

# Efficacy of Donepezil Treatment in Alzheimer Patients with and without Subcortical Vascular Lesions

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## Key Words

Donepezil · Alzheimer's disease · Mixed dementia · Cerebrovascular disease

## Abstract

In a pilot study designed as a case control study the efficacy of donepezil treatment was investigated in patients with Alzheimer's disease (AD). Patients were stratified according to radiological criteria into patients without (AD group) and with subcortical vascular lesions (AD+SVD group). Changes in cognition were assessed as the primary outcome measurement after 6 and 18 months of treatment by the Mini-Mental Status Examination (MMSE) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery. After 6 months, patients had improved from baseline by 0.7 points in MMSE score in the AD group and by 1.8 in the AD+SVD group. After 18 months of treatment, the AD+SVD group performed significantly worse in one CERAD subscore, whereas a deterioration in two subscores was observed in the AD group. A comparison between the 2 groups revealed that treatment did not lead to statistically significant differences between the AD and AD+SVD groups in any of CERAD parameters fol-

lowing 6 or 18 months of treatment. These data support previous observations that donepezil therapy is effective in AD patients with and without subcortical vascular lesions.

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## Introduction

Several studies have suggested that at least a third of Alzheimer disease (AD) subjects bear a significant cerebrovascular pathology [1, 2]. Differentiation between AD and AD with subcortical vascular lesions (AD+SVD) may have important clinical implications. The presence of subcortical infarctions and ischemic white matter lesions is an important distinguishing factor in routine clinical diagnostics for probable AD.

Donepezil was approved for the treatment of patients with mild to moderate AD in autumn 2000. In our outpatient group, a considerable number of patients were radiologically diagnosed as having vascular lesions, mostly as white matter lesions, in addition to other radiological signs indicative for AD. At the beginning of this pilot study there were no reports available investigating whether cholinesterase inhibitors are effective in AD patients

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with cerebrovascular lesions. In the meantime several studies have shown that cholinesterase inhibitors may be effective in the treatment of AD and vascular dementia [3–6].

In the present pilot study, we investigated whether AD patients with and without white matter lesions are different with regard to their clinical outcome. As primary outcome, we used the relative changes in Mini-Mental Status Examination (MMSE) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery. Thus, the pilot study will reveal whether donepezil is effective in AD patients with white matter lesions. The German version of the CERAD test battery was normalized using a large group of healthy controls. The CERAD test battery has not yet been applied in other studies on vascular or mixed dementia, therefore this study will also evaluate its usefulness in AD drug studies.

## Subjects and Methods

### Study Design and Protocol

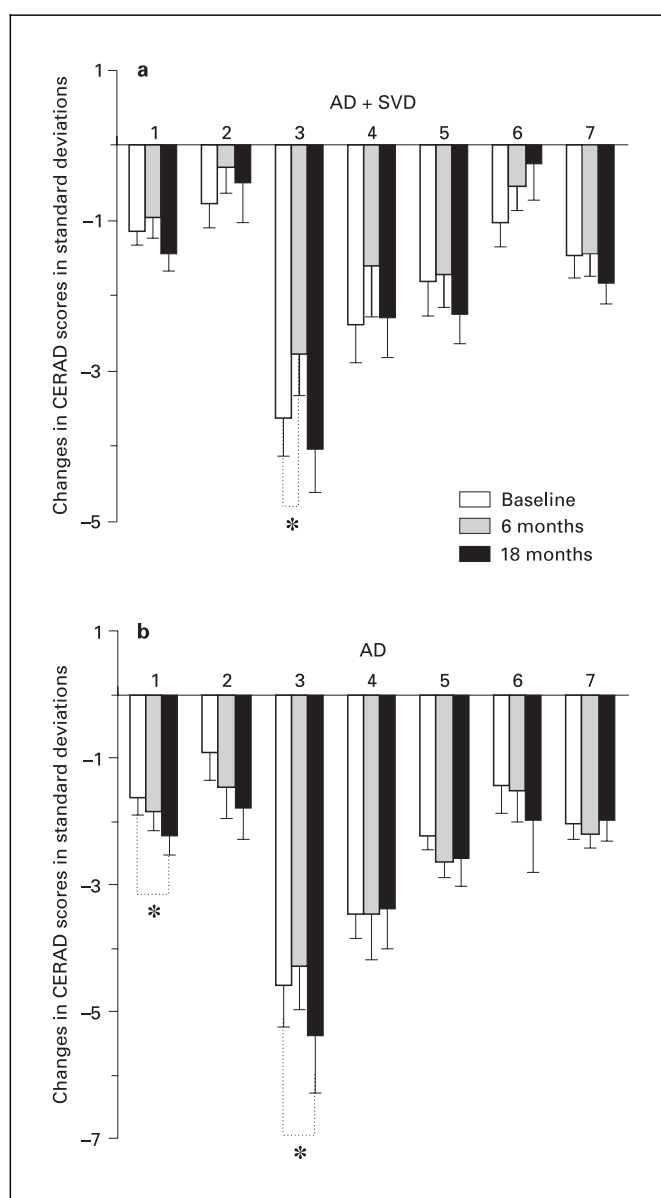
A case control, pilot study was conducted on outpatients. Patients were assessed by standardized diagnostic procedures including neurological, psychiatric and general medical examination. All subjects underwent laboratory tests to exclude secondary causes of dementia. Additional studies including a cerebrospinal fluid analysis and electroencephalogram were performed as the clinical situation indicated.

Afterwards the AD patients were stratified according to magnetic resonance imaging criteria into 2 groups. The first group had no radiological signs of subcortical vascular pathology other than those also found in healthy, age-matched controls. The second group exhibited lacunar lesions, predominately white matter lesions. The white matter lesions were unitary or bilaterally distributed throughout cerebral white matter. Punctate white matter lesions and confluent white matter abnormalities were observed. The white matter lacunar infarcts were presented in white (70% of all) and in both subcortical grey and white brain matter (30%).

Patients were excluded from participating in the study if they had evidence of degenerative neurological disorders other than AD, especially when there was evidence for multi-infarct dementia. The patient and caregiver provided written informed consent prior to the study. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments [7].

### Efficacy Measures

A trained and blinded neuropsychologist administered a standard battery of neuropsychological tests. The severity of disease was assessed at baseline by Clinical Dementia Rating [8] and the CERAD battery, described in detail elsewhere [9–13]. CERAD could be completed by all patients. This CERAD battery consists of 5 tests: Verbal Fluency: Animal Category, a short form of the Boston Naming Test, MMSE [14], Verbal Memory Test (VMT) consisting of word list learning with immediate (sum of 3 trials), delayed recall and a recognition procedure and Constructional Practice (including delayed recall).



**Fig. 1.** The calculations of CERAD cognitive battery in the z-scores in the AD+SVD (a) and AD (b) groups. Bars represent means of z-score values from 10 patients for the group at baseline, 6 months and 18 months. The z-score values of all cognitive tests of both groups are below the mean of the normative population (defined as 0) and are therefore expressed in negative values. The narrative of data at the x axis are depicted as follows: 1 = Verbal Fluency; 2 = Boston Naming Test; 3 = MMSE; 4 = Verbal Memory Test (VMT) immediate recall; 5 = VMT delayed recall; 6 = Constructional Practice total sum; 7 = Constructional Practice delayed recall. \*  $p < 0.05$  in ANOVA analysis.

**Table 1.** Baseline characteristics of AD and AD+SVD patients

	AD	AD+SVD
Patients	10	10
Females	6	7
Age (mean $\pm$ SEM)	71 $\pm$ 2.4 (56–79)	81 $\pm$ 2.4 (64–92)
Education, years (mean $\pm$ SEM, range)	9.3 $\pm$ 1.2	9.5 $\pm$ 0.7
$\geq$ 1 APOE- $\epsilon$ 4 allele, patients	5	6
MMSE (mean $\pm$ SEM)	19.7 $\pm$ 1.9	21.5 $\pm$ 1.3
Clinical dementia rating scores $>$ 1.0	10	10
Risk factors		
Hypertension	4	5
Smoking (past or present)	1	2
Diabetes	1	2
Hypercholesterolemia	8	6
Hypertriglyceridemia	4	4
Comorbidity		
Angina pectoris, coronary artery disease	1	4
Focal neurological signs	0	4
Peripheral vascular disease	0	1
$>$ 60% stenosis of ACI	0	0
Arteriosclerotic plaques in ACI	5	9

SEM = Standard error of the mean; ACI = arteria carotis interna.

**Table 2.** Concomitant medication (number of patients)

	AD	AD+SVD
Antithrombotic agents	4	6
Aspirin	4	6
Vitamins	0	2
Analgesics (including NSAIDs)	0	3
Antihypertensive drugs	5	6
Serum lipid reducing agents	3	2
Antipsychotics	2	3
Antidepressive therapy	4	5

#### Treatment

Initially, all enrolled patients received open-label donepezil 5 mg once daily. After 1 month, the dose was increased to 10 mg once daily for 18 months based on the clinicians' judgment of tolerability and efficacy. Psychometric evaluations took place during clinic visits at baseline and at 6 and 18 months.

#### Data Analysis

Data are expressed as z scores of the normative sample of 1,100 cognitively healthy persons (fig. 1) [13]. Z scores represent the standard deviation of a single person's cognitive scoring in comparison to the median of the normative sample defined as 0. In order to compare the AD plus AD+SVD groups to the normative population, standard deviation values were used. A difference of  $<$ 1 standard deviation was considered to be a normal variation from the control

value. Statistical analysis was performed first by comparing the cognitive scoring of both groups at baseline, and at 6 and 18 months by multiple comparisons using the ANOVA test.

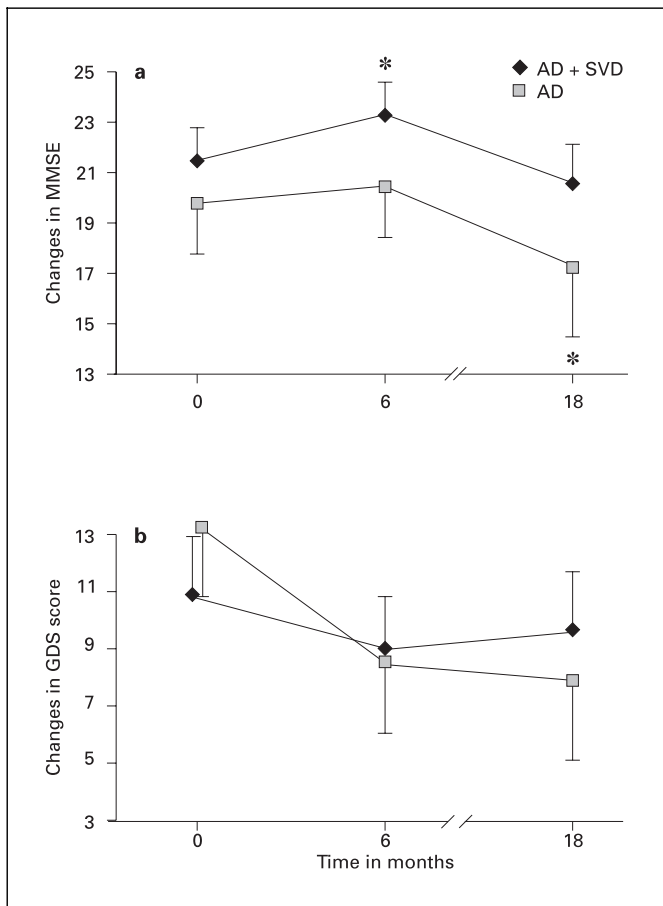
## Results

### Patients' Characteristics

The baseline characteristics of the AD and AD+SVD groups are presented in table 1. The AD+SVD group exhibited a higher prevalence of vascular comorbidities (table 1, 2).

### Clinical Efficacy of Treatment with Donepezil in AD and AD+SVD Groups

The baseline values in CERAD tests of the AD and AD+SVD groups were calculated in z scores and the mean values of 10 patients at each investigated time point are demonstrated in figure 1. At baseline, all z-score values were  $<$ 1 standard deviation except for Boston Naming (fig. 1a, b). Baseline values were not statistically different between the 2 groups as calculated by the Mann-Whitney test. Patients of both groups were treated with a dosage of 10 mg donepezil for at least 18 months. During this period, no patient had to be excluded from the study because of side effects or other serious adverse events. Following 6 months of treatment, AD+SVD patients showed a trend



**Fig. 2.** **a** The time course of mean MMSE scores  $\pm$  standard error of the mean are shown;  $n = 10$  for each group. \*  $p < 0.05$  when compared to baseline. **b** The time course for geriatric depression scale (GDS) during the study period,  $n = 10$  for each group (mean  $\pm$  SEM).

to improvement in all 7 scores of the CERAD battery (fig. 1a).

In contrast, the AD group showed a trend to improvement in only 1 parameter (fig. 1b). Only VMT immediate recall statistically differed between both groups at this time point. After 18 months of treatment the AD+SVD group performed even better in two CERAD items whereas in the AD group one CERAD subscore was improved. Comparing the relative changes between the groups, no statistical differences were detected for any parameter after 18 months of treatment.

In the AD+SVD group, a significant improvement in MMSE score was observed after 6 months of donepezil treatment ( $21.5 \pm 1.3$  versus  $23.3 \pm 1.3$ ; mean  $\pm$  SEM), and was below baseline levels after 18 months ( $20.6 \pm$

$1.5$ ; fig. 2a). In the AD group, the comparative analysis to baseline revealed a nonsignificant improvement in MMSE score after 6 months ( $19.7 \pm 1.9$  versus  $20.4 \pm 2.0$ ) and a statistically significant deterioration after 18 months of treatment ( $17.2 \pm 2.7$ ;  $p < 0.05$  compared to baseline; fig. 2a).

The Trail-Making test (TMT) part B was not completed by all patients, therefore only TMT part A was evaluated. The time to perform the TMT part A increased by 146% in the AD group and by 183% in the AD+SVD group.

In our cohort, as assessed in the geriatric depression scale, both groups suffered from mild depression, e.g. 13.2 in AD versus 10.9 points in AD+SVD group (fig. 2b). Both groups were almost equally treated with antidepressive drugs (table 2) and they improved after 6 months to 8.5 points in AD versus 9.0 points in the AD+SVD group.

## Discussion

In this prospective study, AD patients with and without subcortical vascular lesions were treated with donepezil for 18 months. A deterioration in MMSE was observed when compared to baseline. In comparison to previous placebo studies, the degree of cognitive decline was clearly less in both treatment groups [15].

There is strong evidence that donepezil causes a slowing in disease progression in both groups since different cognitive domains did not change during the course of the disease. In the present study, for example, the degree of impairment in delayed recall was similar between baseline and after 18 months of treatment.

A significant worsening was observed for verbal fluency in the AD group whereas in the AD+SVD group only a trend to a worsening was observed. This coincides with the observation of Schmidtke and Hull [16] who found an inferior performance in verbal fluency in AD patients. The VMT immediate recall (recognition memory) was previously shown to be better preserved in AD patients with subcortical ischemic vascular dementia [17].

In our study, although both patient groups were similar in their z scores for VMT-recognition at baseline and after 18 months of treatment, after 6 months of treatment the AD+CVD group statistically improved in comparison to the AD group. The observed congruence in VMT immediate recall could, however, be due to bias from the small patient cohort or differences in the type of vascular pathologies.

In some studies, donepezil was shown to be effective in vascular dementia [3–6]. However, in most of these studies, the exclusion criteria did not account for the heterogeneity of vascular dementia. There is considerable variation concerning the vascular pathology in AD due to differences in imaging techniques, rating scales, cutoff points in lesion severity grading and study populations.

This study is in line with other reports suggesting that cholinesterase inhibitors are effective for the treatment of AD patients with a significant subcortical vascular pathology. It also indicates that the cholinergic system is

affected in these patients. The cholinergic deficit is well established for AD [18], but considerably less for patients with vascular comorbidity.

Summarizing, the group of patients with AD+SVD had a clear benefit from donepezil treatment. Therefore, this group of patients should not be excluded from treatment with cholinesterase inhibitors due to their vascular comorbidities. In contrast, this group of patients may even have a stronger profit than patients with AD pathology only.

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