

**A community-based factorial trial on Alzheimer's
disease.**

**Effects of expectancy, recruitment methods, co-
morbidity and drug use.**

The Dementia Study in Northern Norway

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'Navigare necesse est. Vivere non est necesse'
Pompeius 56 f. Kr

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3. Summary

BACKGROUND: Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder causing irreversible cognitive impairment. The prevalence of AD increases with age as does a number of other age-related physical illnesses. With an exception for a genetic impact and risk factors such as cardiovascular and cerebrovascular diseases no etiological factors have been identified. Usually, clinical trials on AD have recruited participants from memory clinics, hospitals or nursing homes using stringent inclusion criteria. These sampling methods could be at risk of selection bias. Current therapy for AD includes non-pharmacological and pharmacological symptomatic treatment. A number of studies on symptomatic treatment have reported contradictory results. Drug treatment of co-morbidities in AD could reinforce cognitive disabilities.

AIM OF THE STUDY: The main purpose of the present study was to examine the effects of stimulation therapy on cognitive test performance in community dwellers 65 years of age or older with a recent diagnosis of mild to moderate AD in Northern Norway. A secondary purpose was to examine whether donepezil increased the effect of stimulation therapy on cognition (Paper 3). During the study two additional purposes were included:

1. To compare baseline characteristics between participants included by two different recruitment methods within the same geographical area (Paper 1)
2. To compare co-morbidities, current medical treatment and inappropriate medication between participants with and without AD (Paper 2).

DESIGN:

1. A cross-sectional comparison of baseline characteristics between participants
 - a. with AD included by two different recruitment methods (Paper 1)
 - b. with and without AD regarding co-morbidities, current drug treatment and inappropriate medication (Paper 2)
2. A two-by-two factorial interventional study comparing stimulation therapy and standard care to which a randomised, double-blinded, placebo-controlled trial with donepezil was added (Paper 3)

PARTICIPANTS AND METHOD: The present study was population-based and conducted at a community level. One hundred and eighty-seven participants 65 years or older with a recent diagnosis of AD were recruited in nine rural municipalities; 100 by postal screening and 87 by general practitioners (GPs). In five municipalities the AD participants received structured stimulation therapy, and in the remaining four standard care. All participants were randomised in a double-blinded manner to donepezil or placebo. In addition 200 cognitively healthy participants 65 years or older were randomly selected by the screening program and included as control group. The clinical part of the study lasted from January 2006 until June 2009.

RESULTS: AD participants recruited by screening were younger, more frequently men and had a higher Mini-Mental-State-Examination (MMSE) ¹ sum score as compared to those recruited by GPs (Paper 1). In a cross-sectional comparison of co-morbidities and current medical treatments between AD participant and cognitively healthy controls, a significantly higher number of drugs were found in AD participants, despite no

significant differences in co-morbidities..Mean arterial blood pressure was significantly reduced and the mean number of antihypertensive drugs significantly increased among AD participants. The mean number of drugs and the frequency of inappropriate medication increased in AD nursing home residents (Paper 2).

No time-point differences were found between AD participants receiving stimulation therapy and those receiving standard care. Both groups retained cognitive test performances during the one-year follow-up. Donepezil had no additional effect but significantly more adverse reactions (95% CI 1.5 to 8.7 p=0.002) as compared to placebo. A head-to-head comparison between stimulation therapy and donepezil did not reveal any time-trend differences in cognitive test performance (Paper 3).

CONCLUSION: A community-based postal screening of cognitive function preceding clinical examination may be a suitable recruitment strategy in studies of early-stage AD. An increased number of drugs and inappropriate medication combined with reduced mean arterial blood pressure could deteriorate cognitive test performances in AD participants. AD participants retained cognitive test performance by receiving stimulation therapy during one year, but no better than those receiving standard care. Adding donepezil to these non-pharmacological treatment options did not improve outcome measures.

ClinicalTrials.gov (Identifier: NCT00443014). EudraCT database (no; 2004-002613-37).

4. List of publications

Paper 1

Fred Andersen, Torgeir A Engstad, Bjørn Straume, Matti Viitanen, Dag S Halvorsen, Samuel Hykkerud and Kjell Sjøbrend.

Recruitment methods in Alzheimer's disease research: general practice versus population based screening by mail. BMC Med Res Methodol 2010; 10:25.

Paper 2.

Fred Andersen, Bjørn Straume, Matti Viitanen, Dager Seeger Halvorsen, Torgeir Engstad,

Co-morbidity and drug treatment in Alzheimer’s disease. A cross sectional study of participants in The Dementia Study in Northern Norway. Submitted BMC Geriatrics.

Paper 3.

Fred Andersen, Dag S. Halvorsen, Bjørn Straume, Matti Viitanen, Tom Wilsgaard, Torgeir A Engstad

The effect of stimulation therapy and donepezil on cognitive function in Alzheimer’s disease. A community based RCT with a two-by-two factorial design. Submitted Journal of the American Geriatrics Society.

5. Abbreviations

AD	Alzheimer’s disease
ADAS-Cog	Alzheimer’s disease Assessment Scale, cognitive (Scale 0—70, increasing disability with increasing score)
ADL	Activities of daily living
BI	Barthel Index (Scale 0—20, better function with increasing score)
ChEI	Cholinesterase inhibitor
CSF	Cerebrospinal fluid
DSM-IV-TR	Statistical Manual of Mental Disorders fourth edition
EOAD	Early-onset Alzheimer’s disease
GCP	Good clinical practice
GDS	Global Deterioration Scale
GP	General Practitioner
ICD-10	International classification of diseases 10th Revision
IQ-CODE	Informant Questionnaire—Cognitive Decline in the Elderly
LOAD	Late onset Alzheimer’s disease
MADRS	Montgomery and Aasberg Depression Rating (Scale 0—60 increasing depression by increasing number)
MCI	Mild cognitive impairment

MMSE	Mini-Mental State Examination (Scale 0—30, better function with increasing score)
NPI	NeuroPsychiatric Inventory (Scale 0—144, increasing number of psychiatric symptoms by increasing number)
NINCDS-ADRDA	National Institute of Neurological Disorders and Stroke- Alzheimer Disease's and Related Disorders
OR	Odds Ratio
PET	Positron emission tomography
RCT	Randomised clinical trial
SCI	Subjective cognitive impairment
VaD	Vascular dementia

6. Introduction

6.1 Casuistry

In 1994, the Department of Psychiatry at the County Hospital in Bodø was invited to participate in a multicentre international Phase III clinical trial on AD. One of my patients with a recent diagnosis of AD was included in the study and allocated to active drug or placebo treatment in a double-blinded randomised manner. This patient was followed carefully every second week for four months. During this period, the patient's cognitive function, quality of life and activity of daily living (ADL) improved, both subjectively and according to observations and formal testing. Patient and family were satisfied with the treatment. After four months the randomisation code was broken. My patient was a placebo users. I was astonished and the patient were disappointed. How could the cognitive and executive functions improve by placebo treatment?

The question remained in my consciousness for years. Nine years later the first protocol of the Dementia Study in Northern Norway was written.

7. Background

7.1 Definition of dementia

Dementia is an acquired organic mental syndrome followed by general impairment of cognitive abilities such as memory, judgement and abstract thinking as well as personality changes. Dementia is irreversible and progressive and does not include functional mental disorders such as delirium or temporary impaired consciousness².

The present study focus on AD, a syndrome first described by the German psychiatrist Alois Alzheimer in 1906^{3;4}.

7.2 Literature on the topic

The main focus of the present study is the effect of stimulation therapy on cognitive test performance in an early-stage AD, to which donepezil treatment is added. Stimulation therapy comprises reality orientation, physical exercise, cognitive stimulation, reminiscence activities and various sophisticated sensory stimulations. Pharmacological treatment mainly involves cholinesterase inhibitors (ChEIs) and memantine.

Scandinavian research centres have participated in interventional AD studies with ChEIs organised as multicentre RCTs⁵⁻⁷. Only a few population-based screening programs aimed to recruit AD participants in clinical trials have been conducted^{8;9}. A head-to-head comparison between stimulation therapy and ChEIs examining the effects on cognition in AD has been requested by the scientific community¹⁰ but has to my knowledge not been published.

The literature listed below represents a brief review of the available knowledge of the effect of stimulation therapy and drug treatment on AD at the onset of the present study¹¹ and a sample of recently published studies on the topic. A brief review of new evidence of the impact of placebos in clinical trials is added. A complete and updated reference list is attached.

Stimulation therapy

When the present study was initiated, three review papers of the effect of stimulation therapy on AD were identified in PubMed.

1. In 2004 Heyn et al. published a meta-analysis of the effect of exercise training on elderly individuals with cognitive impairment and dementia. Published articles and non-published manuscripts from 1970 to 2003 were identified and 30 studies (2020 participants) were included. Heyn et al concluded that “physical training increased fitness, physical function, cognitive function, and positive behaviour in people with dementia and related disorders”¹².
2. In 2003 a review by Clare et al evaluated the impact of cognitive training and cognitive rehabilitation on early-stage AD. Records from MEDLINE, EMBASE, CINAHL, PsycINFO and many other databases, were searched in April 2003. Six studies comprising cognitive training with a RCT design were included. Clare et al concluded that the results did not provide strong support for the use of cognitive training for early-stage AD or VaD. However, only a few studies were available, hampered with methodological limitations. No conclusion could be drawn about cognitive rehabilitation due to a complete absence of RCTs on the topic¹³.
3. In 2003 Luijpen et al published a review of studies examining the effects of non-pharmacological stimulation on cognition, affective behaviour and the sleep—wake rhythm of cognitively impaired and demented elderly. The stimulation therapy comprised bright light, physical activity and tactile stimulation. Luijpen et al concluded that all three types of stimulation appeared to increase cognitive function¹⁴.

Several clinical trials examining the effect of stimulation therapy on AD have been reported during the last 15 years¹⁵⁻¹⁹. In some of them stimulation therapy was added to ChEI treatment²⁰⁻²². The most important recent trials and review papers on the topic are listed below.

1. In 2003 Spector et al published a well-designed single-blinded randomised multi-centre controlled trial with stimulation therapy for people with

dementia. The study included 201 individuals with dementia. The main outcome measures were changes in cognitive function and quality of life as measured by MMSE, ADAS-Cog and the Quality of life – AD scale. The authors reported significant improvement in cognition and quality of life in the intervention group²³.

2. In 2006 Graff et al published a single-blinded randomised controlled trial to assess the effectiveness of community-based occupational therapy for the ADL functions of patients with dementia and the sense of competence of their caregivers. The study included 135 participants with mild to moderate dementia. Ten sessions with occupational therapy during 5 weeks were provided, and the results were evaluated after 6 weeks and after 3 months. The authors concluded that occupational therapy improved activities of daily living of the patients and reduced the burden of the caregiver¹⁶.
3. In 2010 Olazaran et al published a systematic review and meta-analysis of the entire field of evidence-based knowledge of non-pharmacological therapy to treat AD. They concluded that non-pharmacological therapy was a useful and cost-effective approach to improve outcomes in AD and related disorders.²⁴
4. Yamaguchi et al (review 2010) focused on how therapists should communicate with patients and caregivers and offered some proposals for non-pharmacological intervention in suitable supportive psychosocial context to obtain optimal results²⁵.
5. In two recent review papers on stimulation therapy in AD, Ballard et al. (March 2011) and Andrade et al. (March 2009) both emphasise the positive impact of cognitive training, occupational activities and physical exercise on cognition and activities of daily living in patients with early-stage AD^{26:27}

ChEI treatment

Early loss of basal forebrain cholinergic neurotransmission is a biochemical hallmark of AD^{28:29}. Since the early 1990s several drugs with cholinesterase-inhibiting effects have been developed and tested in clinical trials, including symptomatic treatment of mild to moderate AD. However, the clinical effects, relevance and the cost-effectiveness of these

drugs have been questioned. The literature listed below reflects some of the scientific uncertainty related to the effect of ChEI treatment of AD at the time when this study began, in addition to recently published papers on the topic. A number of review papers on ChEIs have been identified and all of them concluded that ChEIs have a small to modest beneficial effect on cognition. One of the review papers included clinical recommendations³⁰⁻³⁶. Four of the review papers are summarised below.

1. Trinh et al reviewed papers with ChEI-treated AD participants from 1966 to December 2001. Twenty-nine parallel groups or crossover double-blinded RCTs of outpatients treated for at least four weeks were included. They concluded that ChEIs had modest beneficial effects on neuropsychiatric and functional outcomes for patients with AD. No conclusion could be drawn as to institutionalisation or quality of life³³.
2. A Cochrane review by Birk et al 2002 included 16 trials of 12, 24 or 52 weeks involving 4365 participants treated with donepezil 5 mg or 10 mg. A statistically significant effect on cognition measured by ADAS-Cog was reported after 52 weeks of treatment. Some improvement was found in global clinical state as rated by an independent clinician. Benefits of treatment were also seen in measures of activities of daily living and behaviour. Significantly more adverse reactions were found in participants on 10 mg donepezil compared to placebo³⁰.
3. Raina et al.(2008) conducted a review of 59 unique studies from 1986 through 2006 that evaluated the effectiveness of ChEI and memantine in achieving clinically relevant improvements, primarily in cognition, global function, behaviour and quality of life, in patients with dementia. Both ChEI and memantine had consistent but small effects in the domains of cognition and global assessment (the clinical-based impression of changes with caregiver input). Fewer consistencies were found for behaviour and quality of life. Most studies had short duration. The authors concluded that “treatment of dementia with ChEI or memantine can result in statistically significant but clinically marginal improvement of cognition or global assessment”³².
4. A clinical practice guideline for current treatment of AD in the US was published by Qaseem et al. in March 2008. The guideline recommended that clinicians base

the decision to initiate a trial of therapy with ChEI or memantine on individualised assessment taking tolerability, adverse effect profile, ease of use and medical cost into consideration³¹.

One of the classic trials examining donepezil for AD treatment was published by Rogers et al. in 1998³⁷. They highlighted cognitive deterioration as an inherent trajectory of AD and showed that cognitive performance could be maintained by nearly one year of donepezil treatment. However, this randomised, placebo-controlled and blinded part of trial was run for only three months. At that time the study was opened and the AD participants in both groups were treated only with donepezil without a control group. However, the reference to the inherent AD trajectory as the background for evaluating the effects of symptomatic treatment with donepezil makes this study one of the most important on the topic. Stabilising cognitive performance has for a long time been identified as an important treatment outcome in AD research³⁸.

Due to ethical considerations few placebo-controlled trials with ChEIs for AD treatment have been conducted during the last 10 years

Several RCTs with disease-modifying drugs, including the phenserine enantiomer (a derivate of physostigmine) have been published⁷. The results for phenserine enantiomer were not clinically significant as measured by ADAS-cog, the clinician's impression of change and the caregivers' input²⁹. The results of other RCTs of disease-modifying drugs for AD have so far been disappointing²⁹.

Placebo

A placebo was originally defined as a dummy medical treatment but has recently been described as any dummy treatment administered to the control group in a controlled clinical trial². The placebo effect is defined as the favourable impact of placebo (with a biologically inert substance or sham intervention) on the course of a disease state. The placebo effect is reinforced by classical Pavlovian conditioning, firm diagnosis, clinical testing, novel therapeutic procedures, verbal suggestion of a beneficial outcome and a

positive doctor-patient relationship³⁹⁻⁴¹. The placebo effect in clinical trials has gained more attention in recent years. Several studies have described the placebo effect as a complex interaction between the psychosocial context of the intervention and the expectation of a clinical benefit^{42;43}. In brain-activating rehabilitation the treatment is recommended to be implemented in a favourable psychosocial context utilising the impact of expectation and verbal suggestion²⁵. The impact of the placebo effect in clinical trials has probably been underestimated⁴³. In a recent review Fournier et al (2011) found that a true effect of antidepressant drugs was nonexistent or negligible compared to placebo amongst depressed patients with mild, moderate and even severe baseline symptoms, whereas the true antidepressant drug effect was large for patients with very severe depressive symptoms⁴⁴. The first evidence of a biochemical mechanism underlying the placebo effect, was demonstrated by Levine et al. in 1978. They found that the placebo analgesia effect could be blocked by naloxone. This observation suggested that a placebo could induce the release of endogenous opioids. In recent years several studies using functional magnetic resonance imaging techniques have visualised the role of placebos in releasing endogenous neurotransmitters in the brain^{40;43;45}

Few studies have focused on the placebo effect in AD. Benedetti et al. have postulated that the placebo mechanism depends upon preserved frontal lobe function. They evaluated lidocaine pain relief in AD individuals compared to controls. The placebo effect in AD participants with mild cognitive impairment (MMSE 24 ± 1.22) was preserved but it was significantly reduced in patients with moderate to severe AD (MMSE 15.6 ± 1.9) compared to controls. A reduced placebo effect was found to be correlated to reduced frontal executive function as measured by the Frontal Assessment Battery^{40;46}.

7.3 Aging and cognition

Memory complaints amongst the elderly are usually interpreted as a clinically normal age-related condition. However, approximately half of elderly subjects have no cognitive complaints and objectively normal neuropsychiatric performance. The prevalence of age-related self-reported cognitive disturbances constituted 20% in one study and varied

between 25% and 56% in three other studies of individuals 65 years of age or older^{47;48}. Cognitive complaints in the elderly are also associated with co-morbidities such as depression and pain^{48;49}.

Age-related memory impairment and mild cognitive impairment (MCI)

MCI⁵⁰ is supposed to be a continuum or an intermediary stage of cognitive disability between age-related memory impairment and early dementia stages, and it could be reversible⁵¹. The most commonly used criteria define MCI as a condition of subjective memory complaints, abnormal memory for age, normal executive functions and no dementia⁵²⁻⁵⁴. Cognitive impairment should be present without any interaction with ADL. Depending on the diagnostic tools and criteria⁵⁵, the incidence rate of MCI individuals \geq 65 years of age progressing to dementia range from 1 to 25% in one review paper⁵⁶, from 10 to 15% in another⁵⁷ and was 5.4% in one single cohort study⁵⁸. In the cognitively healthy population \geq 65 years, the incidence rate of dementia is 2%⁵⁷⁻⁵⁹. Amnesic MCI is a pre-clinical phase of AD lasting several years before the diagnostic criteria of AD are fulfilled^{48;60}. According to Reisberg et al. (2008) individuals with subjective cognitive impairment (SCI) and normal MMSE are at a significantly higher risk of cognitive decline compared to individuals with no subjective cognitive impairment (NCI) and normal cognition. During a mean follow-up of seven year, 54.2% (n=90) of the SCI group revealed cognitive deterioration compared to 14.9% (n=7) of the NCI group ($p < 0.001$)⁶¹. In the SCI group 71 of 90 individuals declined to MCI and 19 to dementia.

7.4 Alzheimer's disease

AD represents 65—70% of all dementia diagnoses, 90% of which occurs in individuals who are 65 years of age or older. The cardinal initial symptom of AD is impaired episodic memory and an inability to retain recently acquired information. With disease progression impairment of other cognitive domains, such as visuospatial, verbal and executive functions and semantic memory, occurs. Changes of social behaviour and personality are common, especially in advanced disease stage⁶². Increasing cognitive disability gradually influence ADL⁶³. Delusions and psychotic behaviour are not typically initial symptoms but can occur at any time during the disease course⁶². The natural

cognitive deterioration is characterised by a yearly 2 – 3-point decrease in MMSE sum score corresponding to an increase of 6 – 12 points in Alzheimer’s disease Assessment Scale, cognitive (ADAS-Cog)⁶⁴ score⁶⁵⁻⁶⁷.

7.5 Epidemiology of AD

The incidence and prevalence of AD increase steeply with ageing and depend strongly on the diagnostic criteria⁶⁸⁻⁷⁰. The overall prevalence ranges from 5.4 to 10.3% in a population ≥ 65 years^{3;71}. The prevalence of AD is 3% in the 65—74 year age group and increases to 47% in those above 85 years. No significant differences amongst countries have been reported⁷²⁻⁷⁴, although differences amongst ethnic groups are found^{75;76}. Increased longevity and a steadily increasing number of individuals reaching the age of retirement in developed countries in the years to come will reinforce the impact of AD on public health services and may represent an unsustainable economic burden on societies^{3;72;73;77-81}.

AD is a heterogeneous syndrome. Both genetic and environmental factors have an etiological impact⁸². The genetically attributable risk of AD is postulated to be 70%²⁷. Early-onset AD (EOAD) (<65 years of age) accounts for less than 10% of all AD individuals^{83 84}. Late-onset AD (LOAD) is a sporadic condition with an inherent but not genetically dominant disposition^{85;86}. Individuals who are homozygous for the APOE $\epsilon 4$ allele are at an increased risk of LOAD⁸⁵ and having a close relative with AD increases the risk of AD. Known environmental risk factors include negative lifestyle habits (i.e. excess weight, inactivity, smoking) and co-morbidities such as metabolic syndrome, hypertension in midlife and cardiovascular and cerebrovascular diseases^{87;88}

Level of education may modify the deterioration of AD^{89;90}, providing support to the “cognitive reserve” model⁶⁵. A meta-analysis in 2006 confirmed that low education may be a risk factor for dementia⁹¹.

Insufficient nutrition, especially reduced consumption of vitamin B12 and folic acid, has been associated with AD, but convincing causal interaction is still lacking⁹², and the deficiency stages can be secondary.

7.6 The histopathological findings in AD

The AD brain shows medial temporal lobe atrophy especially in the entorhinal cortex and hippocampus (in the floor of the inferior horn of the lateral ventricle) and in parts of the frontal and parietal lobes⁹³. The histopathological hallmarks of AD are senile plaques and neurofibrillary tangles in the cortex²⁷.

7.7 Diagnosing AD

The diagnosis of AD in general practice is based on a careful medical history usually extended by a caregiver; cognitive and neuropsychiatric tests; clinical examination and neuroimaging. In memory clinics, more advanced diagnostic tools and procedures are provided. Typical findings are problems in episodic memory, visuospatial tasks, verbal and executive functions. The diagnosis is supported with hippocampal atrophy in magnetic resonance imaging (MRI), changes in biomarkers in cerebrospinal fluid (CSF) such as elevated total tau and phosphorylated tau protein, low level of β -amyloid42 in cerebrospinal fluid (CSF)⁹⁴, temporoparietal hypoperfusion in Single Photon Emission Computer Tomography (SPECT), decreased glucose metabolism in tempo-parietal lobes and increased amyloid deposits in frontal lobes as assessed with positron emission tomography (PET)⁹⁵.

7.8 Screening of cognitive impairment and other functions in AD

MMSE is the test most widely used to screen and monitor changes in cognitive function. The cognitive domains assessed are memory, language, abstraction, visuospatial and executive functions. The test favours individuals with higher education⁹⁶. In Norway the clock drawing test⁹⁷ is also used routinely to assess executive and visuospatial functions. It is validated and easy to use.

In AD drug trials, ADAS-Cog is the most widely applied cognitive test to follow disease progression⁹⁸. ADAS-Cog covers the typically deteriorated cognitive domains in AD, and frequent repetitions do not tend to improve the results. It is validated and translated into Norwegian.

A number of additional cognitive, neuropsychiatric, ADL and depression tests and semi-structured questionnaires have been developed.

Various population-based screening tools of cognitive impairment and AD have been evaluated. Caregiver-based telephone interviews have good agreement with the assessment by general practitioners⁸. A two-step population-based screening of cognitive impairment by a postal questionnaire and a subsequent telephone interview was developed by van Uffelen et al. Individuals with probable MCI as diagnosed by screening were invited to a face-to-face clinical assessment. Screening compared to clinical assessment had a 41% agreement in diagnosing MCI⁹⁹. In general, self-administered postal questionnaires have several advantages over face-to-face assessment. They are cheap and suitable in surveys, requiring no training and provide a high response rate in elderly people. In England and Wales a postal screening approach for morbidity in the elderly has been advocated¹⁰⁰.

7.9 Diagnostic criteria

Three sets of diagnostic criteria based on clinical examination are most frequently used in clinical trials. Two of them have been developed and revised over years (ICD-9 → ICD-10, DSM-III → DSM-III-R → DSM-IV) and have gradually been approached to one another¹⁰¹.

ICD-10

According to ICD-10^{101;102} dementia in LOAD is a chronic neurologic disorder involving several cognitive domains in individuals ≥ 65 years. A LOAD diagnosis presupposes impaired memory (especially short-term and episodic memory) and disturbances in one or more executive functions such as abstracting, judgment and problem solving.

Disturbances in language (especially semantic memory) and visuospatial functions strengthen the diagnosis. The observed cognitive deficits should interfere with social or occupational activities and represent a significant decline from a previous level of functioning. Decline in cognitive function should be steady and progressive and not due to delirium, depression, endocrine disorders, nutrition deficiencies, infectious diseases or other dysfunctions in the central nervous system. Decline in cognitive function should have lasted for at least six months and consciousness disturbances should be excluded⁶⁹.

DSM-IV TR

According to the Statistical manual of mental disorders, fourth addition (DSM-IV-TR)¹⁰³, a dementia diagnosis of AD requires both memory deficits (especially impaired ability to learn new information and recall previously learned information) and deficits in at least one additional cognitive domain (aphasia, apraxia, agnosia, and/or executive functions), both interfering with social functioning and ADL⁹⁴. The course is characterised by gradual onset and continuing cognitive decline. Delirium, depression and other causes of dementia or cognitive impairment should be excluded. Normal consciousness is required.

NINCDS-ADRDA

The National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA)¹⁰³ criteria for probable AD require a clinically and neuropsychologically established diagnosis of dementia including deficits in at least two cognitive domains: 1. Memory impairment; i. e. the loss of learning ability and/or the ability to recall previously learned information. 2. One or more of the following disturbances: apraxia, aphasia, agnosia and executive functions. Loss of function should be a substantial decline from previous abilities and should influence ADL. The disturbances should begin slowly and gradually become more severe. Delirium should be excluded. The criteria include normal motor, sensory, and coordination functions at an early disease stage and the absence of focal neurologic symptoms. Laboratory tests and cerebral computed tomography (CT) should exclude other possible causes of cognitive impairment before the diagnosis of Alzheimer's disease can be made with confidence.

These criteria also include neuropsychological tests to provide confirmatory evidence of the diagnosis.

Although no gold standard diagnostic criteria of AD exist, Ballard et al. emphasise that the diagnostic criteria and procedures mentioned above have a sensitivity and specificity > 80 % for discriminating Alzheimer's disease and healthy cognition²⁷. Dubois et al emphasise that DSM-IV-TR and NINCDS–ADRDA criteria have been validated against neuropathological findings with diagnostic accuracy ranging from 65 to 96%. In a recent study from Lund, Sweden, 84% of patients with a clinical AD diagnosis had a significant Alzheimer neuropathological component¹⁰⁴. The specificity of the present diagnostic criteria against other dementias is only 23–88%⁹⁴. New diagnostic options such as CSF biomarkers and functional PET have increased accuracy and are currently closest to a gold standard diagnostic tool⁹⁴. However, the sensitivity and specificity of the current routinely available diagnostic tools, relying on cognitive tests and medical history, are still insufficient. In combination with various diagnostic criteria, this insufficiency could influence the calculation of both prevalence and incidence rate^{69;70} and makes the calculation of predictive values and the accuracy of current tests less certain.

7.10 Therapeutic options

As long as no causal treatment of AD exists, therapies must concentrate on prevention and symptomatic treatment¹⁰⁵⁻¹⁰⁷ by means of stimulation with and without pharmacological treatment or pharmacological treatment alone. The development of efficient disease-modifying drugs has until recently failed²⁷. The unsuccessful approach focused on a causal therapy has demonstrated a probably insufficient basic understanding of AD pathogenesis²⁹. AD is a multifactor disorder¹⁰⁸. A single drug acting against a single target linked to a single pathogenic pathway or disease is not likely to be found²⁹. At the moment, intervention against risk factors and symptomatic treatment is the only therapeutic option¹⁰⁵.

Intervention on risk factors in AD

With the growing prevalence of AD, sustainable intervention methods against known risk factors are important. Health conditions and lifestyle are risk factors associated with AD and could be the most reasonable targets of an optimal preventive strategy^{87;88}. Lifestyle habits including nutrition and physical activities may modify many risk factors¹⁰⁹.

Increasing evidence suggests that an active lifestyle among the elderly including social, mental, and physical engagement may prevent AD. The strongest evidence is found for increasing an individual's level of physical activity, followed by the cessation of smoking^{110;111}.

Treating hypertension in midlife may reduce the risk of dementia¹¹². Interventions and medical treatment of cardiovascular risk factors in AD are supposed to delay AD progression and improve prognosis. So far treating cardiovascular risk factors and metabolic syndrome have not influenced cognitive decline or AD progression¹¹³. There is conflicting evidence about the preventive effect of antihypertensive treatment^{27;113}.

However, physical activities and interventions to promote a healthy lifestyle will probably reduce the incidence of several AD risk factors²⁷ and are the most promising AD-modifying efforts¹¹⁴.

Symptomatic treatment (non-pharmacological and pharmacological therapy)

As AD is a progressive neurodegenerative disease, any considerable improvement of cognition is not likely. The best obtainable result of symptomatic treatment would be postponing an inevitable cognitive deterioration. This is an esteemed goal for symptomatic treatment, and verified by a number of clinical trials on the topic^{37;115;115;116}. How sustainable this postponement of cognitive decline could be is still unknown, but any postponement of cognitive deterioration will be valuable both for the patients and the caregivers.

Stimulation therapy

Various non-pharmacological interventions for individuals with dementia are available, including physical exercise, occupational therapy, cognitive rehabilitation and social

stimulation.^{12;13} A number of small interventional studies have been conducted in recent years and most of them report positive effects of stimulation therapy compared to control treatment^{10;15;23;117;118}. A meta-analysis from 2004 on exercise training in elderly with dementia reported improved fitness, physical and cognitive function, and positive behaviour¹². A new systematic review performed by Olazaran et al. (2010)²⁴ examined 179 RCTs on stimulation therapy. According to the criteria of Oxford University's Centre for Evidence-Based Medicine, 13 high-quality trials were found of which seven (54%) reported positive results; 113 of 166 (68%) low-quality trials were positive. In spite of these results, Olazaran et al. concluded in this way: "Non-pharmacological treatment emerges as a useful, versatile and potentially cost-effective approach to improve outcomes and quality of life in AD and related disorders for both persons with dementia and caregivers". A third systematic review (2008) dealing with mild to moderate AD, provided practical recommendations on non-pharmacological and pharmacological interventions. One conclusion was that there is good evidence that individualised exercise programs have an impact on functional performance¹¹⁹. Furthermore, Lujipen et al concluded in a review that improvement in cognition and affective behaviour by bright light, physical activity and tactile stimulation and by cholinesterase inhibitors had similar effect sizes. All three types of stimulation appeared to increase cognitive function¹⁴.

Drug treatment (ChEI and memantine)

During the last 15 years, the AD neuropathological focus has been on insufficient neurotransmission in affected brain areas, initially on cholinergic and glutamate synapses in particular. Since the early 1990s several drugs with ChEI effects have been developed and tested. The external validity of these early phase III RCTs on ChEI was hampered by short duration and by the restrictive subject selection criteria¹²⁰ which would have excluded 90% of eligible community-dwelling AD individuals¹²¹. One large community-based industry-independent donepezil study included 595 AD individuals and lasted for more than one year (the AD2000 trial)¹²². An increase in mean MMSE sum score of 0.8 points in the donepezil group over placebo was found ($p < 0.001$) whereas other outcomes were insignificant³². The main conclusion from meta-analyses of cholinesterase inhibitors is that ChEIs (donepezil, rivastigmine and galantamine) have a modest beneficial effect

on cognition and a questionable clinical efficacy^{30;36;123;124}. In Norway, three cholinesterase inhibitors have received legal marketing for symptomatic treatment of mild to moderate AD. A guideline for dementia treatment in general practice recommends that clinicians should base their decision to prescribe ChEI or memantine on individualised assessment, taking tolerability, adverse effect profile, ease of use and medical cost into consideration³¹.

Therapy combining non-pharmacological and pharmacological treatment

The effect of stimulation therapy in patients treated with ChEIs has been evaluated in several studies^{19;20;22;125}. In these studies, AD individuals were randomised to stimulation therapy combined with ChEI or ChEI only (controls). These studies were open or single-blinded and reported significant effects of stimulation therapy added to ChEI. No studies have so far compared ChEI with stimulation therapy in a head-to-head clinical trial¹⁰.

7.11 Clinical trials, recruitment methods and external validity

Most clinical trials on AD using stringent inclusion criteria have recruited participants from memory clinics, hospitals or nursing homes¹²⁶. In contrast, some trials have recruited AD participants by advertising in newspapers. These methods provide samples with different characteristics. Hence, the validity of these studies is questionable and the results from some of these studies could hardly be generalised¹²⁷.

7.12 Co-morbidities and drug treatments in AD individuals

As a consequence of the increased number and severity of co-morbidities in AD individuals¹²⁸⁻¹³⁰ necessary medical treatment could be more extensive compared to cognitively healthy individuals. Neuropsychiatric symptoms in AD are common, especially in advanced disease stages. The symptoms could require treatment with psychotropic drugs. Increasing the number of drugs administered, especially psychotropic drugs and drugs with anticholinergic activity, is prone to influence cognition negatively^{131;132}.

Co-morbidity and Alzheimer's disease

AD is associated with metabolic syndrome¹³³, hypertension in midlife¹³⁴ and increased cardio- and cerebrovascular disease burden⁸⁸. Ischemic disease affects 60% to 90% of AD individuals, with major cerebral infarctions representing one-third of vascular lesions in autopsy cases¹⁰⁸. Arteriosclerosis and reduced cerebral perfusion reinforce cognitive impairment in AD individuals in an additive or synergistic manner^{82;135-138}. The Cache study has reported a more rapid AD progression in patients with atrial fibrillation, hypertension or coronary heart disease¹³⁹. Deschaintre et al. have reported similar results¹⁴⁰. The number of co-morbid medical illnesses in AD increases with disease severity^{128;141}. In addition, AD individuals have more serious medical co-morbidities than comparable persons without cognitive impairment¹²⁹. Dementia in elderly people is associated with low blood pressure¹⁴², but this could be a confounder, as low blood pressure by itself may predict death¹⁴³. Pneumonia, febrile episodes, and eating problems are frequent complications in patients with advanced dementia, and these complications are associated with high 6-month mortality rates¹⁴⁴.

Inappropriate drugs

Inappropriate medical treatment in the elderly has been an increasing concern in geriatric practice for years. Few studies have specifically addressed inappropriate treatment in AD^{145;146}. Increasing the number of drugs increases the risk of adverse reactions and inappropriate medication^{131;146-148}. Efforts have been made to define suitable guidelines and treatment criteria in the elderly. Beers' criteria for inappropriate drugs were the first guidelines in the field. The criteria defined inappropriate medications in geriatric practice according to drugs licensed in the USA¹⁴⁹ but did not address drug interactions or inappropriateness with or without specific diagnoses^{150;151}. Rognstad et al. have through a Delphi process compiled a list of 36 explicit criteria for drugs clinically relevant for general practice in Norway, and considered potentially inappropriateness for elderly people (≥ 70 years). This list does not address specific diagnoses either¹⁵¹. The STOPP criteria define inappropriate drugs according to drug interactions and common geriatric disorders¹⁵². However, Barnett et al. question the validity of the full list of potentially

inappropriate drugs in older people because no significant impact on mortality has been found^{153;154}

More serious medical co-morbidities in AD individual may call for more extensive medical treatment compared to cognitively healthy persons. As a result, AD individuals have an increased risk of adverse drug reactions and inappropriate drug treatment^{147;148}

8. Purpose of the study

The main aim of this study was to examine the impact of stimulation therapy on cognitive performance in individuals ≥ 65 years old with a recent diagnosis of mild or moderate AD.

A secondary aim was to examine whether donepezil had an additional effect on cognitive performance when combined with stimulation therapy.

During the progression of the trial, two additional study aims were adopted to compare:

1. baseline characteristics in AD individuals recruited by two different methods from the same population
2. the prevalence of co-morbidity and drug burden between AD individuals and cognitively healthy controls.

9. Methods

9.1 Participants and recruitment methods

In clinical practice

Two hundred participants with a recent diagnosis of AD were expected to be examined and included in the study by general practitioners in nine rural municipalities in Northern Norway between January 2006 and December 2007. However, during 2006 only 27 AD participants were included in the study. By then it was obvious that a presupposed sample size of 200 participants could not be reached by recruitment in general practice separately.

The participating municipalities were selected from municipalities employing competent and professional health providers in rural Northern Norway. The general practitioners were well prepared for scientific studies and engaged in evidence-based medicine. However, as it came to examining and diagnosing dementia, only 14 of 70 GPs in the participating municipalities diagnosed and recruited AD patients to the study. This is in line with experiences from other studies^{155;156}. GPs hesitate to diagnose mild cognitive impairment or early-stage dementia and cognitive impairment is disregarded both by relatives and health professionals, although this stage of cognitive impairment gives the most promising interventional opportunity^{8;157;158}.

Population-based screening

As a consequence of the low inclusion rate by GPs during the first year, the recruitment method was extended in June 2007 to include a population-based screening of cognitive impairment by mail. An invitation letter enclosing a questionnaire modified from the Cambridge Examination for Mental Disorders of the Elderly¹⁵⁹ and Strawbridge et al¹⁶⁰ was sent to all inhabitants ≥ 65 years old in the participating municipalities. The questionnaire comprised six questions concentrating on the main cognitive domains affected in AD (see Postal Questionnaire). To my knowledge this was the first community-based screening of cognitive impairment in Scandinavia and one of the first screening procedures by mail presented in the literature^{47;155}.

Postal Questionnaire

1. Do you want to participate in the Dementia study?
2. Has your memory deteriorated?
3. Do you forget where objects were left?
4. Do you have difficulties finding the appropriate words?
5. Do you have difficulties in managing daily activities, which earlier represented no problem?
6. Have you been examined for memory impairment before?

An algorithm was defined, and individuals answering in accordance with it were invited to undergo cognitive tests and clinical examination (see Algorithm). To reach a sufficient sample size the recruitment period was extended to March 2008.

Algorithm

Individuals invited to undergo cognitive tests and clinical examination answered

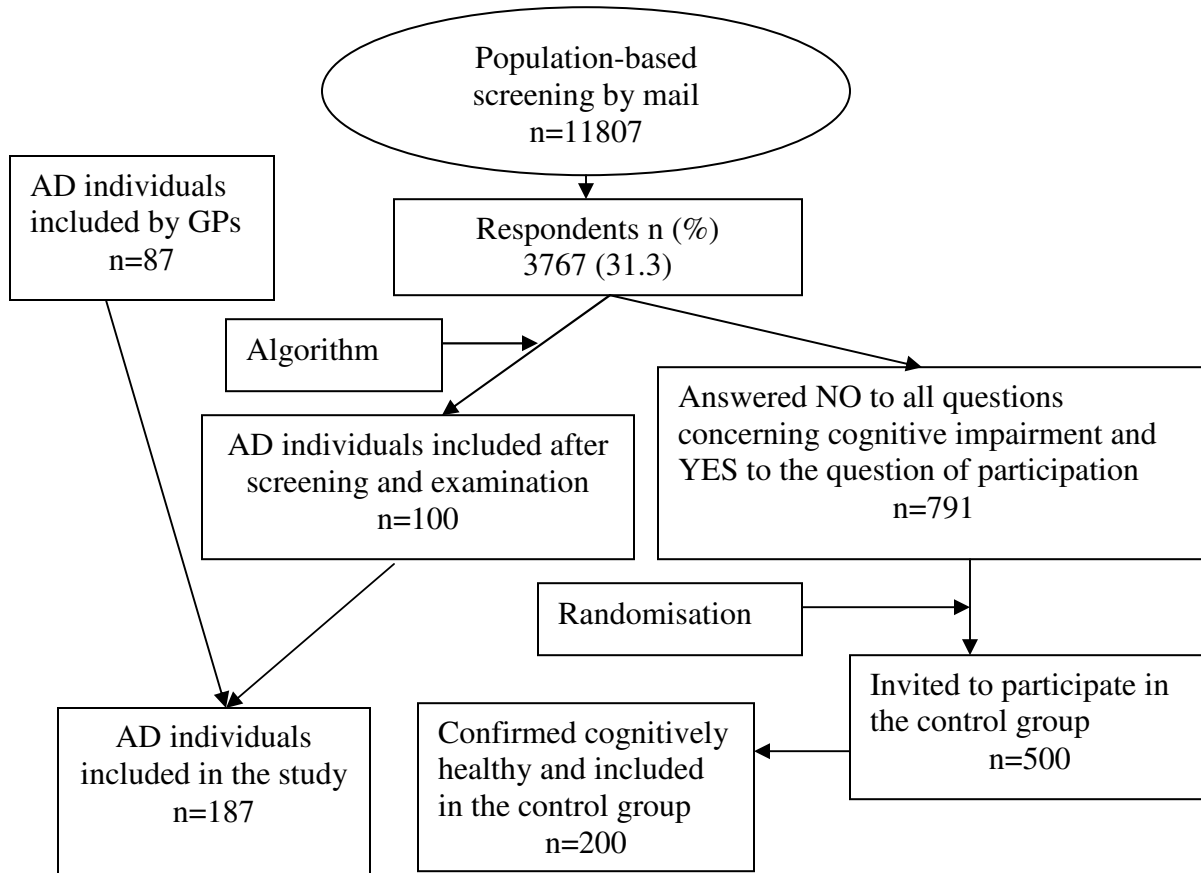
1. “Yes” on question 1, 2, 3, 4, and 5. “No” on question 6
2. “Yes” on question 1, 2, 5 and 3 or 4. “No” on question 6

At the end of the recruitment period, 187 participants were included in the study; 87 were recruited by GPs and 100 were recruited by population based screening (Flowchart 1). Because two different recruitment methods were used in the study, it was important to determine whether baseline characteristics differed across recruitment methods and whether the two samples were equally distributed in the municipality groups. Other studies have shown that different recruitment methods could have a significant impact on study results and reduce validity. The first paper from the study compares baseline characteristics between the two samples⁴⁷. The study period was 39 months, 27 of which were devoted to recruitment.

Cognitively healthy controls

Seven hundred ninety-one individuals answered “Yes” to the question on participation and “No” to the rest. From this group, 500 individuals were randomly selected by the Clinical Research Centre at the University Hospital in Northern Norway and invited to a clinical examination, including cognitive testing, aiming to act as a control group for the AD participants. Two hundred individuals were confirmed cognitively healthy, and then included in the study (Flowchart 1). The third paper from this study presents the main results of the interventional program whereas the second paper compares co-morbidities and drug use between AD participants and the cognitively healthy controls.

Flowchart 1

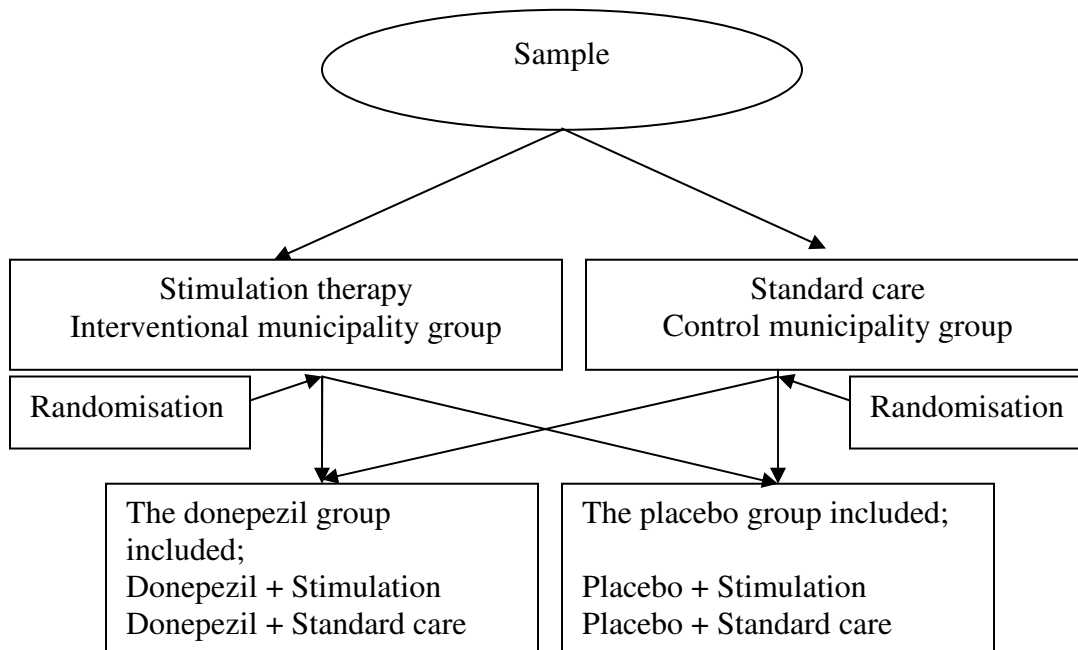


9.2 Two-by-two factorial design

As a consequence of the diversity of design, study duration and number of stimulation sessions in prior studies of stimulation therapy, we aimed to design a study being able to cope with these methodological challenges. The study had an open branch consisting of AD participants receiving stimulation therapy or standard care. All AD participants were double-blinded randomised to donepezil or placebo in a two-by-two factorial fashion. This design enabled a number of cross-analyses between subgroups including a head-to-

head comparison between donepezil and stimulation therapy (Flowchart 2). To our knowledge, no study with the same design has been published in the field of AD research.

Flowchart 2



9.3 Outcomes

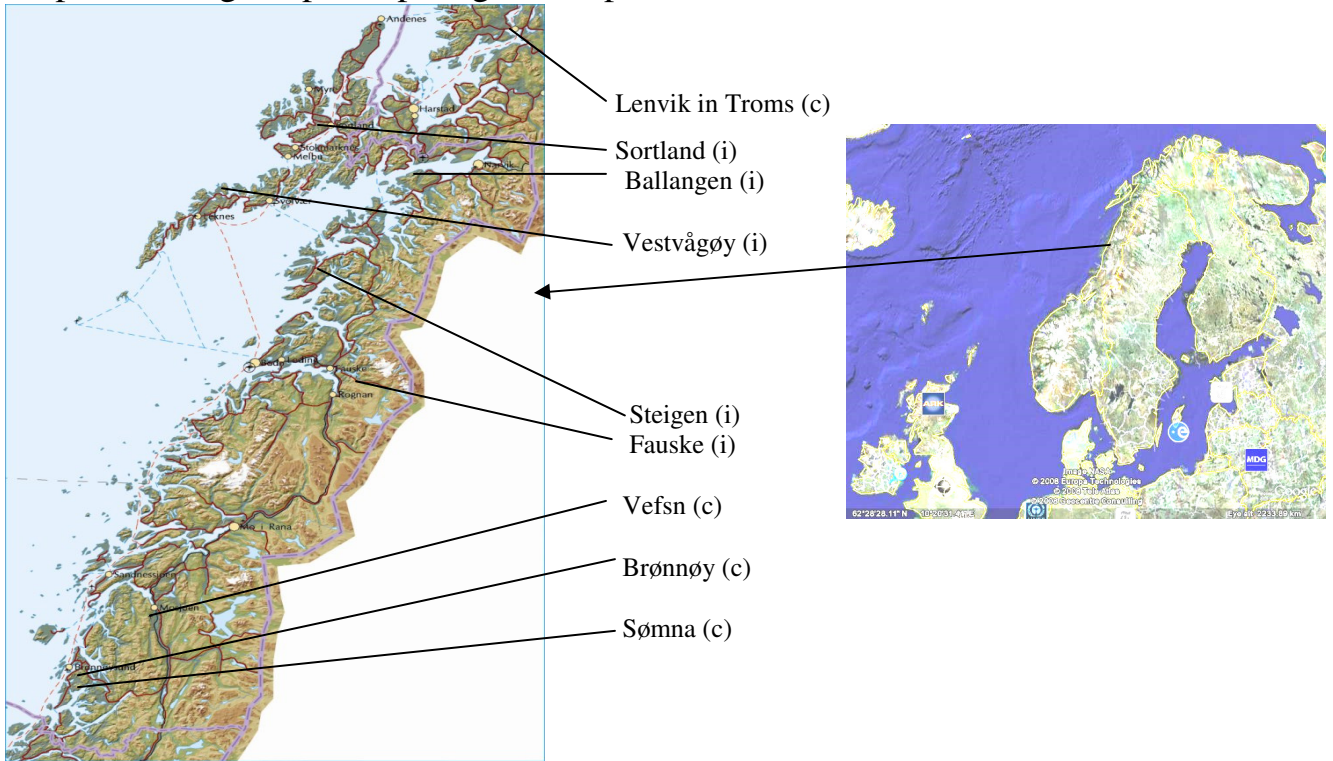
MMSE sum score was defined as the primary outcome. The results of ADAS-Cog and Clock drawing test were defined as secondary outcomes. Basic activities of daily living were assessed with the Barthel Index (BI)¹⁶¹, the Neuropsychiatric Inventory (NPI)¹⁶² was used to identify psychiatric symptoms whereas depression was assessed with a semi-structured questionnaire and with the Montgomery and Aasberg Depression Rating Scale (MADRS)¹⁶³.

9.4 Organisation and management of the study

The study was administered from a rural municipality, Steigen, in the county of Nordland. The study centre was situated approximately half-way between the

northernmost and the southernmost points of the participating municipalities. The distance between these extreme points was 800 km (Map 1).

Map 1 showing the participating municipalities



c= control municipality
i= Interventional municipality



The staff of the Dementia Study in Northern Norway in front of the research vehicle. From the left hand side: Herdis Svendsen, Fred Andersen, Merethe Hjertø and Kristin Tverback

The staff consisted of two test technicians, one research nurse and the project leader. They were all employed at the municipality of Steigen, which also offered office facilities for the study. The test technicians performed all tests in the study, among AD participants and in cognitively healthy controls. In addition, they acted as monitors of the interventional program. The monitoring procedures were approved by the Norwegian Medicine Agency. As the AD participants were diagnosed and included consecutively and followed up every fourth month for one year, the test technicians had to visit the participating municipalities regularly during a total study period of three years. The research nurse conducted the daily administration of the study and scheduled travel for the test technicians. She also made appointments with the participants and their caregivers. All participants were examined, tested and monitored at the municipality level, sometimes in their own homes. All data were collected while the participants were

situated in their own district, and the data were recorded consecutively by the staff at the study centre. The project leader surveyed and supervised the daily administration.

All participants recruited by screening with and without cognitive impairment were examined and diagnosed in their own district by the project leader and physicians from the Geriatric Department at the University Hospital in Northern Norway.

The scientific advisory board at The University of Tromsø, the County Hospital of Bodø and the Geriatric Department at Karolinska Institutet in Stockholm supervised the study regularly.

9.5 Validating study groups

The study was community-based and run on a municipality level. Nine rural municipalities in Northern Norway with 70000 inhabitants were engaged. The population in the age group ≥ 65 years was 11807. The participants in five of the municipalities received stimulation therapy whereas the participants in the remaining four received standard care (the control municipality group) (Flowchart 1 and 2).

The municipalities were selected for the study and allocated to offer stimulation therapy or standard care according to some basic criteria including number of inhabitants, age distribution and ethnic homogeneity. A high professional competence level was required, and the primary health facilities needed to be organised and developed in accordance with the principles of good clinical practice and national guidelines. Choosing a maximum distance and pursuing the least contact between municipalities offering stimulation therapy or standard care were done to minimise the risk of dilution. These selection criteria were difficult to comply with at random.

All participants were allocated to donepezil or placebo in a randomised manner, in blocks of four to six by the Clinical Research Centre at the University Hospital in Northern Norway. No significant differences in baseline characteristics were found between participants receiving stimulation therapy or standard care at entry.

Dementia competence

The deficit in professional competence was reflected in an unsustainable organisation of dementia care in general and a lack of any option for individual therapeutic adjustment both in nursing homes and amongst outpatients in some of the participating municipalities. Cognitive impairment amongst the elderly was ignored, or inappropriately diagnosed and treated by the family physician, the relatives and the patient him/her self. Nursing homes were only partly set up to take care of dementia patients.

In light of these observations and in order to ensure a professional care and follow-up of AD participants in the Dementia Study in Northern Norway, the study administration had to provide competence building and assistance with the construction of a suitable dementia care in participating municipalities offering stimulation therapy. Health professionals from all municipalities were invited to 3 main courses dealing with general knowledge on dementia, diagnostic procedures in particular, but only 14 out of 70 GPs in the participating municipalities attended these courses. Further more, several teaching courses were provided at the municipality level.

9.6 Diagnosis

The same diagnostic tools and diagnostic criteria were used independently of recruitment method. Participants recruited in general practice were examined by the community health professionals whereas individuals recruited by screening were examined and diagnosed by physicians from the study visiting each of the participating municipalities. In both cases, experienced physicians conducted the clinical and neurological examination and referred the participants to cerebral CT. Cognitive performance was assessed by MMSE and the clock drawing test. In the present study depression was assessed through a semi-structured questionnaire and MADRS, and basic activities of daily living were assessed by BI. NPI identified psychiatric symptoms. Social living, medical history and current medical use were recorded. A comprehensive number of biochemical analyses were obtained and recorded from each AD participant. A family member or a caregiver completed or extended the medical history and described the impact of the disease on the caregiver's health and social life and on patient's ADL by

answering the Informant Questionnaire-Cognitive Decline in the Elderly (IQ-CODE)¹⁶⁴. Blood pressure was recorded automatically by DINAMAP¹⁶⁵ as mean arterial blood pressure (MAP) (Appendix 1). Dementia and Alzheimer's disease were diagnosed by experienced physicians and geriatricians using the ICD-10 and DSM-IV-TR criteria. Diagnostic discrepancies were discussed with another geriatric colleague (Matti Viitanen) and solved by consensus using NINCDS-ADRDA criteria for probable AD. Those complying with the ICD-10, DSM-IV-TR and NINCDS-ADRDA criteria for probable AD and fulfilling the inclusion/exclusion criteria were asked to participate in the study.

Inclusion criteria

Patients could be included in the study if they had a recent diagnosis of probable AD, had not received any symptomatic treatment and were not suffering from any co-morbidity interfering with cognitive testing or ChEI treatment. MMSE sum score needed to be 10 points or more, and age ≥ 65 but <100 years. Each participant signed informed consent before inclusion. As a majority of the AD participants were anticipated to have reduced consent competence, the informed consent was also co-signed by a spouse or next to kin to comply with Norwegian national guidelines and research legislations.

Exclusion criteria

Patients suffering from dementia other than AD, serious brain injuries, infectious diseases of the central nervous system or serious depression or psychosis were excluded. Patients with delirium or behavioural disturbances interfering with cognitive or clinical testing, reluctance to participate, or inability to understand the purpose of the study, or who had relatives/caregivers who disapproved participation were also excluded.

9.7 Intervention

Stimulation therapy

A panel consisting of psychiatric nurses, university lecturers and members of the Competence Centre of Dementia in Northern Norway (Kløveråsen) developed a program of stimulation therapy including physical activities and cognitive, sensory and social stimulation. A number of activities were recommended within each area (see Proposal for

intervention). This program was adjusted for each participant living in the interventional municipalities taking functional and educational level and occupational experiences into consideration. The stimulation was conducted for a minimum of 30 minutes 5 days a week for one year in close co-operation with the patient and his/her family or with trained health providers. A weekly log was used to record the daily stimulation activities. Health professionals conducted the stimulation in nursing homes, while community nurses or other caregivers guided by the nurses were responsible for the stimulation therapy of community dwellers living in their own homes. The stimulation program was monitored and adjusted during the period of intervention. Individuals living in municipalities offering standard care received ADL support, supervision and sustainable care, as required.

Proposal for intervention

Physical stimulation

Walking with or without an assistant, preferably outdoors

Other outdoor activities

Training in fitness centre (therapeutic sport)

Sensory stimulation

Music, video

Aromatherapy

Wheel chair outdoors

Sensory garden

Cognitive and social stimulation

Conversation or reminiscence groups

Reading and remembering

Playing card, chess or puzzles

Problem solving or memory training

Combined activities

Training activities of daily living

Learning hand crafts in groups

Visiting museums, farms and similar institutions

Donepezil

All AD participants were randomised double-blinded to donepezil or placebo in blocks of four to six by the Clinical Research Centre at the University Hospital in Northern Norway. (Flowchart 2) The randomisation codes were transferred to the pharmacy at the County Hospital of Nordland, Bodø. Donepezil was prescribed to each AD participant by their GP according to national guidelines. Then, the pharmacy distributed donepezil or placebo to the AD participants in accordance with the prescription and the randomisation codes.

Donepezil and placebo were delivered by Pfizer, who had no influence on the study, the analyses of the results or publications.

9.8 Testing and follow-up

The two test technicians were trained at the Department of Geriatrics at the University Hospital. To improve intra- and inter-rater reliability they observed and evaluated each other by testing a number of patients with MMSE, ADAS-Cog, the clock drawing test, NPI and MADRS. The same test technician followed each participant during the study period over one year. The same diagnostic procedures were used to test the self-reported cognitively healthy control group.

During the one-year follow-up period MMSE, the clock drawing test and ADAS-Cog were performed at baseline and at 4, 8 and 12 months, whereas NPI, MADRS and BI were performed at baseline and at 12 months.

At the end of the study, blood samples were collected from 152 of the AD participants and from 200 of the cognitively healthy controls.

10. Ethical considerations

10.1 Consent competence

AD individuals included in a clinical trial have varying degrees of reduced consent competence and reduced ability to understand oral or written information. In early disease stages, they usually are able to decide in a rational manner which choices will fit them best, participating in the study or not. At this stage a stand in should not be allowed to interfere with the patient's decision. Later on, a spouse or a next of kin should be asked to take responsibility for the decision-making process on behalf of the patient.

Monitoring patients with impaired cognitive functions who participate in an interventional clinical trial requires specially awareness. The monitor and caregiver must observe sign of adverse reactions and any expressed reluctance to participate or inability to understand the purpose of the study. Signs such as these require immediate exclusion from the study at any time during follow-up. Participants' well-being must always be considered a main concern in any clinical trial, especially when it comes to participants with cognitive impairment

10.2 Study design

Ethical considerations of randomised placebo-controlled, double-blinded trials with new drugs for AD have been discussed since 1996¹⁶⁶. It has been argued that Phase IV studies of ChEIs could be unethical according to the modest and statistically significant effect of the drugs on cognition^{167;168}. However, the contradictory outcome of numerous RCTs on ChEI in addition to high drug costs and fear of adverse reaction underlay the decision to perform the present study.

The medical history of chemicals with ChEI effects is scaring and should be considered carefully, especially as it comes to the development of new drugs aimed to treat individuals with reduced consent competence (see Appendix).

10.3 Approvals

The present study was approved in advance by national authorities including the Regional Committee for Medical Research Ethics in Northern Norway, the Privacy Ombudsman for Research, the Directory of Health and Social Welfare and the Norwegian Medicine Agency included registration of the study in the EudraCT database (no 2004-002613-37). Each AD participant gave written informed consent co-signed by a spouse, a close relative or a guardian. The national authorities listed above approved the consent formula and the study is also registered as an International Standard Randomized Controlled Trial within ClinicalTrials.gov (Identifier: NCT00443014). In October 2008 The Norwegian Medicine Agency conducted an inspection according to the principles of Good Clinical Practice (GCP) in a randomised clinical trial. All remarks from this assessment, including monitoring routines were closed and approved. The study was then given a signed approval by the Norwegian Medicine Agency as a RCT in accordance with the GCP criteria. All publications from this study comply with the CONSORT statements and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals^{169;170}.

11. Data and statistics

11.1 Data recording

The demographic characteristics, medical history, clinical examination, cognitive tests and current medical use of AD participants and cognitively healthy controls were recorded at study entry. Cognitive tests were registered at four time points during one year for each AD participant. At the end of the study period the database was assessed, secured and locked by the Clinical Research Centre at The University Hospital in Northern Norway

11.2 Statistics

Statistical analysis was conducted using SPSS version 15.0 and 16.0 (SPSS Inc. Chicago, IL, USA). Based on the calculation of power, a sample size of 64 in each group was necessary to detect a 2-point difference in mean MMSE sum score with 80% power, provided a standard deviation of 4 and a two-sided significance level of 5%. Differences in demographic characteristics between municipality groups and medicine groups and between recruitment methods as well as the comparison of co-morbidity and drug use

between AD participants and cognitively healthy controls were assessed by Chi-square and independent-samples t-tests. Analyses of co-variance (ANCOVA) and logistic regression were used for age and gender adjustment. Linear mixed models were used to assess time-trends in cognitive function over four time points and to assess differences in time-trends between groups of AD participants. Including an unstructured covariance matrix in the model controlled for possible dependences between repeated observations. In the municipality groups, time-trend differences in cognitive function were assessed between the stimulation group and control group, and differences in the medicine groups were assessed between the donepezil treatment group and the placebo group. Finally, the subgroup treated by stimulation therapy and donepezil was compared to the subgroup receiving usual care and placebo. Model assumptions were assessed by means of residual analyses. The statistical analyses were performed with intention-to-treat, per-protocol and subgroup analyses in order to estimate the homogeneity and consistency of the data. In the sensitivity analyses we included municipality as a random effect in the linear mixed models in order to control for possible clustering of data within the municipalities.

12. Results

12.1 Recruitment methods and baseline characteristics

During the first year 27 AD individuals were included by GPs. After extending the recruitment method to comprise a population-based postal screening of cognitive function in individuals ≥ 65 years another 160 participants were included during the next year, 100 by screening and 60 by GPs in clinical practice. In this way the study AD participants were included by two different recruitment methods (Flowchart 3).

Participants recruited by screening were more frequently male ($p < 0.001$), younger ($p = 0.006$), more independent and needed less community support ($p < 0.001$), as compared to those recruited by GPs. Also, they had a higher ADL function as assessed by the Barthel Index ($p = 0.011$) and had a significantly higher MMSE sum score ($p = 0.001$). No significant differences in neuropsychiatric symptoms (NPI) were found. Participants recruited by screening had a significantly higher MADRS score compared to participants recruited in clinical practice (Table 1).

Further analyses revealed that each sample was equally distributed across the main study groups. No significant differences in age, gender, cognitive function, neuropsychiatric symptoms or need for ADL support were found between AD participants in the interventional municipalities compared to AD participants in the control municipalities (Table 2).

Flowchart 3 Population-based screening of self-reported cognitive impairment

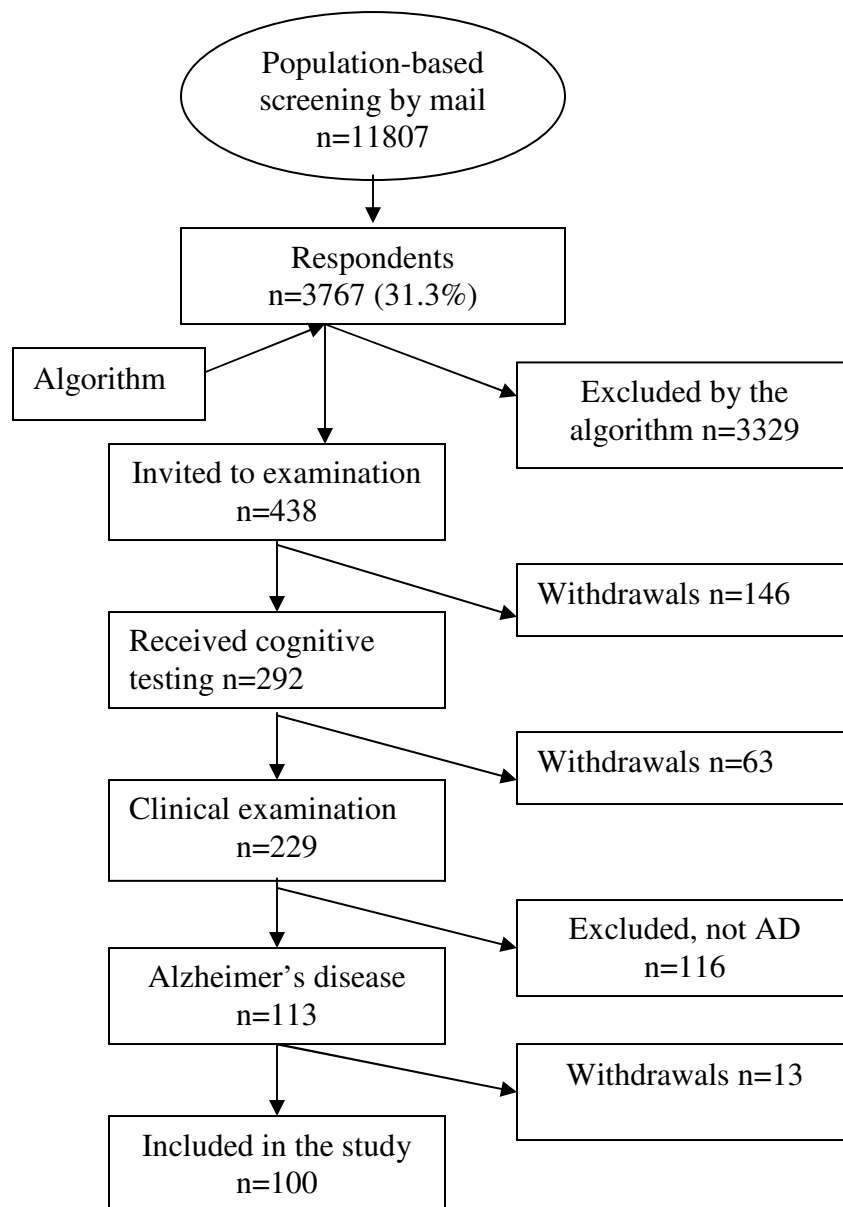


Table 1 Comparison of age, gender and MMSE score at baseline between recruitment methods

	Recruitment method		p-value
	Screening	Clinical practice	
Age \pm SD	79.5 \pm 7.5	82.3 \pm 6.1	0.006
MMSE \pm SD	24.4 \pm 2.9	21.3 \pm 4.2	<0.001*
Female n (%)	46 (46)	67 (77)	<0.001*
Barthel Index \pm SD	19.23 \pm 2.07	17.96 \pm 3.38	0.011*
NPI \pm SD	6.14 \pm 8.49	8.18 \pm 11.50	0.20*
MADRS \pm SD	3.19 \pm 4.25	1.18 \pm 2.70	0.001*
In need of ADL support n (%)	28 (28)	57 (66)	<0.001*

* Adjusted for age

Table 2 Comparison of baseline characteristics between stimulation therapy and standard care.

	AD participants receiving		p-value
	Stimulation therapy	Standard care	
Age \pm SD	81.2 \pm 6.7	79.5 \pm 7.3	0.10
MMSE \pm SD	22.6 \pm 4.0	23.5 \pm 3.7	0.14
Female n (%)	59 (60)	54 (64)	0.25
Barthel Index \pm SD	18.64 \pm 2.55	18.64 \pm 3.20	0.995
NPI \pm SD	6.08 \pm 9.59	8.49 \pm 10.52	0.12
MADRS \pm SD	2.56 \pm 4.29	2.12 \pm 3.10	0.49
In need of ADL support n (%)	53 (51)	32 (39)	0.09

12.2 A cross-sectional comparison of co-morbidities and current medication between participants with and without AD

Data on past medical history, co-morbidities and current medication was recorded at study entry. AD participants were older (80.9 ± 7.0 vs 72.5 ± 5.5 $p < 0.001$) and the female fraction was significantly higher (60% vs 43% $p < 0.001$) compared to controls. No significant age- or gender-adjusted differences in co-morbidities were found between AD participants stratified on disease stages. However, the total number of drugs was significantly higher in AD participants compared to controls despite no differences in co-morbidities. When participants were stratified by ATC group a significant higher use of drugs with anticholinergic activity, anxiolytics/hypnotics and antidepressants was found in the AD group compared to the control group. Only four of the AD participants used antipsychotics. The number of antihypertensive drugs was significantly higher, nearly doubled, in AD participants compared to controls.

One hundred and forty-two AD participants were living at home, 40 of them received ADL support from community nurses at least once a week. Forty-five AD participants lived in nursing homes (1 missing). Nursing home AD residents and the most disabled community dwellers used significantly more drugs than those living in their own homes without any regular ADL support. This included both the total number of drugs ($p < 0.001$), drugs classified as inappropriate according to the STOPP criteria¹⁵² ($p < 0.001$), drugs exhibiting the two highest levels of anticholinergic activity assessed by the Anticholinergic Risk Scale (ARS) ($p = 0.001$)¹⁷¹, antidepressants ($p < 0.001$) and anxiolytics/hypnotics ($p < 0.001$) (Table 5).

MAP (Formula 1) adjusted for age and gender was significantly lower in AD participants compared to controls. A family history of AD was significantly more common in AD participants compared to controls. Sixty-three per cent of the participants in the control group had completed ≥ 10 years of education compared to 17% in the AD group. However, after age and gender adjustment this was not significant ($p = 0.33$).

Table 3 Comparison of drug use between AD participants with and without regular ADL support

	Without community ADL support n=102	In need of community ADL support n=85	p-value
Age \pm SD	78.5 \pm 6.9	83.7 \pm 6.0	p<0.001
MMSE \pm SD	24.6 \pm 3.8	21.2 \pm 4.6	p<0.001*
Mean drug number \pm SD	3.8 \pm 2.5	6.7 \pm 4.0	p=0.001*
Inappropriate drugs n(%)	23(23)	46 (54)	p=0.003*
Anticholinergic drugs n (%)	14 (14)	29 (34)	p=0.13*
Anxiolytics/hypnotics n (%)	4(4)	20 (24)	p=0.003*
Antidepressants n (%)	11(11)	31 (36)	p<0.001*

* Age-adjusted

12.3 Symptomatic treatment

The follow-up period of AD individuals included in the study was one year. Cognition was tested four times at four-month intervals. Forty-one individuals dropped out during follow-up as a consequence of death (n=7), disease progression (n= 8), co-morbidities (n= 8) and withdrawal for unknown reason (n=18). One hundred forty-six completed the program (Flowchart 4). Forty-one AD participants (41.5%) in the stimulation therapy group completed a total of 200 or more sessions of stimulation therapy as assessed by approved logs during one-year follow-up whereas 53 AD participants (55.9%) in the donepezil group completed drug treatment for 42 weeks or more.

No significant time-trend differences in cognitive test performance were found between AD participants receiving stimulation therapy and standard care as assessed by MMSE (primary outcome), the clock drawing test and ADAS-Cog (secondary outcome) during the one-year follow-up. Both AD participants allocated to stimulation therapy and AD participants allocated to standard care with or without donepezil retained cognitive function as assessed by the three tests. The results were consistent in the intention-to-treat

and per-protocol analyses (Chart 1). Subgroup analyses of participants with MMSE score ≤ 25 (Chart 2 and Table 5), and MMSE score ≤ 21 at entry and stratified on recruitment methods (not in chart) were consistent with the intention-to-treat analyses.

No significant time-trend differences in cognitive function between groups with donepezil and placebo with or without stimulation therapy were found (Chart 3). Participants receiving donepezil had significantly more adverse reactions (28%) than those receiving the placebo (10%) (odds ratio 3.80 95% CI 1.55 to 9.54 $p=0.002$). A subgroup analysis comparing the combined effect of stimulation therapy and donepezil versus standard care and placebo did not reveal any time-trend differences between the groups regarding cognitive achievements (Chart 4). On Chart 4 the expected decline in mean MMSE sum score is plotted. Stimulation therapy with placebo compared to donepezil treatment with standard care (representing a head to head comparison of stimulation therapy versus donepezil) did not demonstrate any time-trend differences in cognitive performance (Chart 5). Only small changes in ADL and neuropsychiatric functions were found after one-year follow-up (Table 4). Intention-to-treat, per-protocol and the subgroup analyses were consistent across the three independent cognitive tests.

Flowchart 4

Dropouts during follow-up

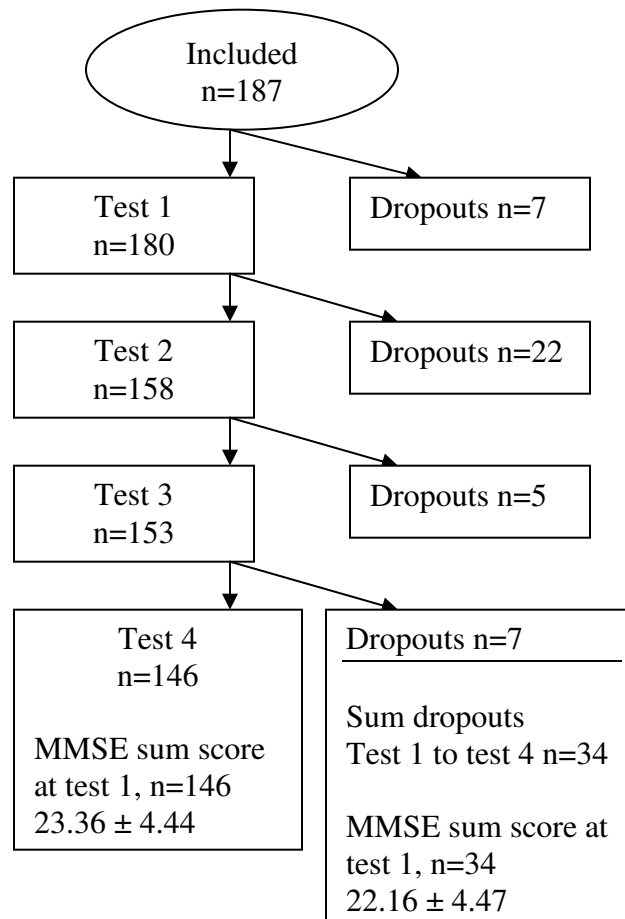


Chart 1 A comparison between stimulation therapy and standard care at each time point

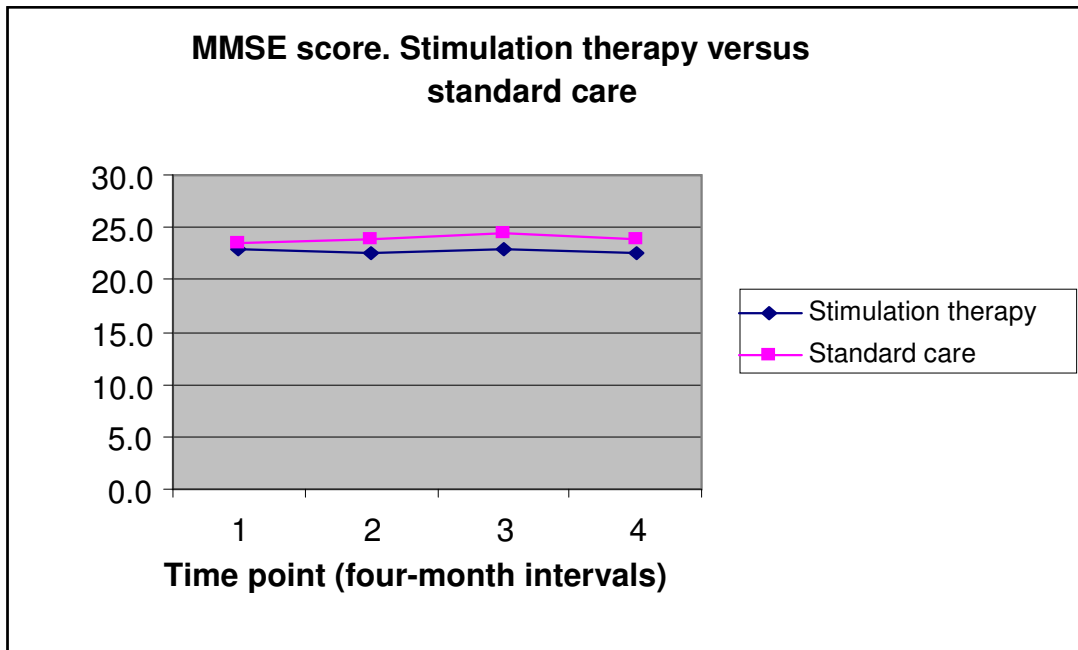


Chart 2 Mean MMSE sum score at each time point for all participants compared to participants with mean MMSE score < 26 at entry

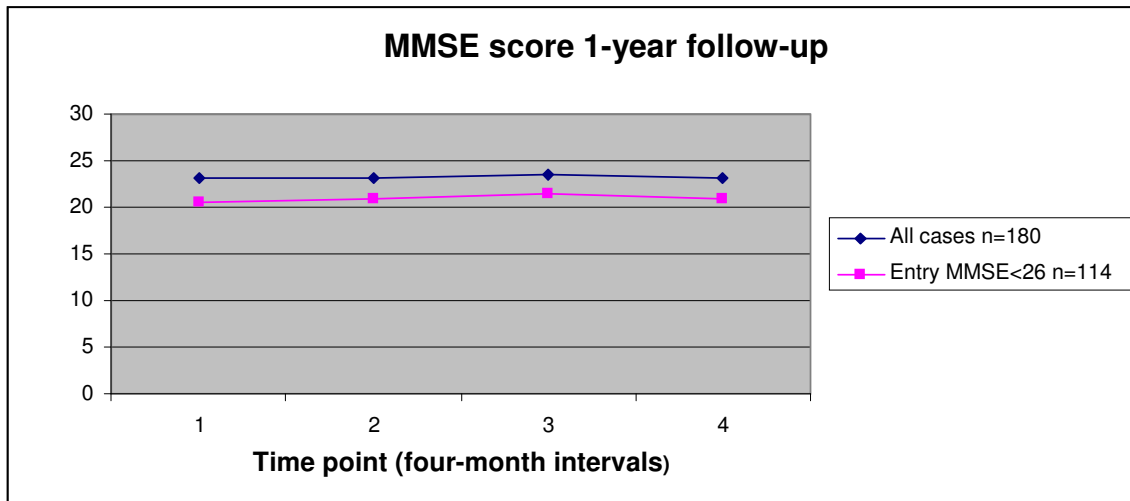


Chart 3 Comparison between donepezil and placebo

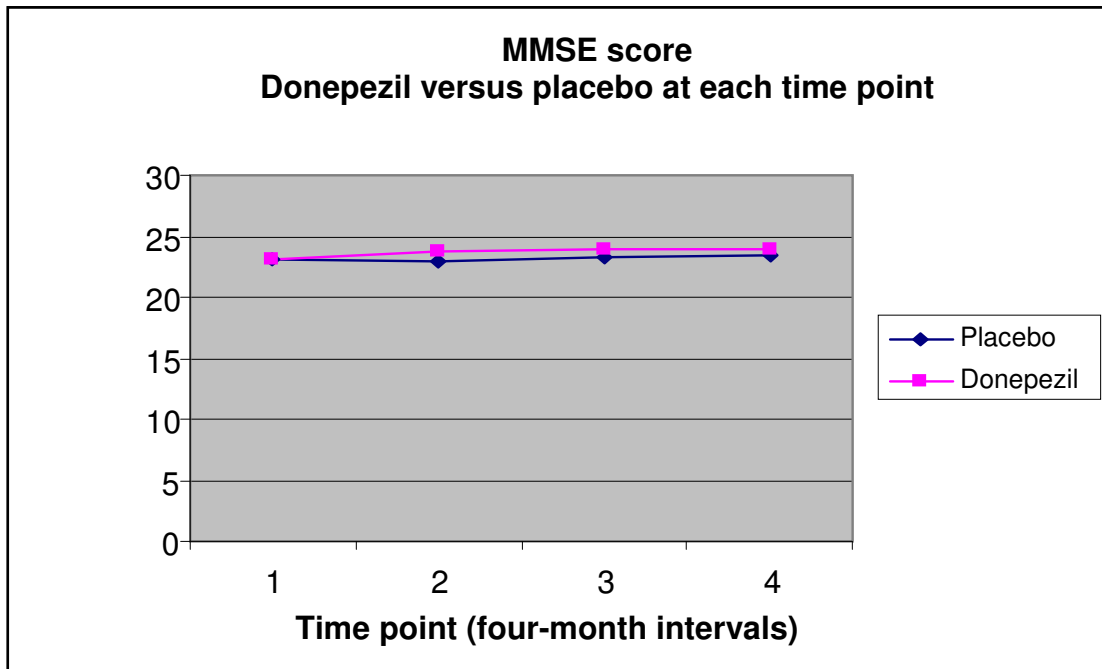


Chart 4 The extreme limit comparison between donepezil combined with stimulation therapy and placebo combined with standard care at each time point

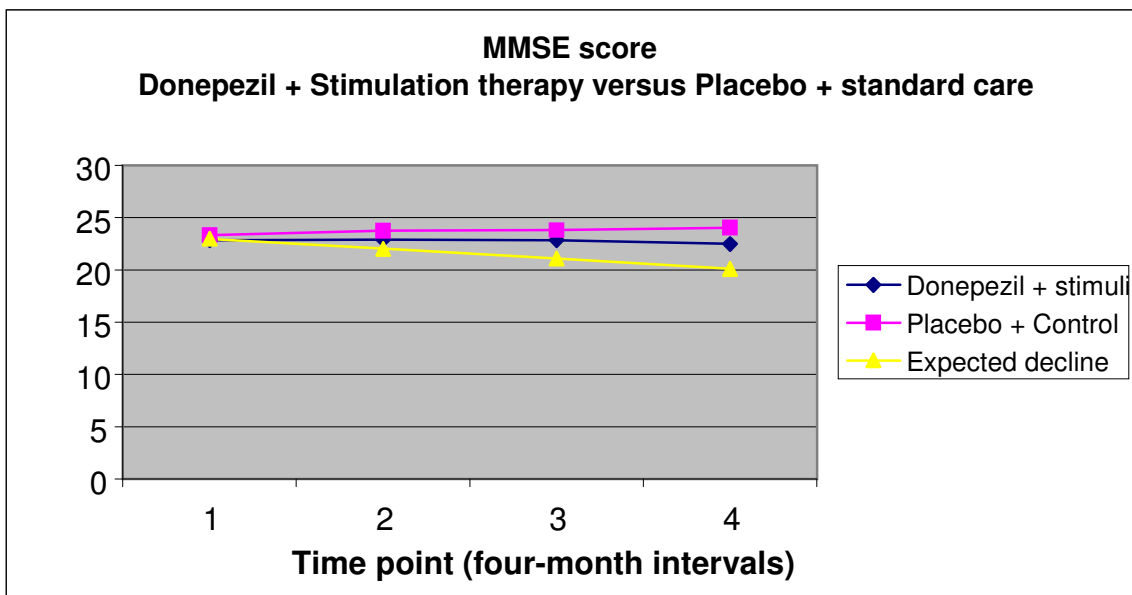


Chart 5 Head to head comparison of stimulation therapy + placebo versus donepezil + standard care measured by ADAS-Cog (stimulation n= 50, donepezil n=37)

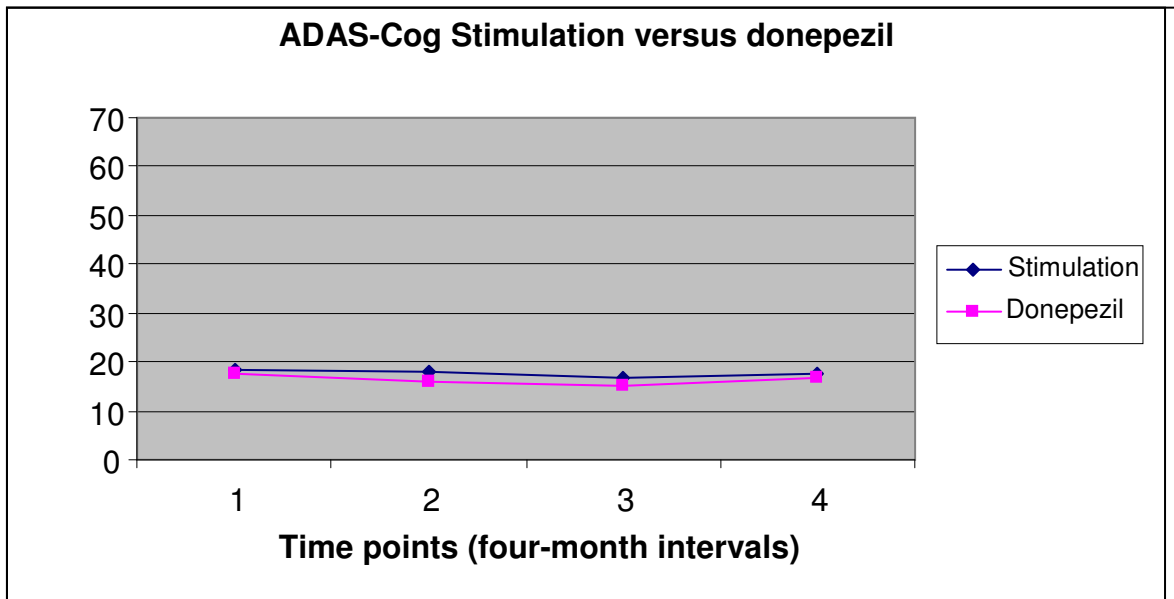


Table 4 Neuropsychiatric symptoms and ADL function at entry and after one-year follow-up stratified by interventional groups.

Test	Time point	Intervention			
		Stimulation therapy	Standard care	Donepezil	Placebo
Barthel index	Entry	18.64± 2.55	18.64 ± 3.20	18.87±2.12	18.41 ± 3.38
	One year	18.41± 2.87	18.25 ± 3.59	18.50±2.45	18.17 ± 3.83
MADRS	Entry	2.56 ± 4.29	2.12 ± 3.10	2.70 ± 4.22	2.04 ± 3.38
	One year	2.63 ± 3.88	2.09 ± 3.61	2.71 ± 3.95	2.02 ± 3.52
NPI	Entry	6.08 ± 9.59	8.49 ± 10.52	7.49±11.14	6.70 ± 8.85
	One year	6.56 ± 9.57	9.61 ± 12.88	7.83±11.32	7.97 ± 11.27

Table 5. Mean cognitive test performances at follow-up time points in AD participants receiving stimulation therapy compared to standard care, and donepezil compared to placebo. Patients with entry MMSE ≤ 25 (n=114)

Groups	Moments of follow up				P-values, equal time trends between groups
	Baseline, n=114	4 months, n=110	8 months, n=105	12 months, n=99*	
MMSE					
Stimulation	21.49	21.11	21.33	20.88	0.044**
Standard care	21.42	21.87	22.68	21.91	
Donepezil	21.85	21.92	22.37	21.42	0.695
Placebo	21.05	20.84	21.39	21.22	
Clock drawing					
Stimulation	2.56	2.65	2.51	2.74	0.478
Standard care	2.50	2.51	2.64	2.67	
Donepezil	2.69	2.53	2.44	2.69	0.050†
Placebo	2.37	2.66	2.69	2.73	
ADAS-cog					
Stimulation	21.16	21.08	19.59	19.77	0.334
Standard care	20.33	19.13	19.09	19.38	
Donepezil	20.85	19.78	18.96	19.16	0.670
Placebo	20.79	20.84	19.82	20.09	

*n varies due to dropouts during follow-up. ** Adjusted for gender p=0.37 Adjusted for age p=0.11

† Adjusted for gender p=0.23. Adjusted for age p=0.85

Adjusting for age or gender did not change other p-values in the analyses

13. Discussion

13.1 Recruitment methods and selection bias.

Baseline characteristics differed significantly between AD individuals recruited in clinical practice and by population-based screening. These findings underscore the impact of sampling methods aimed to select a representative study sample from the source population. Baseline characteristics of the AD participants should be similar to or not differ significantly from, the source population (internal validity). The present study was community-based with an unselected population of recently diagnosed AD participants recruited by GPs or by population-based screening (Flowchart 1). The clinical examinations were performed by experienced general practitioners supervised by geriatric specialists. The results confirm that different recruitment methods within the same population provide samples with significant differences in several baseline characteristics. Similar findings have been reported by Izal et al. who emphasise that recruitment method can specifically influence the outcomes of studies with elderly people and limit the generalization of their results⁹. Population-based recruitment conducted in the community without stringent inclusion criteria is supposed to come closest to a representative sample and should achieve the highest external validity^{99;172}.

Assessing internal validity¹⁷² in dementia studies is challenging. Dementia is still a syndrome based on clinical criteria without a golden standard. Few, if any, positive biomarkers are routinely in use and the current diagnostic tools rely upon questionnaires, tests and clinical examinations with insufficient accuracy and corresponding low sensitivity and specificity^{27;94}. Sampling will therefore always be at risk of misclassification and selection bias. Women are at a higher risk of AD than men in some studies^{173;174}. It is therefore important that gender distribution in the sample match that of the study population. According to 2008 Norwegian statistics, the female proportion of the population 67 - 79 years and 80 years and above are 53.6% and 65.0%, respectively¹⁷⁵. In our study the gender distribution is similar to national statistics (Mean age 80.9 ± 7.0 ; 60.4% female).

According to the known incidence rate (2 – 4%)¹⁷⁶ and prevalence (10%)⁷¹ of AD in the population 65 years and above, the number of eligible individuals with a recent diagnosis of AD in the participating municipalities was at least double what we were able to recruit. The screening program recruited younger and healthier individuals. Older eligible AD individuals with more advanced disease were possibly not accessible by a postal questionnaire as some of them were diagnosed earlier or lived in nursing homes. Studies on elderly may be biased by this healthy participant bias. GPs often hesitate to diagnose mild cognitive impairment or early-stage of dementia¹⁵⁸. Mild to moderate cognitive impairment in the elderly, including early-stage AD, seems to be disregarded by both relatives and health professionals, even though this stage of cognitive impairment has the best response to intervention. Our findings are in accordance with others who reported that GPs tend to postpone a comprehensive examination of patients who complain of memory problems. When dementia is mild more than 90.9% of the cases are overlooked¹⁷⁷. When dementia is severe the specificity is greater than 99%^{157;177;178}.

The questionnaire developed from the Cambridge Cognitive Examination and Strawbridge et al. along with the defined algorithm seemed to be highly valid in selecting individuals with cognitive impairment. Of 438 individuals selected by the algorithm to have probable cognitive impairment 229 underwent cognitive testing and clinical examination. Of these 113 were diagnosed with probable AD representing 2.9% of the responders (Flowchart 1) and more than one quarter of those selected by the algorithm. Seven hundred and ninety-one responders from the screening reported no cognitive impairment but still wanted to participate in the study. Five hundred individuals from this group were randomly allocated to the control group, and 200 received cognitive and clinical examination. All of them were confirmed to be cognitively healthy. In this way the present postal questionnaire combined with the algorithm was able to identify individuals with cognitive disabilities corresponding to early AD.

In a large-scale community memory screening by Lawrence et al (2003) community dwellers were invited through the media to undergo cognitive assessment. Of those attending the screening program 1.5% had an undiagnosed AD. Considering the

prevalence of dementia, this was lower than expected, and the cost-effectiveness of the screening procedures could be questioned¹⁵⁶. However, in their study the invitation to the screening program came through media. No preliminary questionnaire specifically addressing cognitive complaints followed the invitation and no algorithm was used. Crew et al. (2009) also used the media and flyers to recruit participants to be screened for cognitive impairment and neuropsychiatric symptoms. They found that 24% of the participants who completed the screening program received follow-up recommendation secondary to objectively identified age-inappropriate memory impairment. Crew et al. concluded that there appears to be a critical need for widespread use of screening programs to identify early age-inappropriate memory impairment¹⁵⁵.

According to the experiences of the present study, screening of cognitive impairment by mail with a preliminary questionnaire covering main cognitive domains followed by cognitive tests and clinical examination could be a useful tool to identify early stage AD in the community. However, screening such as this does not comply with a preclinical dementia stage or dementia risk factors¹⁷⁹.

13.2 Co-morbidities and current medication in participants with and without AD

The cross-sectional analyses compared co-morbidities and current medication between AD participants and a cognitively healthy control group (paper 2). The results reveal an increased number of daily medications in AD individuals, especially anticholinergic and psychotropic drugs compared to the control group. Increasing drug consumption was associated with cognitive deterioration, the need for ADL support and institutionalisation. Psychotropic drugs exhibit an additional suppression of cognitive abilities in AD^{131;132}. Adverse drug events increase from 10% with one drug to 75% in patients taking five drugs¹⁸⁰. An increased number of drugs also increases the risk of potentially inappropriate medication¹⁸¹. In our study 48% of AD participants used five drugs or more. Nursing home AD residents used nearly seven drugs a day. Fifty-four per cent of AD participants living in nursing homes or in their own homes with regular ADL support from community nurses used drugs defined inappropriate according to the STOPP criteria¹⁵². This finding could call for a more extensive adjustment of drug treatment

amongst AD individuals in primary health care or nursing homes. Interruption of inappropriate drugs may represent a therapeutic option to improve cognitive performance¹⁸², especially when it comes to simultaneous treatment with drugs exhibiting anticholinergic activities and ChEIs.

AD is associated with cardiovascular risk factors and metabolic syndrome. However, the comparison of other co-morbidities between individuals with and without dementia has given ambiguous results^{82;183-185}. In the present study, no age- or gender-adjusted differences in the number of co-morbidities between individuals with and without AD were found. This is in line with other studies^{184;185}. However, AD individuals may suffer from more advanced illnesses¹⁸⁶. In our study further analyses revealed a significantly lower mean arterial blood pressure and more antihypertensive drug use in AD participants compared to controls. This is in accordance with the findings of Guo et al¹⁸⁷. The combination of reduced blood pressure and increased occurrence of vascular disorders, especially small-vessel diseases, could have an impact on cerebral perfusion and reinforce cognitive disabilities in individuals with a neurodegenerative disease¹⁰⁸. When this is added to the heavy burden of inappropriate medical treatment both cognitive and ADL functions could be further suppressed.

Low education has been identified as a risk factor in AD. Only 17% (33 of 187) of the AD participants had completed ≥ 10 years of education compared to 63% (126 of 200) of the control group. The mean age difference between the two study groups was approximately eight years, and this age difference could be related to differences in education attainment. At the beginning of World War II (1939/1940), the mean age of the AD participants in the present study was 12 years. Many inhabitants in Northern Norway lost several years of education as a consequence of the warfare. The mean age of the participants in the control group in 1939/1940 was 3 years, and they could easily make up for delayed school attendance after 1945. In our study, therefore, the difference in education level between the two study groups could be explained by World War II.

13.3 Symptomatic treatment

The main result of this one year trial was that no differences in cognitive performance were detected between AD participants receiving stimulation therapy compared to AD participants receiving standard care. To our surprise both groups retained cognitive performance during the study period. The results were consistent for three different cognitive tests. This observation differs from other comparable studies^{23;125}. The inherent trajectory in AD represents a decline in MMSE sum score of 2-3 points and an increase in ADAS-Cog score of 6 -12 points per year. The cognitive deterioration depend upon disease severity at baseline^{66;67;188}. The milder the baseline cognitive impairment, the slower the disease progression¹⁸⁸. Stabilising cognitive performance is an important outcome in symptomatic treatment of AD³⁸. Previous studies of symptomatic treatment with various designs have reported a postponement of disease progression for approximately one year in interventional groups^{37;125} and a variable cognitive decline in the control groups^{16;18;21;125;189}. Equal effects, with retention of cognitive performance in both the interventional as well as the control groups, have to our knowledge not been reported. In concordance with results of previous studies, stimulation therapy and/or donepezil treatment in the present study was presumed to delay cognitive deterioration in the follow-up period. To our surprise, the control group receiving standard care with or without donepezil retained cognitive performance as well.

Several events and mechanisms may explain the similar cognitive performances between participants receiving stimulation therapy and standard care. The equal effects on cognitive test performance in AD participants receiving stimulation therapy compared to standard care with and without donepezil with preservation of cognitive abilities during one year could partly be explained by a placebo, expectancy or Hawthorne effect^{43;44;190;191}. The present study was not designed to evaluate the placebo effect and the outcomes of the study have to be discussed with caution. However, participation in a trial like the present study, with frequent monitoring and follow-ups, may create expectancy¹⁹² and act as cognitive stimulation by itself. The test-technicians visited the municipalities regularly for three years. Their visits were obviously an important event booth for the AD participants and the caregivers. The question arises whether the placebo

effect of study participation could have provided high expectancy and cognitive stimulation in all subgroups leaving a possible stimulation and/or donepezil effect undetectable^{42;190;193}. In a review of stimulation therapy in AD Olazaran et al. (2010) found that increased attention to the control groups reduced the differences in cognitive functions between interventional and control groups and could blur study results²⁴. If so, this could have hampered other trials with symptomatic treatment of AD individuals and partly explain the contradictory results of many dementia studies. Neuropsychological mechanisms within the placebo effect could have seriously biased the outcomes.

Benedetti et al found that the placebo effect depends upon preserved frontal lobe function. Decreasing executive functions were associated with a reduced placebo effect. In our study, frontal executive functions were not explicitly assessed, and retaining cognitive function during one-year follow-up was independent of disease stage measured by MMSE sum score at entry. The subgroup of AD participants with MMSE ≤ 21 at entry (n=59, mean MMSE sum score 18.4 ± 2.7) preserved cognitive performance during one-year follow-up as well.

Previous studies of symptomatic treatment have reported a postponement of disease progression for approximately one year^{45;194}. The stabilising effect on cognitive performance seems to occur irrespective of what symptomatic treatment was offered, whether stimulation therapy, symptomatic drug treatment, or stimulation therapy added to the symptomatic drug treatment (donepezil)¹²⁵. The maintenance of the cognitive performances is an important treatment goal in AD. Postponing functional worsening is favourable for both the patients and their caregivers³⁸ and may delay institutionalisation for some AD patients¹⁸.

Health professionals in both municipality groups attended the same dementia competence courses; whereas courses that aimed to qualify stimulation therapy providers were reserved for interventional municipality health professionals. A national campaign on AD was launched around the time of our study. These concomitant events could have diluted the municipality differences and influenced standard care in control municipalities. The

stimulation program in our study was developed by experienced dementia therapists, adjusted individually and provided by trained primary health nursing staff or caregivers/family members and was designed to be sustainable for months without extensive costs. So far, no standardised and validated stimulation therapy programmes are available¹⁹⁵. Growing evidence indicates that combining the stimulation benefits of educational, occupational and mental activities (cognitive reserves) with physical activities and a healthy life style are the most important modifiable risk factors in AD^{13;27}. The stimulation program in the present study was in accordance with these recommendations.

Except for adverse reactions, an effect of donepezil compared to placebo with or without stimulation therapy was not detectable. Both the donepezil and the placebo group retained cognitive function during one year follow-up.

Interestingly the main result of the present study is in agreement with the casuistry described in the introduction.

13.4 Strengths and weaknesses

The present study was community-based with well defined but not too stringent inclusion/exclusion criteria. The sampling method was designed to recruit a representative sample of newly diagnosed AD participants from the source population. The population-based screening program provided in the present study is to, my knowledge, the only one conducted in Scandinavia. The participants remained in their own environment, and a significant number of participants completed the one-year follow-up. Few interventional studies with stimulation therapy have accomplished a one-year follow-up. A study design such as ours, with a two-by-two factorial design, focusing on stimulation therapy and donepezil treatment and including a head-to-head comparison, has previously been advocated by the scientific community¹⁰ but has previously not been accomplished. The control group, consisting of self-reported and clinical confirmed cognitively healthy individuals, constitutes the only randomly selected control group in AD research in Norway. In April 2009, after an inspection according to the principles of

GCP in a randomised clinical trial, the study was given signed approval by the Norwegian Medicine Agency as an RCT conducted in accordance with the GCP criteria.

The participating municipalities were not randomly selected but recruited according to a number of criteria, including the competence of the health providers, demographic characteristics of the population and geographic location. Choosing maximum distance and pursuing the least contact between interventional and control municipalities were done to minimise the risk of dilution. Such a non-randomised selection could be considered as a limitation of the study. However, the study population in the participating municipalities was ethnically and socially homogenous, and the baseline characteristics did not differ either between AD participants receiving stimulation therapy compared to standard care or between AD participants receiving donepezil or placebo. In addition, a sensitivity analysis in order to control for possible clustering of data within the municipalities did not change the results.

The retention of cognitive function in the present study could have occurred because of early AD stage at entry with minimal cognitive decline during follow-up¹⁸⁸. In a review by Sevigny et al. (2010) of a 12-month, multicentre, double-blinded RCT, the AD participants in the placebo group were dichotomised according to baseline MMSE sum score into mild disease (MMSE 21 – 26) and moderate to severe disease stage (MMSE 14 - 20). The outcome measure was the percentage changes in ADAS-Cog score during the 12-month follow-up. The total rate of cognitive decline in participants with mild AD according to ADAS-Cog was less than that of participants with moderate to severe AD¹⁹⁶. Although AD participants in our study were examined, diagnosed and followed with a variety of tests, diagnosing mild AD remains a challenge. The mean MMSE sum score at baseline was 23.0 ± 3.9 , representing the mild AD stage. According to Sevigny et al the cognitive decline in our study could therefore have been less than expected during follow-up. However, in the study analysed by Sevigny et al., all AD participants were treated with ChEI or memantine¹⁹⁶, which could have had a different impact on cognitive decline in participants with mild AD compared to participants with moderate to severe

AD during the 12-month follow-up. In our study, subgroup analyses of AD participants recruited by GPs (n=87), AD participants with MMSE sum score ≤ 25 at entry (n=121) and with MMSE sum score ≤ 21 at entry (n=55) were consistent with the intention to treat analysis.

The subgroup analyses of the study cover a wide range of possible interactions between strata, independent variables and outcomes (Charts 2 and 5). Some of these two-by-two factorial strata are small and could be at risk of type II error. However, the results of all analyses were consistent across a number of different comparisons and three cognitive tests.

14. Conclusion

A population-based postal screening of cognitive function with a subsequent clinical examination is suitable to identify early-stage AD.

AD individuals used significantly more medication than controls, and particularly the use of anticholinergic drugs is worrying. A careful evaluation and interruption of possible inappropriate drug use in AD individuals at any disease stage may represent a therapeutic option to improve cognitive performance.

The two-by-two factorial design of The Dementia Study in Northern Norway provides an opportunity to compare the effects of two different interventional methods on cognitive performance in AD individuals. The negative effect of symptomatic treatment in AD with or without donepezil compared to controls, with retention of cognitive abilities in all groups during a one-year follow-up was a surprise and may have been a consequence of participants' expectancy and the psychosocial context of the intervention. The possibility of postponing cognitive deterioration by at least one year in AD individuals with mild to moderate cognitive impairment was confirmed.

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16. Appendix

Appendix 1 Mean arterial pressure (MAP)

$$\text{MAP} = \frac{(\text{Diastolic blood pressure} \times 2) + \text{Systolic blood pressure}}{3}$$

Appendix 2

The history of cholinesterase inhibitors (ChEI)

The comprehensive neurological and toxicological effects of ChEIs have gradually been revealed in biological and medical literature over approximately 135 years, beginning with the discovery of physostigmine. The natural source of physostigmine was the calara bean from tropical West Africa which was brought to England in 1875. The effect was first described in the ophthalmology literature by Laqueur in 1876 and in 1936 the drug was synthesised by Percy Lavon Julian¹⁹⁷. ChEIs play still a significant role in modern medicine as an important therapeutic option in ophthalmology and in the treatment of myasthenia gravis.

The history of nerve gases began on 23 December, 1936, when Gerhard Schrader first prepared tabun which exhibits a strong non-competitive inhibition of acetyl cholinesterase. He continued to prepare new forms of tabun and observed the toxic effect of vaporised tabun on him self and his laboratory assistant. In 1939 a pilot factory for vaporised tabun production was set up at Munster-Lager, and the history of Nazi gas chambers was initiated (Paxman J et al: A higher Form of Killing: The Secret Story of Chemical and Biological Warfare, 1982).

The vast majority of pesticides and herbicides have their main impact on neurotransmission. Some of the most neurotoxic chemicals, such as organophosphate and carbamate, are highly potent non-competitive ChEIs¹⁹⁸ and may produce serious toxic reactions in mammals.

Most health professionals are well aware of the biological mechanisms behind ChEIs, their toxicity and their antidotes. During my own military service in the medical corps of the Norwegian Air Force I gave lectures about the disaster caused by chemical weapons including nerve gases, many of which have cholinesterase inhibition properties. Later on as a general practitioner, I taught farmers about the risks of pesticides, herbicides and insecticides for the farmer him/herself, the environment and the consumers.

This brief review summarises the well-known physiological effect and toxicity of ChEIs. The possibility of adverse reactions to any chemicals with a ChEI effect must always be considered. Their conflicting and dramatic history in combination with their potential impact on vital neural and neuromuscular transmission in any creature makes the preparing of new ChEI derivatives for neurological purposes an ethical question, especially when it comes to “improving memory and learning in healthy subjects”¹⁹⁹ and in studying and treating individuals with reduced consent competence.



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