Donepezil in patients with severe Alzheimer’s disease: double-blind, parallel-group, placebo-controlled study

Bengt Winblad, Lena Kilander, Sture Eriksson, Lennart Minthon, Steffan Båtsman, Anna-Lena Wetterholm, Catarina Jansson-Blixt, Anders Haglund, for the Severe Alzheimer’s Disease Study Group*

Summary

Background The cholinesterase inhibitor donepezil is used to treat mild-to-moderate Alzheimer’s disease. Its efficacy in severe dementia has not been assessed and is controversial. Our aim was to ascertain the effectiveness of donepezil in patients with severe Alzheimer’s disease, by focusing primarily on cognition and activities of daily living.

Methods We did a 6-month, double-blind, parallel-group, placebo-controlled study in 248 patients with severe Alzheimer’s disease (mini mental state examination score 1–10) who were living in assisted care nursing homes ran by trained staff in Sweden. We assigned patients oral donepezil (5 mg per day for 30 days then up to 10 mg per day thereafter, n=128) or matched placebo (n=120). Our primary endpoints were change from baseline to month 6 in the severe impairment battery (SIB) and modified Alzheimer’s Disease Cooperative Study activities of daily living inventory for severe Alzheimer’s disease (ADCS-ADL-severe). We analysed outcomes for patients with data at baseline and at one or more other timepoints (modified intent-to-treat population) with last observation carried forward used to replace missing data.

Findings 95 patients assigned donepezil and 99 patients assigned placebo completed the study. Patients treated with donepezil improved more in SIB scores and declined less in ADCS-ADL-severe scores at 6 months after initiation of treatment compared with baseline than did controls (least squares [LS] mean difference, 5·7–7·7, 95% CI 1·5–9·8; p=0·008, and 1·7, 0·2–3·2; p=0·03, respectively). The incidence of adverse events was comparable between groups (donepezil 82% [n=105] vs placebo 76% [n=91]), with most being transient and mild or moderate in severity. More patients discontinued treatment because of adverse events in the donepezil group (n=20) than in the placebo group (n=8).

Interpretation Donepezil improves cognition and preserves function in individuals with severe Alzheimer’s disease who live in nursing homes.

Introduction Individuals with Alzheimer’s disease eventually develop severe dementia and as a result become further cognitively impaired. As their health deteriorates they become less able to communicate and less mobile, develop apraxia, agnosia, and neuropsychiatric symptoms, and need increasing amounts of nursing care. About 20% of patients with Alzheimer’s disease have severe dementia.1 The cholinesterase inhibitors donepezil, galantamine, and rivastigmine stabilise or slow down progression in mild-to-moderate disease,2–4 but do not prevent eventual development of severe disease. Some specialists and treatment guidelines3 recommend discontinuation of cholinesterase inhibitors once a patient reaches this stage.

Results of studies of donepezil that have included patients with severe Alzheimer’s disease are not consistent, since improvement in some variables (global function and cognition) but not all (behaviour and function) were noted in patients living in nursing homes,4 whereas there was effective management of cognitive, functional, and behavioural symptoms in those living in the community.4 Co-administration of the N-methyl-D-aspartate receptor antagonist memantine with donepezil further slows cognitive and functional deterioration in patients with moderate-to-severe Alzheimer’s disease.4 As a monotherapy, memantine has positive effects on global function and cognition in individuals with moderate-to-severe Alzheimer’s disease6 and on global function in severe Alzheimer’s disease.10 Our aim was to assess the effect of donepezil on cognition and activities of daily living in patients with severe Alzheimer’s disease living in nursing homes ran by trained staff.

Methods Patients

Between October, 2002, and October, 2004, we did a double-blind, parallel-group, placebo-controlled study in patients living in 50 assisted-care facilities (nursing homes run by trained staff) in Sweden. Our inclusion criteria were age 50 years or older, ability to walk alone or with help, a mini mental state examination (MMSE)11 score of 1–10, and a functional assessment staging (FAST) rating of stage 5 (requires assistance in choosing proper clothing) to 7c (non-ambulatory—unable to walk without assistance).12 All patients considered for inclusion had a diagnosis of probable or possible Alzheimer’s disease consistent with the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV)13 and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s...
A CT or MRI scan consistent with Alzheimer’s disease (mostly done at the time of diagnosis) was required. Providing the patient had no other change in clinical status suggestive of stroke or possible neurological disease between the time of the scan and the screening visit they were allowed to participate. Vital signs and laboratory values had to be within their normal range for age. Our exclusion criteria included the presence of dementias not associated with Alzheimer’s disease, and primary psychiatric and neurological disorders.

The independent ethics committees of the participating centres approved the study. We obtained written consent from the patient (if capable) and in all cases from the patients’ next of kin before enrolment. The trial was done in compliance with the Declaration of Helsinki.

Procedures

Most participants lived in care units exclusively for patients with dementia. Each patient had his or her own room in a department or unit housing 5–15 individuals. All units had a central nurses’ station staffed by professional nurses who developed care plans, dispensed drugs, and oversaw care, and by nursing assistants who provided assistance with activities of daily living. To enable adequate reporting of functional and neuropsychiatric assessments, we required that nursing assistants had known their patient for at least 12 weeks and that they had spent at least 4 h with them on at least 3 days every week. Although some institutions had their own physicians, most were visited on a weekly basis by a family doctor or, in some instances, a geriatrician.

The randomisation schedule was generated centrally by the Global Clinical Data Services at Pfizer, Groton, Connecticut, USA. The randomisation was in a one-to-one ratio, with a block size of four and we provided each site with a set of unique numbers. Patients were randomised to donepezil or placebo sequentially, starting from the lowest allocation number, according to the computer-generated randomisation schedule. Patients received a daily dose of oral donepezil 5 mg for the first 30 days followed by daily donepezil 10 mg (or 5 mg if not well tolerated) for the remainder of the 6 months, or matching placebo.

Our primary outcome measures were the change from baseline to month 6 in the scores for the severe impairment battery (SIB) and the Modified Alzheimer’s Disease Cooperative Study activities of daily living inventory for severe Alzheimer’s disease (ADCS-ADL-severe). The SIB is a 40-item questionnaire designed to assess the severity of cognitive dysfunction in advanced Alzheimer’s disease and is divided into nine domains: memory, language, orientation, attention, praxis, visuospatial, construction, orientation to name, and social interaction. Total scores for the questionnaire range from zero (greatest impairment) to 100 (no impairment). The modified ADCS-ADL-severe is a 19-item scale used to measure basic and

---

Figure 1: Trial profile

<table>
<thead>
<tr>
<th>Donepezil (n=128)</th>
<th>Placebo (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>84.5 (6.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (21%)</td>
</tr>
<tr>
<td>Female</td>
<td>101 (79%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>128 (100%)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.7 (11.3; n=104)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 (9.3; n=93)</td>
</tr>
<tr>
<td>MMSE screening scores</td>
<td>6.0 (3.0)</td>
</tr>
</tbody>
</table>

FAST stage:

5: Requires assistance in choosing proper clothing
   for the season or occasion
6a: Difficulty putting clothing on properly without assistance
6b: Unable to bathe properly
6c: Inability to handle mechanics of toileting
6d: Urinary incontinence
6e: Fecal incontinence
7a: Ability to speak limited to about 12 words in an average day
7b: Intelligible vocabulary limited to one word in an average day
7c: Non-ambulatory (unable to walk without assistance)

Data are number (%) or mean (SD).

Table 1: Baseline characteristics

---
complex abilities and validated in patients with moderate-to-severe dementia; total scores range from zero to 54, with the lowest score indicating the greatest functional impairment and the highest no impairment. Items included basic activities of daily living—e.g., eating and bathing—and complex activities of daily living—e.g., operating water taps and switching on lights. Our secondary outcome measures were change in scores at 6 months compared with screening for the MMSE, baseline for the neuropsychiatric inventory (NPI), and scores at month 6 for the clinical global impression of improvement (CGI-I) scale. We ascertained all scores at baseline, except for MMSE, which was obtained at screening, 3 months (except for MMSE), and 6 months.

We assessed vital signs at screening, baseline, and months 1, 3, and 6, and adverse events at baseline and months 1, 3, and 6. Nursing staff also recorded adverse events daily. We did physical examinations, an ECG, and laboratory tests, at screening and at month 6.

**Statistical analysis**

On the basis of the results of a study of memantine in patients with moderate-to-severe Alzheimer’s disease, we calculated that we needed a sample size of 101 patients per treatment group to detect with 90% power an absolute difference between treatments in ADCS-ADL-severe of 3.5 (SD=7.6) with an α level of 0.05. With the same power and significance level, we needed to enrol 86 patients per group to detect a 7 (SD=14) point absolute treatment difference in SIB scores over time, according to the results of a previous study of donepezil. Since 15% of screened patients would probably not meet our inclusion criteria and only 85% of those randomised would probably complete the trial, we needed to screen about 280 patients.

We did initial analyses of our primary outcome measures—the mean of the change from baseline to month 6 in the SIB and the ADCS-ADL-severe (total scores)—on data obtained from a modified intent-to-treat population, with last observation carried forward to account for missing data. We defined this population as all randomised patients who took at least one dose of medication and who provided a baseline score and at least one corresponding post-baseline score. We did secondary analyses on data from the whole intention-to-treat population—ie, all patients who fulfilled the inclusion criteria and who were randomised—and replaced missing data with the mean of the observed values for the change from baseline to month 6 in the placebo group. We also did analyses for the completer population, defined as the patients who completed the 6-month treatment period with no provision made for missing data. In a post-hoc sub-item analysis, we analysed each of the nine SIB domains and the basic and complex components of ADCS-ADL-severe separately, comparing change from baseline to month 6 for the modified intention-to-treat population.

We did analyses of the secondary outcome measures of the change from screening (MMSE) and baseline (NPI)
to month 6 (total scores) on the modified intention-to-treat population, the intention-to-treat population, and the completer population. We analysed primary and secondary outcome measures with the general linear model, which included treatment and baseline data as covariates. Treatment was included as a fixed effect. Furthermore, as a sensitivity analysis, we included the centre as a covariate in the model (centres with less than five patients in each treatment group were pooled). We analysed the CGI-I scores for the modified intention-to-treat population, the intention-to-treat population, and the completer population, using the Cochran-Mantel-Haenszel $\chi^2$ test stratified by centre.

We used paired $t$ tests to compare pretreatment with post-treatment data in each treatment group. All statistical tests were two-sided and we judged a $p$ value of 0.05 or less significant. 95% CIs are presented for the estimates derived from data from the modified intention-to-treat population and the intention-to-treat population.

For safety variables, we present descriptive statistics for all patients who were randomised and took at least one dose of study medication. We recorded all treatment-emergent adverse events, coding them according to a modified COSTART dictionary. Rates for adverse events, laboratory abnormalities, and changes in ECGs are summarised.

All statistical analyses were done with SAS (version 8.2).

Role of the funding source

Study design and planning, data collection, data analysis, data interpretation, and writing of the report were done in conjunction with the study sponsor. The study sponsor provided the study drugs and funding for study management. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 334 patients screened, we randomised and treated 248 (figure 1). There were no notable differences between the groups with respect to their demographic or psychometric characteristics at baseline (table 1). 95 patients assigned donepezil and 99 controls completed the study. The median duration of treatment with donepezil was 176 days (range 2–231) and with placebo 180 days (5–218). Mean daily doses of donepezil and placebo for the safety population were 8.2 mg (SD 1.5) and 8.4 mg (1.2), respectively. 91% (n=86) of donepezil-treated patients and 94% (n=93) of controls who completed the study took the 10 mg dose.

More than 80% of patients had FAST scores of 6c or higher (table 1). At baseline, in donepezil-treated and placebo-treated patients, hypertension was present in 29% (n=37) and 25% (n=30), heart disease in 29% (n=37) and 23% (n=28), and psychiatric symptoms in 68% (n=87) and 75% (n=90), respectively. All donepezil and most (99%, n=247) placebo patients took concomitant medications during the study. Most commonly used classes of drugs were analgesics, laxatives, hypnotics, sedatives and anxiolytics, diuretics, drugs used to treat anaemia, antidepressants, drugs to treat rheumatic diseases and gout, antibacterial agents, and antipsychotic drugs. More than 80% of patients were taking psychoactive medications, with a breakdown by class as follows: hypnotics, sedatives, and anxiolytics, 61% (donepezil, n=78) versus 58% (placebo, n=70); antidepressants, 52% (n=67) versus 51% (n=61); antipsychotics, 38% (n=48) versus 42% (n=50).

At 6 months, according to last observation carried forward analyses done in the modified intention-to-treat population, patients assigned donepezil had significantly better mean change from baseline scores than controls.
on both SIB (least squares [LS] mean difference 5·7, 95% CI 1·5–9·8; p=0·008) and ADCS-ADL-severe (1·7, 0·2–3·2; p=0·03). Indeed, donepezil-treated patients showed a mean improvement in SIB, whereas those receiving placebo showed a mean decline (table 2). The donepezil group showed less of a decline than the placebo group in ADCS-ADL-severe (table 2). Figure 2 shows the results for the modified intention-to-treat population and for the completer population. The outcome analyses in which we replaced missing values by the mean of the observed values for the change from baseline to month 6 in the placebo group revealed similar results as for the primary modified intention-to-treat population (table 2). We noted significant treatment differences for the intention-to-treat population: SIB (LS mean difference 4·5, 1·1–7·9; p=0·01) and ADCS-ADL-severe (1·4, 0·1–2·7; p=0·03).

Analysis of the individual SIB domains at 6 months for the modified intention-to-treat population showed donepezil to be more effective than placebo in all items, with improvement above baseline in eight domains, compared with only two for placebo (figure 3). At 6 months, for the same population, donepezil positively affected five of six basic ADCS-ADL-severe items and 11 of 13 complex ADCS-ADL-severe items, resulting in improvement in four items compared with one item for placebo (figure 4).

Two of the three secondary outcome measures—the CGI-I scores and the mean change from screening scores on the MMSE at 6 months’ follow up—favoured donepezil treatment over placebo (table 2). For the CGI-I score, the difference between treatment groups was almost significant in the modified intention-to-treat population (p=0·055) and significant when only the data for the completer population were analysed (p=0·008; figure 5). For the MMSE, donepezil-treated patients had a greater mean improvement than controls, with LS mean changes of 1·5 and 0·1, respectively, for the modified intention-to-treat population (LS mean difference 1·4, 95% CI 0·4–2·4; p=0·009). There was no significant difference between treatment groups on the NPI for the modified intention-to-treat population (1·5, –5·3 to –2·2; p=0·43).

The overall incidence of adverse events was comparable between groups (donepezil 82% [n=105] vs placebo 76% [n=91], with most being transient and mild or moderate in severity. Of the most common adverse events (occurring in ≥5% of patients in either group), only diarrhoea and hallucinations were reported at more than twice the rate in donepezil-treated patients compared with controls (table 3). A similar number of deaths occurred during and within 30 days after the study in the donepezil (14% [n=18]) and placebo (16% [n=19]) groups. We did not consider any of the deaths treatment related. The proportion of patients who had a serious adverse event (including one with an outcome of death) during the study or within the 30-day study lag period did not differ between groups (24% [n=31] vs 26% [n=31],
respectively). More patients treated with donepezil than controls discontinued their treatment, however, because of adverse reactions (16% [n=20] vs 7% [n=8]).

We noted no great changes in the results of laboratory tests, ECGs, physical examinations, or vital signs over time.

**Discussion**

Our findings indicate that donepezil can improve cognition and preserves function in patients with severe Alzheimer’s disease. The data presented lend support to the neurobiological premise that cholinergic deficits in the brain of people with severe Alzheimer’s disease can be, at least in part, alleviated by cholinesterase inhibitors. Our patients had not received cholinergic inhibitor therapy for 3 months before study entry and for the most part had a limited exposure to such agents during the course of their disease. The study was not designed to further clarify the issue of discontinuation of therapy once the patient reaches this juncture.

Similar to results obtained in patients with moderate-to-severe Alzheimer’s disease living in the community, the advantages afforded by 6 months of treatment with donepezil in cognition, activities of daily living, and global function included improvements above baseline or less decline compared with placebo. The improvements in cognition seem to have a positive effect on the functioning of the patients, potentially indicating a direct correlation between these two domains. The pronounced improvement in SIB scores in patients treated with
donepezil might have been driven by an improvement in delirium or confused states in a subset of patients or by direct action of donepezil against the anticholinergic or sedative effects of concomitant medications. Analyses of subsets of patients taking different classes of medication need to be done to explore these possibilities.

As in the study by Reisberg and colleagues of memantine, we noted little effect of donepezil compared with placebo on the NPI. This finding also concurs with that of a previous study of donepezil in patients with mild-to-severe Alzheimer’s disease living in nursing homes, but contrasts with significant differences noted in favour of donepezil in a study based in the community. As such, there might be an inherent difference between studying behavioural aspects of Alzheimer’s disease in patients residing in different settings and a differential sensitivity of the NPI in these settings. Alternatively, use of concomitant psychoactive medication might have masked a behavioural response to donepezil in some patients. Sub-item and responder analyses need to be done to fully ascertain the effects of donepezil on behaviour.

Sustained use of cholinesterase inhibitors is not associated with any survival advantage. Thus, if treatment can help patients in the late phase of dementia, without necessarily increasing the length of time they have severe Alzheimer’s disease, then this is a treatment option that should be available. Results of sub-item analysis of the SIB showed nearly all aspects of cognition measured to be improved in patients treated with donepezil. An increase in the ability to communicate is especially important, since it facilitates caregiving through improved interaction and helps to maintain contact with family members. More in-depth analysis of basic activities of daily living showed donepezil-treated patients to have better outcomes on most items. As well as improving wellbeing of patients, benefits in functional capacity could translate to decreased workload and less stress for nursing staff in assisted-care facilities and for other caregivers, including relatives. Indeed, donepezil has been shown to reduce burden of caregivers of patients with moderate-to-severe Alzheimer’s disease.

Comparisons between our study and those of other treatments for dementia are difficult to make. The only other study of treatment of severe dementia in patients living in nursing homes was of a relatively short course of memantine and only half those enrolled had Alzheimer’s disease. Nevertheless, similar results on the CGI-I were obtained. In a study of memantine in patients with moderate-to-severe Alzheimer’s disease living in the community, treatment duration was more similar to that in our study. In that study, as in ours, significant treatment differences at final follow-up were noted in favour of active medication compared with placebo on the SIB and ADCS-ADL-severe. However, whereas both medications slowed functional decline, cognitive improvements above baseline were noted only for donepezil.

To calculate the sample number needed to sufficiently power our study, we set a clinical significance, based on studies in a population of patients with moderate-to-severe Alzheimer’s disease, at a treatment difference of 7 points on the SIB and 3-5 points on the ADCS-ADL-severe. Although the point estimates of the treatment differences at 6 months were smaller than specified a priori and than those noted in the memantine study (SIB 6-1 points; ADCS-ADL-severe 2-1 points), the range of values for SIB was within that of clinical significance. The high baseline scores for the SIB (by 20%) and the ADCS-ADL-severe (by 75%) in the memantine trial compared with ours could have affected the possible range of the changes in a different way to those noted here because of differential sensitivities in different parts of the scale. Before we did our study, it was difficult to define clinically relevant effect size in a population with severe Alzheimer’s disease because of the limited data available. Moreover, treatment effects of cholinesterase inhibitor therapies are not large. Small numerical changes on scales used to measure symptomatic changes in trials might nevertheless be clinically meaningful in practice. It is noteworthy that this elderly patient population, with multiple comorbidities, is a vulnerable one. As such, changes to their condition, mediated by factors other than Alzheimer’s disease—eg, infection—might result in a high level of variation in response.

Over the past few years, a study period of around 6 months seems to have become the optimum duration for assessing the efficacy of dementia medications; its use here enables comparison with other studies of Alzheimer’s disease. A shorter study period of 3 months might not be sufficient to observe effects. Moreover, a high attrition rate, a common problem in clinical trials that enrol elderly and vulnerable populations, is

<table>
<thead>
<tr>
<th></th>
<th>Donepezil (n=128)</th>
<th>Placebo (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>22 (12%)</td>
<td>19 (16%)</td>
</tr>
<tr>
<td>Accidental fall</td>
<td>17 (13%)</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8 (6%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>7 (6%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>8 (6%)</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12 (9%)†</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12 (9%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>8 (6%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (6%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 (3%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Accidental bone fracture</td>
<td>7 (6%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (4%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>8 (6%)† †</td>
<td>1 (1%)§</td>
</tr>
<tr>
<td>Total</td>
<td>311</td>
<td>220</td>
</tr>
</tbody>
</table>

*Possibly treatment-related in eight (6%) patients. †Possibly treatment-related in four (3%) patients. †‡ Present before start of study in three patients. § Present before start of study in one patient.

Table 3: Adverse events (all causalities) reported in at least 5% of patients in either treatment group.
exacerbated when studies continue over a long period (12 months or more), compromising the validity of the end results. Indeed in this 6-month trial, the overall withdrawal rate was 22%. Although different imputation methods for handling missing data revealed similar results, this high drop-out rate should be considered during interpretation of the data.

As in studies of mild-to-moderate20–23 and moderate-to-severe Alzheimer’s disease,24 donepezil was well tolerated, with side-effects typical of cholinesterase inhibitor therapy—eg, diarrhoea and hallucinations. Hallucinations were present, however, before the start of the study in three of the eight donepezil-treated patients and in one placebo patient, and might be a manifestation of the disease rather than a side-effect of treatment. As expected, more patients taking donepezil than placebo left the study.

Overall, our data suggest that donepezil is an effective and well tolerated treatment even when initiated in patients with severe Alzheimer’s disease.

Contributors
B Winblad conceived the study, secured funding from Pfizer, and, together with A Haglund, designed the study protocol. A Haglund and A-L Wetterholm helped find study centres, oversaw good clinical practice, monitored study sites, and, in conjunction with C Jansson-Blxt, developed an IT report forms. A-L Wetterholm also ensured that staff at study centres were adequately trained. C Jansson Blxt was involved in the verification of randomisation. L Kilander and S Båtsman helped enrol patients and, together with B Winblad, S Eriksson, and C Jansson-Blxt, were involved in data analysis. B Winblad, I Kilander, S Eriksson, S Båtsman, I Minthon, C Jansson-Blxt, and A Haglund were involved in writing of the report.

Conflicts of interest statement
B Winblad and S Eriksson have taken part in advisory board meetings of drug companies producing drugs to treat dementia. L Kilander has received honoraria from Pfizer to speak at meetings and is on their advisory board. S Båtsman has taken part in advisory board meetings of Pfizer and Lundbeck and has received honoraria to speak at meetings from Pfizer, Novarts, and Lundbeck. I Minthon has arranged lectures paid for by Janssen Cilag and Pfizer, is on the advisory board of Pfizer and Lundbeck and for the Severe Alzheimer Dementia Study, and has received funding from Pfizer to arrange a national conference (Specialistförum Demens). C Jansson-Blxt and A Haglund are, and A-L Wetterholm was, employed by Pfizer.

Severe Alzheimer’s Disease Study Group
Bo Sundquist, Vårdcentralen Vännäs, Vännäs; Sigrítt Rasmussen, Norrlands Universitetssjukhus, Umeå; Anders Nelvig Länssjukhus, Sundsvall; Ingrid Johansson, Hemoderna Vårdcentral, Hemedemor; Boris Klarger, Läkargruppen 1, Västerås; Satu Ekelund, Runby Vårdcentral, Upplands Väsby; Karl Malmö; Gustavbergs Vårdcentral, Gustavbergs; Wilhelmina Hoffman, Stockholms Sjukhem, Geriatrik och Neurologisk Rehabiliterande, Stockholm; Karin Fröjd, Vårdcentralen Kronoparken, Karlstad; Thomas Eriksson, Aneby Vårdcentral, Aneby; Sune Johansson, Hälsan Tornet, Jönköping; Tomas Svensson, Dalbo Vårdcentral, Växjö; Eva Molt, Vårdcentralen Stattena, Helsingborg; Göran Sundbäck, Geriatrik Rehab-kliniken, Avesta; Leif Wretnam, Geriatrika Rehab-kliniken, Borlänge; Per Von Hofsten, Palghårds Vårdcentral, Degerfors; Lars Gustafsson, Ekeby Vårdcentral, Eskilstuna; Marie Holmgren-Clausen, Medicinmottagningen, Eskilstuna; Mats Elm, Vårdcentralen, Fritsla; Torben Ulvatne, Vårdcentralen, Göteborg; Förberget, Barbro Nordenhäll, Vårdcentralen, Munkfors; Jarl Tillberg, Geriatrika Rehab-kliniken, Näsjö; Carl-Magnus Molstad, Vårdcentralen Ingelstad, Ingelstad; Jan Wellander, Vårdcentralen Partille, Partille; Anders Green, Vårdcentralen, Rättvik; Lars Sköldstam, Neurolougmottagningen, Visby; David Karlsson, Geriatrika Rehab-kliniken, Värnamo; Birger Ossiansson, Vårdcentralen Birka, Växjö; Göran Rehn, Smördynsberget, Åkersberga; Elin Gille, Årsta Vårdcentral, Årsta; Per Åkesson, Vårdcentralen, Sunne; Viveka Norlund-Elmroth Distriktsläkarmott, Östersund; Lars-Bertil Olsson, Vårdcentralen Kristina, Kristinhamn; Benny Lorentzon, Vårdcentralen Källstorp, Trollhättan; Ingvar Granlund, Vårdcentralen Jönkoping, Jonkoping; Hans-Högesten, Tyresöhuskan Husekare AB, Tyreso; Martin Frykholm, Åsö Vårdcentral, Stockholm; Kent Fredriksson, Säro Vårdcentral/Säro Hemsjukvård, Säri; Tom Roffey, Agårdskogens Vårdcentral, Lidköping; Lars Paulsson, Västra Ekotors Läkaromtgagn, Gullspång; Lars-Olof Persson, Lovåsens Vårdcentral, Katrineholm; Bengt Kvarnlund, Storviks Hålsocentral, Sandviken; Holger Källqvist, Vårdcentralen Nygårds, Bensfors; Anders Wimo, Bergsjö Hålsocentral, Bergsjö; Carl-Johan Westberg, Björkans Vårdcentral, Boden; Jerry Dahlberg, Sollebrunn Vårdcentral, Sollebrunn; Pirkko Olsson, Vårdcentralen, Tullinge.

Acknowledgments
This study was funded by Pfizer Pharmaceuticals, Solentuna, Sweden.

References


