three-year follow-up. *Int J Geriatr Psychiatry* 2006;21(3):288-95.
549. Kleijer BC, van Marum RJ, Egberts AC, Jansen PA, Frijters D, Heerdink ER, et al. The course of behavioral problems in elderly nursing home patients with dementia when treated with antipsychotics. *Int Psychogeriatr* 2009;21(5):931-40.

550. Nijk RM, Zuidema SU, Koopmans RT. Prevalence and correlates of psychotropic drug use in Dutch nursing-home patients with dementia. *Int Psychogeriatr* 2009;21(3):485-93.
551. Feng Z, Hirdes JP, Smith TF, Finne-Soveri H, Chi I, Du Pasquier JN, et al. Use of physical restraints and antipsychotic medications in nursing homes: a cross-national study. *Int J Geriatr Psychiatry* 2009.
552. Herrmann N. Recommendations for the management of behavioral and psychological symptoms of dementia. *Can J Neurol Sci* 2001;28 Suppl 1:S96-107.
553. Lee PE, Gill SS, Freedman M, Bronskill SE, Hillmer MP, Rochon PA. Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. *BMJ* 2004;329(7457):75.
554. Aupperle P. Management of aggression, agitation, and psychosis in dementia: focus on atypical antipsychotics. *Am J Alzheimers Dis Other Demen* 2006;21(2):101-8.
555. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev* 2006(1):CD003476.
556. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294(15):1934-43.
557. Herrmann N, Lanctot KL. Pharmacologic management of neuropsychiatric symptoms of Alzheimer disease. *Can J Psychiatry* 2007;52(10):630-46.
558. Jeste DV, Blazer D, Casey D, Meeks T, Salzman C, Schneider L, et al. ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharmacology* 2008;33(5):957-70.
559. Rochon PA, Normand SL, Gomes T, Gill SS, Anderson GM, Melo M, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. *Arch Intern Med* 2008;168(10):1090-6.
560. Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 2004;161(6):1113-5.
561. Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. *CMAJ* 2002;167(11):1269-70.
562. Wooltorton E. Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials. *CMAJ* 2004;170(9):1395.
563. Herrmann N, Lanctot KL. Do atypical antipsychotics cause stroke? *CNS Drugs* 2005;19(2):91-103.
564. Zheng L, Mack WJ, Dagerman KS, Hsiao JK, Lebowitz BD, Lyketsos CG, et al. Metabolic changes associated with second-generation antipsychotic use in Alzheimer's disease patients: the CATIE-AD study. *Am J Psychiatry* 2009;166(5):583-90.
565. Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005;353(22):2335-41.
566. Bronskill SE, Rochon PA, Gill SS, Herrmann N, Hillmer MP, Bell CM, et al. The relationship between variations in antipsychotic prescribing across nursing homes and short-term mortality: quality of care implications. *Med Care* 2009;47(9):1000-8.
567. Kales HC, Valenstein M, Kim HM, McCarthy JF, Ganoczy D, Cunningham F, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. *Am J Psychiatry* 2007;164(10):1568-76; quiz 1623.
568. McShane R, Keene J, Gedling K, Fairburn C, Jacoby R, Hope T. Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. *BMJ* 1997;314(7076):266-70.

569. Scharre DW, Chang SI. Cognitive and behavioral effects of quetiapine in Alzheimer disease patients. *Alzheimer Dis Assoc Disord* 2002;16(2):128-30.
570. Elie M, Boss K, Cole MG, McCusker J, Belzile E, Ciampi A. A retrospective, exploratory, secondary analysis of the association between antipsychotic use and mortality in elderly patients with delirium. *Int Psychogeriatr* 2009;21(3):588-92.
571. Mulsant BH, Gharabawi GM, Bossie CA, Mao L, Martinez RA, Tune LE, et al. Correlates of anticholinergic activity in patients with dementia and psychosis treated with risperidone or olanzapine. *J Clin Psychiatry* 2004;65(12):1708-14.
572. Ballard CG, Margallo-Lana M, Fossey J, Reichelt K, Myint P, Potkins D, et al. A 1-year follow-up study of behavioral and psychological symptoms in dementia among people in care environments. *J Clin Psychiatry* 2001;62(8):631-6.
573. Cohen-Mansfield J, Lipson S, Werner P, Billig N, Taylor L, Woosley R. Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home: a controlled, double-blind study. *Arch Intern Med* 1999;159(15):1733-40.
574. Ballard CG, Thomas A, Fossey J, Lee L, Jacoby R, Lana MM, et al. A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. *J Clin Psychiatry* 2004;65(1):114-9.
575. Bridges-Parlet S, Knopman D, Steffes S. Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double-blind, baseline-treatment-controlled pilot study. *J Geriatr Psychiatry Neurol* 1997;10(3):119-26.
576. Ballard C, Lana MM, Theodoulou M, Douglas S, McShane R, Jacoby R, et al. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). *PLoS Med* 2008;5(4):e76.
577. Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurol* 2009;8(2):151-7.
578. Suh GH. The use of atypical antipsychotics in dementia: rethinking Simpson's paradox. *Int Psychogeriatr* 2009;21(4):616-21.
579. Wagner CH. Simpson's paradox in real life. *American Statistician* 1982;36:46-48.
580. Verstraete M. Value and limitation of meta-analysis. *Pathophysiol Haemost Thromb* 2002;32(5-6):278-81.
581. Haupt M, Cruz-Jentoft A, Jeste D. Mortality in elderly dementia patients treated with risperidone. *J Clin Psychopharmacol* 2006;26(6):566-70.
582. Suh GH, Shah A. Effect of antipsychotics on mortality in elderly patients with dementia: a 1-year prospective study in a nursing home. *Int Psychogeriatr* 2005;17(3):429-41.
583. Nonino F, De Girolamo G, Gamberini L, Goldoni CA. Survival among elderly Italian patients with dementia treated with atypical antipsychotics: observational study. *Neurol Sci* 2006;27(6):375-80.
584. Barnett MJ, Perry PJ, Alexander B, Kaboli PJ. Risk of mortality associated with antipsychotic and other neuropsychiatric drugs in pneumonia patients. *J Clin Psychopharmacol* 2006;26(2):182-7.
585. Barnett MJ, Wehring H, Perry PJ. Comparison of risk of cerebrovascular events in an elderly VA population with dementia between antipsychotic and nonantipsychotic users. *J Clin Psychopharmacol* 2007;27(6):595-601.
586. Raivio MM, Laurila JV, Strandberg TE, Tilvis RS, Pitkala KH. Neither atypical nor conventional antipsychotics increase mortality or hospital admissions among elderly patients with dementia: a two-year prospective study. *Am J Geriatr Psychiatry* 2007;15(5):416-24.

587. Simoni-Wastila L, Ryder PT, Qian J, Zuckerman IH, Shaffer T, Zhao L. Association of antipsychotic use with hospital events and mortality among medicare beneficiaries residing in long-term care facilities. *Am J Geriatr Psychiatry* 2009;17(5):417-27.
588. Nasrallah HA, White T, Nasrallah AT. Lower mortality in geriatric patients receiving risperidone and olanzapine versus haloperidol: preliminary analysis of retrospective data. *Am J Geriatr Psychiatry* 2004;12(4):437-9.
589. Trifiro G, Verhamme KM, Ziere G, Caputi AP, Ch Stricker BH, Sturkenboom MC. All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. *Pharmacoepidemiol Drug Saf* 2007;16(5):538-44.
590. Nyberg P, Adolfsson R, Hardy JA, Nordberg A, Wester P, Winblad B. Catecholamine topochemistry in human basal ganglia. Comparison between normal and Alzheimer brains. *Brain Res* 1985;333(1):139-42.
591. Cummings JL, Back C. The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. *Am J Geriatr Psychiatry* 1998;6(2 Suppl 1):S64-78.
592. Reinikainen KJ, Paljarvi L, Huuskonen M, Soininen H, Laakso M, Riekkinen PJ. A post-mortem study of noradrenergic, serotonergic and GABAergic neurons in Alzheimer's disease. *J Neurol Sci* 1988;84(1):101-16.
593. Keverne EB. GABA-ergic neurons and the neurobiology of schizophrenia and other psychoses. *Brain Res Bull* 1999;48(5):467-73.
594. Adams DB, Boudreau W, Cowan CW, Kokonowski C, Oberteuffer K, Yohay K. Offense produced by chemical stimulation of the anterior hypothalamus of the rat. *Physiol Behav* 1993;53(6):1127-32.
595. Rissman RA, De Blas AL, Armstrong DM. GABA(A) receptors in aging and Alzheimer's disease. *J Neurochem* 2007;103(4):1285-92.
596. Arundine M, Tymianski M. Molecular mechanisms of glutamate-dependent neurodegeneration in ischemia and traumatic brain injury. *Cell Mol Life Sci* 2004;61(6):657-68.
597. Lanctot KL, Herrmann N, Mazzotta P, Khan LR, Ingber N. GABAergic function in Alzheimer's disease: evidence for dysfunction and potential as a therapeutic target for the treatment of behavioural and psychological symptoms of dementia. *Can J Psychiatry* 2004;49(7):439-53.
598. Chambers CA, Bain J, Rosbottom R, Ballinger BR, McLaren S. Carbamazepine in senile dementia and overactivity - a placebo controlled double blind trial. *IRCS Med Sci* 1982(10):505-506.
599. Tariot PN, Erb R, Leibovici A, Podgorski CA, Cox C, Asnis J, et al. Carbamazepine treatment of agitation in nursing home patients with dementia: a preliminary study. *J.Am.Geriatr.Soc.* 1994;42(11):1160-1166.
600. Cooney C, Mortimer A, Smith A, Newton K, Wrigley M. Carbamazepine use in aggressive behavior associated with senile dementia. *International Journal of Geriatric Psychiatry* 1996;11:901-905.
601. Gleason RP, Schneider LS. Carbamazepine treatment of agitation in Alzheimer's outpatients refractory to neuroleptics. *J Clin Psychiatry* 1990;51(3):115-8.
602. Patterson JF. A preliminary study of carbamazepine in the treatment of assaultive patients with dementia. *J Geriatr Psychiatry Neurol* 1988;1(1):21-3.
603. Essa M. Carbamazepine in dementia. *J Clin Psychopharmacol* 1986;6(4):234-6.
604. Lemke MR. Effect of carbamazepine on agitation in Alzheimer's inpatients refractory to neuroleptics. *J Clin Psychiatry* 1995;56(8):354-7.
605. Marin DB, Greenwald BS. Carbamazepine for aggressive agitation in demented patients during nursing care. *Am J Psychiatry* 1989;146(6):805.

606. Leibovici A, Tariot PN. Carbamazepine treatment of agitation associated with dementia. *J Geriatr Psychiatry Neurol* 1988;1(2):110-2.
607. Narayan M, Nelson JC. Treatment of dementia with behavioral disturbance using divalproex or a combination of divalproex and a neuroleptic. *J Clin Psychiatry* 1997;58(8):351-4.
608. Sival RC, Haffmans PM, van Gent PP, van Nieuwkerk JF. The effects of sodium valproate on disturbed behavior in dementia. *J Am Geriatr Soc* 1994;42(8):906-7.
609. Haas S, Vincent K, Holt J, Lippmann S. Divalproex: a possible treatment alternative for demented, elderly aggressive patients. *Ann Clin Psychiatry* 1997;9(3):145-7.
610. Porsteinsson AP, Tariot PN, Erb R, Gaile S. An open trial of valproate for agitation in geriatric neuropsychiatric disorders. *Am.J.Geriatr.Psychiatry* 1997;5(4):344-351.
611. Lonergan ET, Cameron M, Luxenberg J. Valproic acid for agitation in dementia. *Cochrane Database Syst Rev* 2004(2):CD003945.
612. Tariot PN, Schneider LS, Mintzer J, al. e. Safety and tolerability of divalproex sodium in the treatment of signs and symptoms of mania in elderly patients with dementia: results of a double-blind, placebocontrolled trial. *Curr Ther Res Clin Exp* 2001;62:51-67.
613. Tariot PN, Ryan JM, Porsteinsson AP, Loy R, Schneider LS. Pharmacologic therapy for behavioral symptoms of Alzheimer's disease. *Clin.Geriatr.Med.* 2001;17(2):359-376.
614. Lonergan E, Luxenberg J. Valproate preparations for agitation in dementia. *Cochrane Database Syst Rev* 2009(3):CD003945.
615. Kozman MN, Wattis J, Curran S. Pharmacological management of behavioural and psychological disturbance in dementia. *Hum Psychopharmacol* 2006;21(1):1-12.
616. Regan WM, Gordon SM. Gabapentin for behavioral agitation in Alzheimer's disease. *J Clin Psychopharmacol* 1997;17(1):59-60.
617. Sheldon LJ, Ancill RJ, Holliday SG. Gabapentin in geriatric psychiatry patients. *Can J Psychiatry* 1998;43(4):422-3.
618. Roane DM, Feinberg TE, Meckler L, Miner CR, Scicutella A, Rosenthal RN. Treatment of dementia-associated agitation with gabapentin. *J Neuropsychiatry Clin Neurosci* 2000;12(1):40-3.
619. Raudino F, Mascalzi MG, Zagami A. Gabapentin and behavioral disorders in severe Alzheimer disease. *J Clin Psychopharmacol* 2004;24(4):459-60.
620. Herrmann N, Lanctot K, Myszak M. Effectiveness of gabapentin for the treatment of behavioral disorders in dementia. *J Clin Psychopharmacol* 2000;20(1):90-3.
621. Hawkins JW, Tinklenberg JR, Sheikh JI, Peyser CE, Yesavage JA. A retrospective chart review of gabapentin for the treatment of aggressive and agitated behavior in patients with dementias. *Am J Geriatr Psychiatry* 2000;8(3):221-5.
622. Konovalov S, Muralee S, Tampi RR. Anticonvulsants for the treatment of behavioral and psychological symptoms of dementia: a literature review. *Int Psychogeriatr* 2008;20(2):293-308.
623. Amann B, Pantel J, Grunze H, Vieta E, Colom F, Gonzalez-Pinto A, et al. Anticonvulsants in the treatment of aggression in the demented elderly: an update. *Clin Pract Epidemol Ment Health* 2009;5:14.
624. Aisen PS, Johanessen JD, Marin DB. Trazodone for behavioural disturbances in Alzheimer's disease. *Am J Geriatr Psychiatry* 1993;1:349-350.
625. Houlihan DJ, Mulsant BH, Sweet RA, al. e. A naturalistic study of trazodone in the treatment of behavioural complications of dementia. *Am J Geriatr Psychiatry* 1994;2:78-85.

626. Rojas-Fernandez CH, Eng M, Allie ND. Pharmacologic management by clinical pharmacists of behavioral and psychological symptoms of dementia in nursing home residents: results from a pilot study. *Pharmacotherapy* 2003;23(2):217-21.
627. Martinon-Torres G, Fioravanti M, Grimley EJ. Trazodone for agitation in dementia. *Cochrane Database Syst Rev* 2004(4):CD004990.
628. Teri L, Logsdon RG, Peskind E, Raskind M, Weiner MF, Tractenberg RE, et al. Treatment of agitation in AD: a randomized, placebo-controlled clinical trial. *Neurology* 2000;55(9):1271-1278.
629. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomised, controlled trial with trazodone. *Dement Geriatr Cogn Disord* 2004;17(4):355-9.
630. Olafsson K, Jorgensen S, Jensen HV, Bille A, Arup P, Andersen J. Fluvoxamine in the treatment of demented elderly patients: a double-blind, placebo-controlled study. *Acta Psychiatr Scand* 1992;85(6):453-6.
631. Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study. *Br J Psychiatry* 1990;157:894-901.
632. Pollock BG, Mulsant BH, Rosen J, Sweet RA, Mazumdar S, Bharucha A, et al. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. *Am J Psychiatry* 2002;159(3):460-5.
633. Pollock BG, Mulsant BH, Rosen J, Mazumdar S, Blakesley RE, Houck PR, et al. A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. *Am J Geriatr Psychiatry* 2007;15(11):942-52.
634. Siddique H, Hynan LS, Weiner MF. Effect of a serotonin reuptake inhibitor on irritability, apathy, and psychotic symptoms in patients with Alzheimer's disease. *J Clin Psychiatry* 2009;70(6):915-8.
635. Finkel SI, Mintzer JE, Dysken M, Krishnan KR, Burt T, McRae T. A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. *Int J Geriatr Psychiatry* 2004;19(1):9-18.
636. Bains J, Birks JS, Dening TR. The efficacy of antidepressants in the treatment of depression in dementia. *Cochrane Database Syst Rev* 2002(4):CD003944.
637. Auchus AP, Bissey-Black C. Pilot study of haloperidol, fluoxetine, and placebo for agitation in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 1997;9(4):591-3.
638. Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Arch Gen Psychiatry* 2003;60(7):737-46.
639. Holmes C, Wilkinson D, Dean C, Vethanayagam S, Olivieri S, Langley A, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology* 2004;63(2):214-9.
640. Howard RJ, Juszczak E, Ballard CG, Bentham P, Brown RG, Bullock R, et al. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med* 2007;357(14):1382-92.
641. Birks J, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev* 2006(1):CD001190.
642. Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, et al. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine

in patients with mild to moderate Alzheimer's disease. *Int J Clin Pract* 2002;56(6):441-6.
643. Touchon J, Bergman H, Bullock R, Rapatz G, Nagel J, Lane R. Response to rivastigmine or donepezil in Alzheimer's patients with symptoms suggestive of concomitant Lewy body pathology. *Curr Med Res Opin* 2006;22(1):49-59.
644. Bullock R, Bergman H, Touchon J, Gambina G, He Y, Nagel J, et al. Effect of age on response to rivastigmine or donepezil in patients with Alzheimer's disease. *Curr Med Res Opin* 2006;22(3):483-94.
645. Cummings JL, Koumaras B, Chen M, Mirski D. Effects of rivastigmine treatment on the neuropsychiatric and behavioral disturbances of nursing home residents with moderate to severe probable Alzheimer's disease: a 26-week, multicenter, open-label study. *Am J Geriatr Pharmacother* 2005;3(3):137-48.
646. Burn D, Emre M, McKeith I, De Deyn PP, Aarsland D, Hsu C, et al. Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. *Mov Disord* 2006;21(11):1899-907.
647. Emre M, Cummings JL, Lane RM. Rivastigmine in dementia associated with Parkinson's disease and Alzheimer's disease: similarities and differences. *J Alzheimers Dis* 2007;11(4):509-19.
648. Birks J, Grimley Evans J, Iakovidou V, Tsolaki M, Holt FE. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev* 2009(2):CD001191.
649. Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology* 2000;54(12):2269-76.
650. Wilkinson DG, Hock C, Farlow M, van Baelen B, Schwalen S. Galantamine provides broad benefits in patients with 'advanced moderate' Alzheimer's disease (MMSE < or = 12) for up to six months. *Int J Clin Pract* 2002;56(7):509-14.
651. Cummings JL, Schneider L, Tariot PN, Kershaw PR, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. *Am J Psychiatry* 2004;161(3):532-8.
652. Suh GH, Yeon Jung H, Uk Lee C, Hoon Oh B, Nam Bae J, Jung HY, et al. A prospective, double-blind, community-controlled comparison of three doses of galantamine in the treatment of mild to moderate Alzheimer's disease in a Korean population. *Clin Ther* 2004;26(10):1608-18.
653. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 2004;291(3):317-24.
654. McShane RH. Memantine plus donepezil improves physical and mental health in people with Alzheimer's disease. *Evid Based Ment Health* 2004;7(3):76.
655. Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. Long-term course and effectiveness of combination therapy in Alzheimer disease. *Alzheimer Dis Assoc Disord* 2008;22(3):209-21.
656. Lopez OL, Becker JT, Wahed AS, Saxton J, Sweet RA, Wolk DA, et al. Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. *J Neurol Neurosurg Psychiatry* 2009;80(6):600-7.
657. Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA* 2003;289(2):210-216.
658. Burns A, O'Brien J, Auriacombe S, Ballard C, Broich K, Bullock R, et al. Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology. *J Psychopharmacol* 2006;20(6):732-55.

659. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 2006(1):CD005593.
660. Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. *Ann Intern Med* 2008;148(5):379-97.
661. Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. *Int Psychogeriatr* 2009;21(5):813-24.
662. Cummings JL, Schneider E, Tariot PN, Graham SM. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology* 2006;67(1):57-63.
663. Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol* 2009;8(7):613-8.
664. Emre M. Memantine: a new hope for treatment of Lewy body-related dementias? *Lancet Neurol* 2009;8(7):594-5.
665. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev* 2006(2):CD003154.
666. Wilkinson D, Andersen HF. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease. *Dement Geriatr Cogn Disord* 2007;24(2):138-45.
667. Wilcock GK, Ballard CG, Cooper JA, Loft H. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *J Clin Psychiatry* 2008;69(3):341-8.
668. Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *Int.J.Geriatr.Psychiatry* 2008;23(5):537-545.
669. Grossberg GT, Pejovic V, Miller ML, Graham SM. Memantine therapy of behavioral symptoms in community-dwelling patients with moderate to severe Alzheimer's disease. *Dement Geriatr Cogn Disord* 2009;27(2):164-72.
670. Stahl SM, Markowitz JS, Gutterman EM, Papadopoulos G. Co-use of donepezil and hypnotics among Alzheimer's disease patients living in the community. *J Clin Psychiatry* 2003;64(4):466-72.
671. Ancill RJ, Carlyle WW, Liang RA, Holliday SG. Agitation in the demented elderly: a role for benzodiazepines? *Int Clin Psychopharmacol* 1991;6(3):141-6.
672. Christensen DB, Benfield WR. Alprazolam as an alternative to low-dose haloperidol in older, cognitively impaired nursing facility patients. *J Am Geriatr Soc* 1998;46(5):620-5.
673. Sunderland T, Weingartner H, Cohen RM, Tariot PN, Newhouse PA, Thompson KE, et al. Low-dose oral lorazepam administration in Alzheimer subjects and age-matched controls. *Psychopharmacology (Berl)* 1989;99(1):129-33.
674. Smeraski PJ. Clonazepam treatment of multi-infarct dementia. *J Geriatr Psychiatry Neurol* 1988;1(1):47-8.
675. Freinhar JP, Alvarez WA. Clonazepam treatment of organic brain syndromes in three elderly patients. *J Clin Psychiatry* 1986;47(10):525-6.
676. Ginsburg ML. Clonazepam for agitated patients with Alzheimer's disease. *Can J Psychiatry* 1991;36(3):237-8.

677. Calkin PA, Kunik ME, Orengo CA, Molinari V, Workman R. Tolerability of clonazepam in demented and non-demented geropsychiatric patients. *Int J Geriatr Psychiatry* 1997;12(7):745-9.
678. Covington JS. Alleviating agitation, apprehension, and related symptoms in geriatric patients: A double-blind comparison of a phenothiazine and a benzodiazepien. *South Med J* 1975;68(6):719-24.
679. Kirven LE, Montero EF. Comparison of thioridazine and diazepam in the control of nonpsychotic symptoms associated with senility: double-blind study. *J Am Geriatr Soc* 1973;21(12):546-51.
680. Sanders JF. Evaluation of Oxazepam and Placebo in Emotionally Disturbed Aged Patients. *Geriatrics* 1965;20:739-46.
681. Beber CR. Management of behavior in the institutionalized aged. *Dis Nerv Syst* 1965;26(9):591-5.
682. Chesrow EJ, Kaplitz SE, Veltra H, Breme JT, Marquardt GH. Blind study of oxazepam in the management of geriatric patients with behavioral problems. *Clin Med* 1965;71:1001-1005.
683. Coccaro EF, Kramer E, Zemishlany Z, Thorne A, Rice CM, 3rd, Giordani B, et al. Pharmacologic treatment of noncognitive behavioral disturbances in elderly demented patients. *Am J Psychiatry* 1990;147(12):1640-5.
684. Herz LR, Volicer L, Ross V, Rheaume Y. A single-case-study method for treating resistiveness in patients with Alzheimer's disease. *Hosp Community Psychiatry* 1992;43(7):720-4.
685. Meehan KM, Wang H, David SR, Nisivoccia JR, Jones B, Beasley CM, Jr., et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. *Neuropsychopharmacology* 2002;26(4):494-504.
686. Wagner AK, Zhang F, Soumerai SB, Walker AM, Gurwitz JH, Glynn RJ, et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? *Arch Intern Med* 2004;164(14):1567-72.
687. Hogan DB, Maxwell CJ, Fung TS, Ebly EM. Prevalence and potential consequences of benzodiazepine use in senior citizens: results from the Canadian Study of Health and Aging. *Can J Clin Pharmacol* 2003;10(2):72-7.
688. Cognitive function and dementia in six areas of England and Wales: the distribution of MMSE and prevalence of GMS organicity level in the MRC CFA Study. The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Psychol Med* 1998;28(2):319-35.
689. Mulsant BH, Pollock BG, Kirshner M, Shen C, Dodge H, Ganguli M. Serum anticholinergic activity in a community-based sample of older adults: relationship with cognitive performance. *Arch Gen Psychiatry* 2003;60(2):198-203.
690. Nebes RD, Pollock BG, Halligan EM, Kirshner MA, Houck PR. Serum anticholinergic activity and motor performance in elderly persons. *J Gerontol A Biol Sci Med Sci* 2007;62(1):83-5.
691. Landi F, Russo A, Liperoti R, Cesari M, Barillaro C, Pahor M, et al. Anticholinergic drugs and physical function among frail elderly population. *Clin Pharmacol Ther* 2007;81(2):235-41.
692. Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA, et al. Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc* 2008;56(7):1333-41.

693. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol* 2006;46(12):1481-6.
694. Blix HS, Viktil KK, Reikvam A, Moger TA, Hjemaas BJ, Pretsch P, et al. The majority of hospitalised patients have drug-related problems: results from a prospective study in general hospitals. *Eur J Clin Pharmacol* 2004;60(9):651-8.
695. Kirkevold O, Engedal K. Is covert medication in Norwegian nursing homes still a problem? A cross-sectional study. *Drugs Aging* 2009;26(4):333-44.
696. Ruths S, Straand J, Nygaard HA. Multidisciplinary medication review in nursing home residents: what are the most significant drug-related problems? The Bergen District Nursing Home (BEDNURS) study. *Qual Saf Health Care* 2003;12(3):176-80.
697. Ballard CG, Gauthier S, Cummings JL, Brodaty H, Grossberg GT, Robert P, et al. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol* 2009;5(5):245-55.
698. Shua-Haim JR. Abstract no 3332. In: Patel S SJM, editor. *55th Gerontological Society of America Annual Meeting*, 2005.
699. Shua-Haim JR. abstract no 1324, nov 2002. In: Smith JM, Patel S, Smith MM, editors. *55th Gerontological Society of America Annual Meeting*, 2005.
700. Benedetti A, Lattanzi L, Pini S, Musetti L, Dell'Osso L, Cassano GB. Oxcarbazepine as add-on treatment in patients with bipolar manic, mixed or depressive episode. *J.Affect.Disord.* 2004;79(1-3):273-277.
701. Emrich HM, Altmann H, Dose M, von Zerssen D. Therapeutic effects of GABA-ergic drugs in affective disorders. A preliminary report. *Pharmacol.Biochem.Behav.* 1983;19(2):369-372.
702. Cabrera JF, Korner W, Muller-Oerlinghausen B. [Successful combined neuroleptic and lithium treatment of a chronic schizophrenic patient with recurrent aggressive behavior]. *Nervenarzt* 1986;57(6):366-369.
703. Schachter SC. Antiepileptic drug therapy: general treatment principles and application for special patient populations. *Epilepsia* 1999;40 Suppl 9:S20-S25.
704. Schachter SC, Vazquez B, Fisher RS, Laxer KD, Montouris GD, Combs-Cantrell DT, et al. Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures. *Neurology* 1999;52(4):732-737.
705. Tariot PN. Behavioral manifestations of dementia: a research agenda. *Int.Psychogeriatr.* 1996;8 Suppl 1:31-38.
706. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* 1997;48(5 Suppl 6):S10-6.
707. Lewis H, Beher D, Cookson N, Oakley A, Piggott M, Morris CM, et al. Quantification of Alzheimer pathology in ageing and dementia: age-related accumulation of amyloid-beta(42) peptide in vascular dementia. *Neuropathol Appl Neurobiol* 2006;32(2):103-18.
708. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet* 2001;357(9251):169-75.
709. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J.Psychiatr.Res.* 1975;12(3):189-198.
710. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9(3):179-186.

711. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br.J.Psychiatry* 1982;140:566-572.
712. Landsberger HA. Hawthorne Revisited: Management and the Worker, Its Critics, and Developments in Human Relations in Industry. Ithaca: Cornell University, 1958.
713. Roethlisberger FJ, Dicson WJ. *Management and the Worker*. Cambridge, Mass.: Havard University Press, 1939.
714. Bland JM, Altman DG. Regression towards the mean. *BMJ* 1994;308(6942):1499.
715. Friis ML, Kristensen O, Boas J, Dalby M, Deth SH, Gram L, et al. Therapeutic experiences with 947 epileptic out-patients in oxcarbazepine treatment. *Acta Neurol.Scand.* 1993;87(3):224-227.
716. Rajagopal S. The placebo effect. *Psychiatr Bull* 2006;30:185-188.
717. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry* 2008;65(2):220-31.
718. Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, et al. The functional neuroanatomy of the placebo effect. *Am J Psychiatry* 2002;159(5):728-37.
719. Zubieta JK, Yau WY, Scott DJ, Stohler CS. Belief or Need? Accounting for individual variations in the neurochemistry of the placebo effect. *Brain Behav Immun* 2006;20(1):15-26.
720. Andrews G. Placebo response in depression: bane of research, boon to therapy. *Br J Psychiatry* 2001;178:192-4.
721. McDonald CJ, Mazzuca SA, McCabe GP, Jr. How much of the placebo 'effect' is really statistical regression? *Stat Med* 1983;2(4):417-27.
722. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA* 2002;287(14):1840-7.
723. Ross DC, Quitkin FM, Klein DF. A typological model for estimation of drug and placebo effects in depression. *J Clin Psychopharmacol* 2002;22(4):414-8.
724. Barbui C, Cipriani A, Brambilla P, Hotopf M. "Wish bias" in antidepressant drug trials? *J Clin Psychopharmacol* 2004;24(2):126-30.
725. Rothwell PM, Robertson G. Meta-analyses of randomised controlled trials. *Lancet* 1997;350(9085):1181-2.
726. Brunoni AR, Lopes M, Kaptchuk TJ, Fregni F. Placebo response of non-pharmacological and pharmacological trials in major depression: a systematic review and meta-analysis. *PLoS One* 2009;4(3):e4824.
727. Schneider LS, Sano M. Current Alzheimer's disease clinical trials: methods and placebo outcomes. *Alzheimers Dement* 2009;5(5):388-97.
728. Eek.A, Nygaard AM. Innsyn og utsyn - Tilbud til personer med demens i norske kommuner. *Nasjonalt kompetansesenter for aldersdemens* 1999.
729. Cohen-Mansfield J, Marx MS, Werner P. Agitation in elderly persons: an integrative report of findings in a nursing home. *Int.Psychogeriatr.* 1992;4 Suppl 2:221-240.
730. Archer N, Brown RG, Reeves SJ, Boothby H, Nicholas H, Foy C, et al. Premorbid personality and behavioral and psychological symptoms in probable Alzheimer disease. *Am J Geriatr Psychiatry* 2007;15(3):202-13.
731. Meins W, Frey A, Thiesemann R. Premorbid personality traits in Alzheimer's disease: do they predispose to noncognitive behavioral symptoms? *Int Psychogeriatr* 1998;10(4):369-78.
732. Bartels SJ, Horn SD, Smout RJ, Dums AR, Flaherty E, Jones JK, et al. Agitation and depression in frail nursing home elderly patients with dementia: treatment characteristics and service use. *Am J Geriatr Psychiatry* 2003;11(2):231-8.

733. Cohen-Mansfield J, Werner P. Longitudinal changes in behavioral problems in old age: a study in an adult day care population. *J Gerontol A Biol Sci Med Sci* 1998;53(1):M65-71.
734. Asberg M, Thoren P, Traskman L, Bertilsson L, Ringberger V. "Serotonin depression"--a biochemical subgroup within the affective disorders? *Science* 1976;191(4226):478-80.
735. Gottfries CG, Gottfries I, Roos BE. Homovanillic acid and 5-hydroxyindoleacetic acid in the cerebrospinal fluid of patients with senile dementia, presenile dementia and parkinsonism. *J Neurochem* 1969;16(9):1341-5.
736. Gottfries CG, Nyth AL. Effect of citalopram, a selective 5-HT reuptake blocker, in emotionally disturbed patients with dementia. *Ann N Y Acad Sci* 1991;640:276-9.
737. Soininen H, MacDonald E, Rekonen M, Riekkinen PJ. Homovanillic acid and 5-hydroxyindoleacetic acid levels in cerebrospinal fluid of patients with senile dementia of Alzheimer type. *Acta Neurol Scand* 1981;64(2):101-7.
738. Chaves ML, Camozzato AL, Godinho C, Kochhann R, Schuh A, de Almeida VL, et al. Validity of the clinical dementia rating scale for the detection and staging of dementia in Brazilian patients. *Alzheimer Dis Assoc Disord* 2007;21(3):210-7.
739. Mann AH, Graham N, Ashby D. Psychiatric illness in residential homes for the elderly: a survey in one London borough. *Age Ageing* 1984;13(5):257-65.
740. Teri L, Borson S, Kiyak HA, Yamagishi M. Behavioral disturbance, cognitive dysfunction, and functional skill. Prevalence and relationship in Alzheimer's disease. *J Am Geriatr Soc* 1989;37(2):109-16.
741. Negley EN, Manley JT. Environmental interventions in assaultive behavior. *J Gerontol Nurs* 1990;16(3):29-33.
742. Gibbons P, Gannon M, Wrigley M. A study of aggression among referrals to a community-based psychiatry of old age service. *Int J Geriatr Psychiatry* 1997;12(3):384-8.
743. Swearer JM, Drachman DA, O'Donnell BF, Mitchell AL. Troublesome and disruptive behaviors in dementia. Relationships to diagnosis and disease severity. *J Am Geriatr Soc* 1988;36(9):784-90.
744. Hallberg IR, Luker KA, Norberg A, Johnsson K, Eriksson S. Staff interaction with vocally disruptive demented patients compared with demented controls. *Aging (Milano)* 1990;2(2):163-71.
745. Haller E, Binder RL, McNiel DE. Violence in geriatric patients with dementia. *Bull Am Acad Psychiatry Law* 1989;17(2):183-8.
746. Shah AK. Violence among psychogeriatric inpatients with dementia. *Int.J.Geriatr.Psychiatry* 1995;10:887-891.
747. Nilsson K, Palmstierna T, Wistedt B. Aggressive behavior in hospitalized psychogeriatric patients. *Acta Psychiatr Scand* 1988;78(2):172-5.
748. Ware CJG, Fairburn CG, Hope RA. A community-based study of aggressive behaviour in dementia. *Int.J.Geriatr.Psychiatry* 1990;5:337-342.
749. Lasagna L. Problems in publication of clinical trial methodology. *Clin Pharmacol Ther* 1979;25(5 Pt 2):751-3.
750. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358(3):252-60.
751. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;291(20):2457-65.

752. DeAngelis CD, Fontanarosa PB. Impugning the integrity of medical science: the adverse effects of industry influence. *JAMA* 2008;299(15):1833-5.
753. Scherer RW, Dickersin K, Langenberg P. Full publication of results initially presented in abstracts. A meta-analysis. *JAMA* 1994;272(2):158-62.
754. Dickersin K. How important is publication bias? A synthesis of available data. *AIDS Educ Prev* 1997;9(1 Suppl):15-21.
755. Egger M, Smith GD, Sterne JA. Uses and abuses of meta-analysis. *Clin Med* 2001;1(6):478-84.
756. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA* 1998;279(4):281-6.
757. Gauthier S, Scheltens P. Can we do better in developing new drugs for Alzheimer's disease? *Alzheimers Dement* 2009;5(6):489-91.

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