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Efficacy and Tolerability of Donepezil in Vascular Dementia Positive Results of a 24-Week, Multicenter, International, Randomized, Placebo-Controlled Clinical Trial

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Background and Purpose—Clinical observations suggest that patients with vascular dementia (VaD) may benefit from treatment with cholinesterase inhibitors. This study evaluated the efficacy and safety of donepezil for relieving symptoms of dementia in VaD.

Methods—Patients (n=603; mean age, 73.9 years; 55.2% men) with probable (70.5%) or possible (29.5%) VaD, according to criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and the *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (AIRESN), were randomized to 24 weeks of treatment with donepezil 5 mg/d (n=198), donepezil 10 mg/d (5 mg/d for first 28 days; n=206), or placebo (n=199). Analyses were based on the intent-to-treat population.

Results—At week 24, both donepezil groups showed significant improvement in cognition versus placebo on the Alzheimer's Disease Assessment Scale—cognitive subscale (mean change from baseline score effect size: donepezil 5 mg/d, -1.90 ; $P=0.001$; donepezil 10 mg/d, -2.33 ; $P<0.001$). Significant improvements in patients' global function were seen versus placebo at week 24 (observed cases), on the Clinician's Interview-Based Impression of Change—Plus version only for patients on donepezil 5 mg/d ($P=0.014$), and on the Sum of the Boxes of the Clinical Dementia Rating only for patients on 10 mg/d ($P=0.007$). Donepezil-treated patients showed significant benefits in activities of daily living over placebo on the Alzheimer's Disease Functional Assessment and Change Scale (mean change from baseline score effect size at week 24: donepezil 5 mg/d, -1.31 , $P=0.02$; donepezil 10 mg/d, -1.31 , $P=0.02$). Donepezil was well tolerated. Withdrawal rates due to adverse events were relatively low (placebo, 11.1%; donepezil 5 mg/d, 11.1%; donepezil 10 mg/d, 21.8%; $P=0.005$ versus placebo).

Conclusions—These data demonstrate that donepezil is an effective and well-tolerated treatment for VaD and show it may have an important place in the management of this condition. (*Stroke*. 2003;34:2323-2332.)

Key Words: dementia ■ donepezil ■ randomized controlled trials

During the last 2 decades, studies have confirmed that cognitive impairment arising from cerebrovascular disease (CVD) and resulting in vascular dementia (VaD) is the most common form of dementia after Alzheimer disease (AD) in many parts of the world¹ and may indeed be more common than AD in some populations.²

VaD can result from multiple types of CVD, including recurrent strokes and white matter lesions.³ At present, the management of VaD focuses on secondary prevention strategies to limit the occurrence of further strokes. However, the management of the symptoms of dementia in VaD patients is

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often overlooked because no treatment is currently approved for this indication.

Clinical evidence suggests that, in VaD patients, vascular lesions may produce cholinergic dysfunction similar to that seen in AD patients.^{4,5} Since reduced cholinergic neurotransmission provides the rationale for the use of cholinomimetics in AD,⁶ cholinergic agents that have proven benefits in this condition may also be useful in the management of VaD.

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Donepezil, a potent acetylcholinesterase inhibitor, provides significant benefits in cognition, global function, and activities of daily living (ADL) in patients with mild to moderate AD.^{7,8} In AD patients, donepezil can maintain cognitive status at near baseline values for up to 52 weeks,⁹ as well as preserving functional abilities,¹⁰ delaying nursing home placement,¹¹ and ameliorating behavioral symptoms.¹² Recently, Erkinjuntti et al¹³ demonstrated therapeutic effects of a cholinesterase inhibitor in a heterogeneous group, which included patients with AD plus cerebrovascular lesions (AD plus CVD) and patients with probable VaD; however, coexisting AD may have accounted for the observed treatment effects. Therefore, there is as yet no conclusive evidence of beneficial effects of cholinergic agents in VaD.

We report here the results of a 6-month, randomized, placebo-controlled study of donepezil in VaD patients. The study was designed to determine the efficacy and tolerability of donepezil (5 and 10 mg/d) versus placebo in patients with VaD, excluding patients with AD plus CVD or with prestroke dementia.¹⁴ This study is therefore 1 of the first 2 large-scale, international, randomized, double-blind, placebo-controlled trials of a cholinomimetic in patients with probable or possible VaD, diagnosed according to the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) and the *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (AIREN).¹⁵

Subjects and Methods

Men and women (aged ≥ 40 years) with a diagnosis of possible or probable VaD of >3 months' duration, together with clinical and radiological evidence of CVD, were enrolled. A board-certified radiologist applied the NINDS-AIREN criteria to the CT and MR images, and the investigator classified patients as having probable or possible VaD according to all available clinical and imaging information. Patients with hypertension, type 1 or 2 diabetes mellitus, or heart disease were eligible provided the diseases were stable or controlled by medication for at least 3 months. Patients with medication-controlled depression could be enrolled, and patients with a history of recent stroke were also eligible providing that they had not been hospitalized for stroke in the previous 3 months.

Exclusion criteria included clinical or radiological evidence of neurodegenerative disorders other than VaD (eg, Parkinson disease), dementia due to AD (according to NINDS–Alzheimer's Disease and Related Disorders Association [ADRDA] criteria) or other conditions not associated with CVD, prior diagnosis of AD and subsequent cognitive impairment due to stroke or other CVD (prestroke dementia), a Mini-Mental State Examination (MMSE)¹⁶ score >26 or <10 , and the occurrence of new strokes within the 28 days before baseline. Patients with major depression or other psychiatric disorders (according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) were excluded. Patients who had experienced a myocardial infarction within 3 months of enrollment were excluded (although these patients could be reconsidered for inclusion once 3 months had elapsed), as were those with clinically relevant hepatic, pulmonary, gastrointestinal, or life-threatening disease. Additional reasons for exclusion included pregnancy, a history of alcohol or drug abuse, or a known hypersensitivity to donepezil. Patients were not permitted to receive anticholinergic drugs or cholinergic agents other than donepezil during the study period. Sympathomimetic amines and antihistamines were not permitted within 48 hours of a clinic visit, and anxiolytics, tranquilizers, hypnotics, and antipsychotics were not permitted within 72 hours of any clinic visit.

All subjects had to be outpatients under the care of a consistent caregiver and with sufficient speech, comprehension, and motor

function to enable completion of all procedures. Before study enrollment, the caregiver and patient (or legal representative) gave written, informed consent to participate in the study, which was conducted according to the Declaration of Helsinki and its subsequent amendments and in compliance with the regulations of the US Food and Drug Administration. The protocol was reviewed and approved by the designated human subjects' review board at each participating site.

Study Design

This was a multinational, multicenter, 24-week, double-blind, randomized, placebo-controlled, parallel-group study that ran from June 1997 until September 2001. Patients were assigned to 1 of 3 treatment groups by a computer-generated randomization protocol. Patients received single daily doses of donepezil 5 mg, donepezil 10 mg, or matching placebo to ensure blinding. Patients in the donepezil 10 mg/d treatment arm received donepezil 5 mg/d for the first 4 weeks and 10 mg/d thereafter.

Psychometric evaluations, physical and neurological examinations, laboratory determinations, and measurements of vital signs were performed at screening, baseline, and (together with checks for medication compliance and adverse events) at weeks 6, 12, 18, and 24. Patients also underwent a CT or MRI scan at screening if this had not been performed within the previous 6 months.

Efficacy Assessments

The primary efficacy outcome measures were the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog)¹⁷ and the Clinician's Interview-Based Impression of Change–Plus version (CIBIC-plus).¹⁸ The Clinician's Interview-Based Impression of Severity (CIBIS) at baseline was used as a reference for subsequent CIBIC-plus ratings. The clinician rating the CIBIC-plus was blind to the patient's psychometric test scores and adverse events.

Secondary efficacy end points were based on the MMSE,¹⁶ the Sum of the Boxes of the Clinical Dementia Rating (CDR-SB),¹⁹ and the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS).¹⁰ The ADFACS provides a measure of instrumental and basic ADL. Patients with permanent motor or sensory deficits, in whom a change in ADL may not be observable, were categorized on the ADFACS as "not assessable" in affected domains and assessed only on unaffected domains.

Safety Assessments

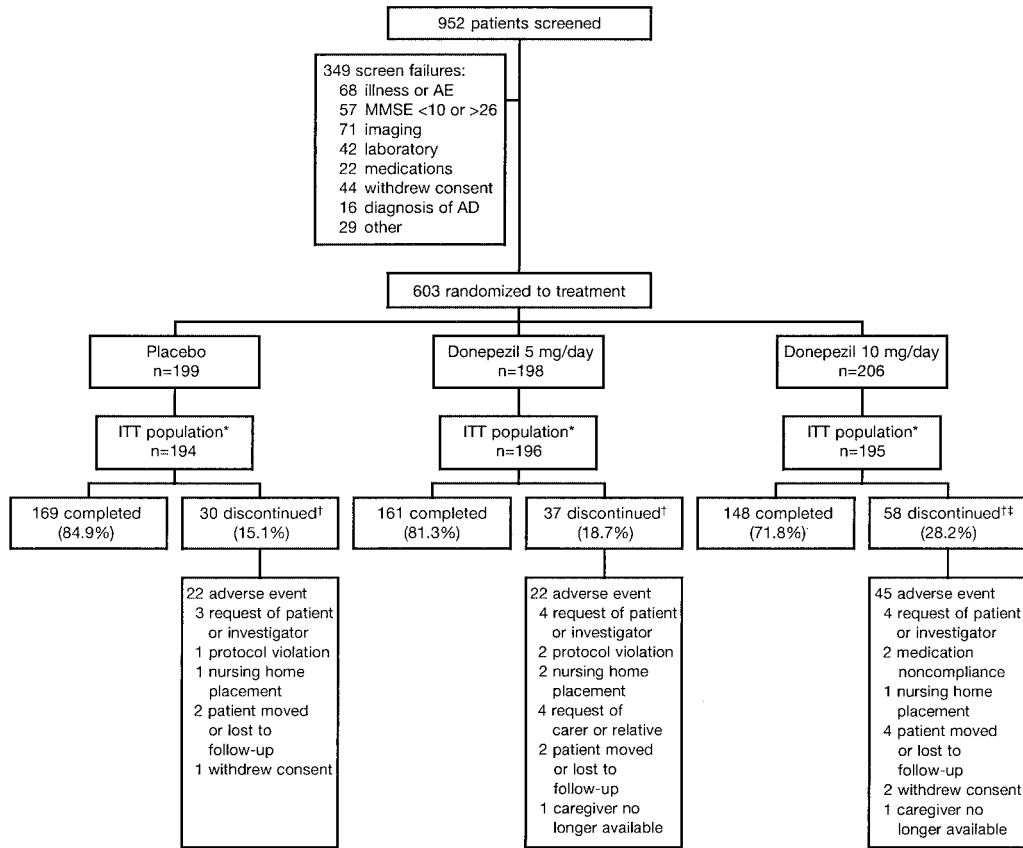
Safety and tolerability of study medication were assessed by comparing rates of discontinuation and treatment-emergent adverse events between treatment groups, as well as changes from baseline in laboratory test values and vital signs, ECG abnormalities, and changes on physical examination.

Statistical Analysis

The determination of sample size was based on a review of the results of phase 3 trials of donepezil in AD patients.^{7,8} The sample size was adjusted from 450 to 600 after a blinded determination of CIBIC-plus variance indicated that a larger sample was required. On this basis, a total population of 600 patients (200 per treatment arm) was required to have an 80% chance of detecting a 0.3-point improvement in CIBIC-plus between active treatment and placebo at the 0.05 significance level, allowing for a dropout rate of 20%. Patients who discontinued treatment were not replaced.

Analysis of efficacy was based on the intent-to-treat (ITT) population, which included all patients who received at least 1 dose of study medication, had baseline data, and had at least 1 postbaseline efficacy assessment. Within the ITT population, analyses were based on either observed cases at week 24 or end point, defined as last observation carried forward (LOCF), to week 24. Subgroup analyses were performed on patients with possible VaD and on patients with probable VaD. All patients who received at least 1 dose of study medication were included in the safety analysis.

Baseline demographic characteristics were analyzed with the Fisher exact test or χ^2 test (for categorical measures) or ANOVA (for



*18 patients were excluded from the ITT population (5 from the placebo group, 2 from the donepezil 5 mg/day group and 11 from the donepezil 10 mg/day group) because they did not have a baseline, or at least one post-baseline assessment, of at least one efficacy assessment.
 †11 patients died during the study (4 in the placebo group, 1 in the donepezil 5 mg/day group, and 6 in the donepezil 10 mg/day group). An additional 4 patients died within 4 weeks of discontinuing from the study.
 ††One patient had two reasons for discontinuation.

Figure 1. Patient disposition. AE indicates adverse event.

continuous measures). Differences between the treatment groups for linear efficacy measures were assessed by ANCOVA models that included baseline score as covariate, treatment (dose), and center. Categorical efficacy assessments were analyzed with a Cochran-Mantel-Haenszel test. The least squares mean changes from baseline scores to weeks 6, 12, 18, and 24 and end point are presented for variables analyzed with the ANCOVA models.

All statistical tests were 2-tailed and were performed at the 0.05 significance level.

Results

Patients

A total of 603 patients were enrolled and randomized to treatment, and 478 (79.3%) completed the study (Figure 1). Premature withdrawal was due primarily to adverse events in both placebo- and donepezil-treated patients.

The placebo and donepezil treatment groups were well matched with respect to baseline demographics, medical history, presence of cardiovascular risk factors, and baseline assessment scores (Table 1). The majority (70.5%) of patients met NINDS-AIREN criteria for probable VaD, and practically all patients (98.7%) had abnormal CT or MRI scans (Table 1). More than 75% of patients had an abrupt onset of cognitive impairment, and 58% showed a stepwise deterioration in cognition after onset of impairment.

Mean overall compliance with study medication was 95.6% in the donepezil 5 mg/d group, 95.0% in the donepezil 10 mg/d group, and 95.7% in the placebo group.

Virtually all enrolled patients (99.2%) were taking concomitant medications. Antithrombotics for stroke prevention were among the most commonly received (83.7% of all patients: placebo, 81.9%; donepezil 5 mg/d, 84.3%; donepezil 10 mg/d, 85.0%), as well as antihypertensive agents acting on the renin-angiotensin system (32.5% of patients) and diuretics (30.8% of patients). Mood-enhancing medications (including antidepressants) were taken by 37.6% of patients, and mood-stabilizing (psycholeptic) medications were taken by 22.6% of patients.

Primary Efficacy Analyses

Patients treated with donepezil 5 mg/d and 10 mg/d demonstrated significant improvements versus placebo at all time points on the ADAS-cog (Figure 2 and Table 2).

Subanalyses of the ADAS-cog results revealed significant differences in favor of donepezil over placebo in probable VaD patients (least squares mean change from baseline score effect size at end point: donepezil 5 mg/d, -1.67, P=0.02; donepezil 10 mg/d, -2.60, P<0.001). A trend toward treat-

TABLE 1. Patient Demographics and Baseline Characteristics

	Donepezil			
	Placebo n=199	5 mg/day n=198	10 mg/day n=206	Total n=603
Male/Female	115/84	111/87	107/99	333/270
Age, mean±SE (range)	74.2±0.6 (45–91)	73.7±0.6 (47–91)	73.9±0.6 (46–89)	73.9±0.3 (45–91)
Clinical diagnosis,* n (%)				
Probable VaD	145 (72.9)	135 (68.2)	145 (70.4)	425 (70.5)
Possible VaD	54 (27.1)	63 (31.8)	61 (29.6)	178 (29.5)
Cardiovascular disease	180 (90.5)	176 (88.9)	182 (88.3)	538 (89.2)
Hypertension	132 (66.3)	143 (72.2)	140 (68.0)	415 (68.8)
Smoking	117 (58.8)	127 (64.1)	130 (63.1)	374 (62.0)
Diabetes	37 (18.6)	32 (16.2)	42 (20.4)	111 (18.4)
Hypercholesterolemia	86 (43.2)	82 (41.4)	83 (40.3)	251 (41.6)
Angina/coronary artery disease	54 (27.1)	55 (27.8)	57 (27.7)	166 (27.5)
Abnormal CT or MRI	195 (98.0)	195 (98.5)	205 (99.5)	595 (98.7)
≥1 stroke or TIA pre-dementia	144 (72.4)	144 (72.7)	147 (71.4)	435 (72.1)
Cortical stroke only	36 (18.1)	44 (22.2)	49 (23.8)	129 (21.4)
Subcortical stroke only	72 (36.2)	65 (32.8)	75 (36.4)	212 (35.2)
White matter lesions only†	35 (17.6)	35 (17.7)	39 (18.9)	109 (18.1)
Multiple lesion locations	45 (22.6)	38 (19.2)	35 (17.0)	118 (19.6)
Minimal lesions	11 (5.5)	16 (8.1)	8 (3.9)	35 (5.8)
Focal signs	152 (76.4)	154 (77.8)	156 (75.7)	462 (76.6)
Focal symptoms	122 (61.3)	117 (59.1)	129 (62.6)	368 (61.0)
Hachinski Ischemia Scale score, mean±SE (range)‡	10.0±0.2 (0–16)	9.8±0.2 (0–17)	10.0±0.2 (3–17)	10.0±0.1 (0–17)
Baseline score, LS mean±SE				
ADAS-cog	20.1±0.7	21.2±0.8	20.9±0.7	...
MMSE	21.7±0.3	21.9±0.3	21.8±0.3	...
CDR-SB	6.1±0.2	6.4±0.2	6.1±0.2	...
ADFACTS	15.9±0.7	17.3±0.8	15.3±0.7	...
CIBIS rating at baseline, n (%)				
Borderline mentally ill	8 (4.0)	10 (5.1)	15 (7.3)	33 (5.5)
Mildly ill	91 (45.7)	87 (43.9)	96 (46.6)	274 (45.4)
Moderately ill	86 (43.2)	71 (35.9)	72 (35.0)	229 (38.0)
Markedly ill	14 (7.0)	26 (13.1)	20 (9.7)	60 (10.0)
Severely ill	0	4 (2.0)	3 (1.5)	7 (1.2)

*By NINDS-AIREN.

†Periventricular and nonperiventricular.

‡Measured at screening.

ment benefit was also observed in the possible VaD group, although conclusions in this subgroup are not robust because of the small sample size (least squares mean change from baseline score effect size at end point: donepezil 5 mg/d, -1.73 , $P=0.07$; donepezil 10 mg/d, -0.94 , $P=0.32$).

Improvement in global function, as assessed by the CIBIC-plus, was observed in a greater proportion of donepezil- than placebo-treated patients in the 5 mg/d group but not in the 10 mg/d group, at week 24 (observed cases) and at end point (Table 2).

Secondary Efficacy Analyses

Significant improvements on the MMSE versus placebo were observed in the donepezil 10 mg/d group at all postbaseline

evaluations and in the donepezil 5 mg/d group at week 18 (observed cases) and at end point (Table 2). Placebo-treated patients demonstrated postbaseline improvements on the MMSE throughout the study.

Results on the CDR-SB demonstrated that overall dementia levels were improved in the donepezil 10 mg/d treatment group compared with placebo at all evaluations, reaching statistical significance at weeks 6 ($P=0.047$), 18 ($P=0.006$), 24 ($P=0.007$), and end point ($P=0.022$) (Table 2). Significant benefits versus placebo were not observed on the CDR-SB in the donepezil 5 mg/d group. After an initial improvement, placebo-treated patients declined below baseline on the CDR-SB at weeks 18 and 24 and at end point.

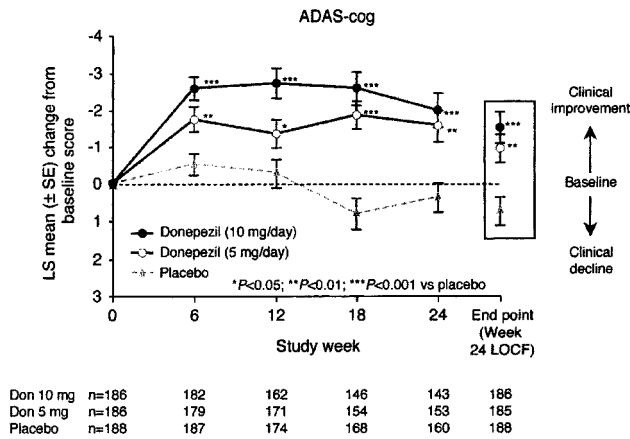


Figure 2. ADAS-cog least squares (LS) mean change from baseline score in donepezil- and placebo-treated patients. Don indicates donepezil.

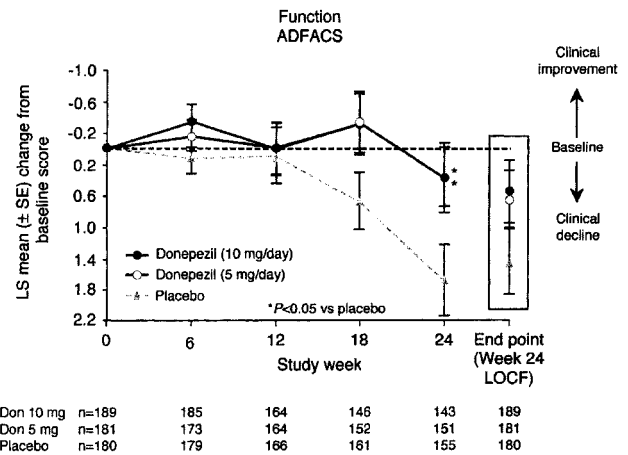


Figure 3. ADFACS least squares (LS) mean change from baseline score in donepezil- and placebo-treated patients. Don indicates donepezil.

Analysis of the ADFACS total scores demonstrated significant functional benefits of donepezil treatment; ADFACS scores in donepezil-treated patients were maintained close to baseline, whereas placebo-treated patients declined (Figure 3 and Table 2). Separate analysis of the ADFACS instrumental ADL (IADL) items also demonstrated significant treatment differences (Table 2).

Safety Analyses

As expected in this patient population, there was a high incidence of adverse events in all treatment groups. The proportion of donepezil-treated patients experiencing

treatment-emergent adverse events was similar to placebo (88.4%) in the 5 mg/d group (88.9%, $P=1.0$) and higher than placebo in the 10 mg/d group (94.7%, $P=0.03$). Generally, adverse events were mild to moderate in intensity, were transient, and resolved without the need to discontinue study medication. The adverse events most commonly reported were those affecting the digestive system, the musculoskeletal system, and the nervous system (Table 3), and the nonserious adverse events most commonly leading to discontinuation were nausea, diarrhea, agitation, and dizziness. A similar number of patients in each group discontinued treat-

TABLE 2. Efficacy Measure Outcomes in Placebo- and Donepezil-Treated Patients at Week 24 LOCF (Primary End Point) and Week 24 Observed Cases

	Week 24 LOCF			Week 24 Observed Cases		
	Placebo n=199	Donepezil		Placebo n=199	Donepezil	
		5 mg/day n=198	10 mg/day n=206		5 mg/day n=198	10 mg/day n=206
CIBIC-plus category, n (%)						
Marked improvement	2 (1.0)	4 (2.0)	3 (1.5)	2 (1.2)	4 (2.5)	3 (2.0)
Moderate improvement	19 (9.8)	13 (6.6)	15 (7.7)	17 (10.5)	11 (6.9)	14 (9.5)
Minimal improvement	37 (19.1)	53 (27.0)	37 (19.0)	33 (20.4)	46 (28.8)	28 (19.1)
No change	76 (39.2)	82 (41.8)	85 (43.6)	60 (37.0)	65 (40.6)	62 (42.2)
Minimal worsening	43 (22.2)	32 (16.3)	47 (24.1)	35 (21.6)	27 (16.9)	35 (23.8)
Moderate worsening	14 (7.2)	9 (4.6)	8 (4.1)	13 (8.0)	6 (3.8)	5 (3.4)
Marked worsening	3 (1.6)	3 (1.5)	0	2 (1.2)	1 (0.6)	0
Change from baseline score, LS mean±SE						
ADAS-cog	0.72±0.40	-0.96±0.39†	-1.52±0.40‡	0.34±0.40	-1.56±0.43†	-1.99±0.45‡
MMSE	0.39±0.23	1.04±0.21*	1.49±0.20‡	0.57±0.24	1.10±0.24	1.53±0.22†
CDR-SB	0.11±0.12	-0.01±0.12	-0.25±0.11*	0.12±0.13	-0.07±0.13	-0.36±0.12†
ADFACTS	1.44±0.42	0.64±0.36	0.53±0.38	1.68±0.46	0.37±0.38*	0.37±0.44*
IADL	0.87±0.32	-0.02±0.25*	0.13±0.27	0.99±0.37	-0.11±0.28*	0.03±0.31*

CIBIC-plus (comparison across all categories): $P<0.05$ for overall donepezil treatment (5 and 10 mg/day) vs placebo, and donepezil 5 mg/day vs placebo, at week 24 observed cases.

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$ vs placebo.

TABLE 3. Adverse Events and Cardiovascular and Cerebrovascular Adverse Events

	Donepezil		
	Placebo n=199	5 mg/day n=198	10 mg/day n=206
≥1 AE, n (%)	176 (88.4)	176 (88.9)	195 (94.7)*
Nausea	14 (7.0)	17 (8.6)	33 (16.0)†
Diarrhea	20 (10.1)	35 (17.7)*	30 (14.6)
Cramps and leg cramps	3 (1.5)	15 (7.6)†	28 (13.6)†
Anorexia	3 (1.5)	11 (5.6)*	17 (8.3)†
Vomiting	6 (3.0)	13 (6.6)	17 (8.3)*
Headache	9 (4.5)	20 (10.1)*	15 (7.3)
Abnormal dreams	4 (2.0)	7 (3.5)	13 (6.3)*
Rhinitis	6 (3.0)	7 (3.5)	14 (6.8)
≥1 cardiovascular AE	36 (18.1)	41 (20.7)	42 (20.4)
Hypertension‡	8 (4.0)	10 (5.1)	11 (5.3)
Syncope	3 (1.5)	4 (2.0)	8 (3.9)
Bradycardia	3 (1.5)	7 (3.5)	3 (1.5)
Hypotension	3 (1.5)	1 (0.5)	3 (1.5)
Stroke	6 (3.0)	8 (4.0)	12 (5.8)
TIA	11 (5.5)	9 (4.5)	3 (1.5)*

Adverse events (AEs) are presented if they occurred in >5% of donepezil-treated patients and at least twice the incidence in the placebo group. Cardiovascular and cerebrovascular AEs are presented if they occurred in >2% of patients, with the exception of hypotension, which is additionally included as it is of particular relevance in this patient population.

* $P < 0.05$, † $P < 0.01$ vs placebo.

‡New onset or worsening.

ment because of stroke (placebo, 4 patients; donepezil 5 mg/d, 4 patients; donepezil 10 mg/d, 6 patients).

Stroke was reported by 6 patients (3.0%) in the placebo group, 8 (4.0%) patients in the donepezil 5 mg/d group, and 12 patients (5.8%) in the 10 mg/d group. Stroke was considered to be unrelated to study medication in all but 2 cases (1 in the donepezil 5 mg/d group and 1 in the 10 mg/d group). Most strokes (placebo, 3 patients; donepezil 5 mg/d, 5 patients; donepezil 10 mg/d, 10 patients) were classified as serious adverse events. Stroke was the most common serious adverse event in the donepezil treatment groups and the second most common serious adverse event (after transient ischemic attack) in the placebo group.

Serious adverse events other than death were reported in 107 patients: 30 (15.1%) in the placebo group, 32 (16.2%) in the donepezil 5 mg/d group, and 45 (21.8%) in the donepezil 10 mg/d group. No apparent treatment effect was associated with the type or incidence of drug-related serious adverse events.

Fifteen patients died during the study or within 4 weeks of discontinuing treatment, of whom 7 (3.5%) were in the placebo group, 2 (1.0%) in the donepezil 5 mg/d group, and 6 (2.9%) in the donepezil 10 mg/d group. Stroke was the cause of death in 3 patients (1 in each treatment group). All deaths were considered by the investigator to be unrelated to

study medication, apart from 1 death (lung carcinoma) in the placebo group.

No clinically meaningful changes from baseline were observed in vital signs, physical examination findings, or ECG status. There were also no clinically meaningful changes from baseline in clinical chemistry, hematology, or urinalysis tests in any of the treatment groups.

Discussion

Donepezil is a beneficial treatment for patients with VaD, defined by NINDS-AIREN criteria, on the basis of this large-scale, international, randomized, double-blind, placebo-controlled clinical trial of donepezil in patients with VaD.

Observations on the ADAS-cog and the MMSE demonstrate that treatment with donepezil 5 or 10 mg/d was significantly more effective than placebo in improving cognition in patients with VaD. Results on the CIBIC-plus, a measure of overall clinical response to treatment, were less conclusive: a significant treatment effect was observed in the donepezil 5 mg/d group but not in the 10 mg/d group. However, treatment with donepezil 10 mg/d was significantly more effective than placebo on other efficacy measures such as the CDR-SB and, importantly, the ADFACS, an assessment of instrumental and basic ADL and a surrogate measure of executive function.²⁰

To determine the efficacy and safety of cholinesterase inhibitors in patients with VaD, it is essential to consider the outcome of treatment in AD and VaD patients separately.²¹ Adherence to the NINDS-AIREN criteria was central to selecting VaD patients and excluding those with AD, and VaD patients enrolled in this and other studies^{13,22–24} differ from patients with AD^{7,8,22} or mixed dementia¹³ with respect to demographics, comorbid conditions, and nature of disease progression. Almost all patients in this study population had a history of clinically evident cerebrovascular or cardiovascular disease, and many had concomitant hypertension, diabetes mellitus, or hypercholesterolemia. Consistent with a diagnosis of VaD, the majority of patients had focal neurological signs, an abrupt onset of dementia, and a history of stepwise cognitive deterioration.²² Placebo-treated VaD patients showed little change from baseline over 24 weeks on both the ADAS-cog and MMSE. CIBIC-plus scores in placebo-treated patients at week 24 were centered on the “no change” category.

Because enrolled patients were required to be stable with respect to comorbid conditions and those with recent or frequent transient ischemic attacks or strokes, major depression, or uncontrolled hypertension or diabetes were excluded, our study population was not typical of all VaD patients. Thus, while longitudinal studies have shown that VaD patients may show rates of cognitive decline similar to those in AD patients over ≥1 year,^{25,26} the populations enrolled in this and other studies^{22–24} represent VaD patients who remain stable for 6 months.

Since the placebo arm did not show decline during this study, it would appear that any progression of underlying vascular disease had little impact on performance. Because vascular disease progression and its (lack of) effect on performance should have been similar among the 3 treatment

groups, benefits in global function were difficult to assess since the active treatment groups were required to show improvement to demonstrate a positive treatment response. Furthermore, any worsening of comorbid conditions, such as recurrent CVD, or adverse events may have masked beneficial treatment effects in VaD patients, particularly in the 10 mg/d group.

Assessment of drug efficacy in VaD patients is still largely dependent on psychometric tools used in, and in some cases specifically designed for, AD trials. However, in contrast to AD patients, those with VaD tend to show early and prominent executive dysfunction,²⁷ for which specific screening tools/efficacy assessments were not widely used when this trial was initiated. If measures that more directly addressed executive dysfunction had been used, it is possible that larger treatment effects would have been identified. In the absence of such tools, a detailed evaluation of ADL, and IADL in particular, may constitute a surrogate measure of executive dysfunction in patients with VaD because executive function is one of the factors thought to influence the ability to perform IADL.²⁰

Cognitive improvements in donepezil-treated patients, as assessed by the ADAS-cog and MMSE, were accompanied by a beneficial effect in IADL/ADL, as measured by the ADFACS. Since stabilization or improvement in IADL is likely to have a significant impact on patient independence and caregiver burden, the changes observed on these psychometric scales could reasonably be expected to translate into real-world clinical benefits. This is consistent with an AD trial in which donepezil increased the "median time to a clinically evident decline in function" by 5 months, compared with placebo, during a 1-year period.¹⁰ Given the functional stabilization observed in the present study, it seems likely that donepezil may exert a similar effect in VaD patients.

Although benefits of a cholinesterase inhibitor in a heterogeneous group predominantly composed of patients with AD plus CVD have been reported by Erkinjuntti et al,¹³ results from large-scale, placebo-controlled trials of cholinesterase inhibitors in patients with VaD, excluding AD patients, have yet to be published. The overall study results presented here suggest that treatment with donepezil is effective in improving cognition and preventing functional deterioration in patients with mild to moderate possible or probable VaD. Furthermore, although the level of statistical significance on the CIBIC-plus is reduced in this study when controlling for multiple comparisons, beneficial effects were seen in other global measures (such as the CDR-SB) that may be less affected by worsening comorbid conditions or adverse events. Significant results in a second, randomized, double-blind trial of identical design to this study (n=616) have also been reported.²⁸ Combined analyses performed on the overall cohort from these 2 trials extend the findings of this study and reveal significant cognitive benefits in donepezil- versus placebo-treated patients in the subgroups of possible VaD and probable VaD.²⁹

Donepezil was well tolerated by VaD patients in this study, despite the prevalence of comorbid cardiovascular disease and high rates of administered concomitant medications. The adverse events that occurred with greater frequency in

donepezil-treated patients were similar to those seen in earlier AD trials⁷⁻¹⁰ as well as the VaD trial with an identical design to this study²⁸ and were consistent with the cholinomimetic action of donepezil. In most cases, adverse events were transient, were mild to moderate in intensity, and rarely resulted in the need to withdraw study medication. The overall rates of treatment-emergent adverse events in both placebo- and donepezil-treated VaD patients were similar to those in the comparable VaD study.²⁸ The higher incidence of adverse events in VaD versus AD trials^{8,9} is likely the result of the significant comorbid medical conditions in the VaD population. Indeed, many adverse events and almost all serious adverse events reported were associated with underlying medical conditions and were considered to be unrelated to study medication.

These data suggest that donepezil offers a safe and effective means of treating VaD. Given the observation that dementia is a significant independent risk factor for reduced survival after ischemic stroke, possibly because of a greater burden of underlying CVD in stroke patients who develop dementia,³⁰ these findings have important implications for the management of patients with VaD. The dose of 5 mg/d is clinically effective, although 10 mg/d may be better in some patients provided that it is well tolerated. Thus, to achieve maximal efficacy the dose may be increased slowly, with careful monitoring for adverse effects.

In summary, this large-scale, randomized, double-blind, placebo-controlled trial demonstrated that, compared with placebo, treatment with donepezil 5 or 10 mg/d produced significant cognitive and functional benefits in patients with probable and possible VaD. Donepezil was also well tolerated in this population. Despite the limitations of using AD psychometric tools, this study nonetheless provides a good indication of the potential benefits to be gained from the use of donepezil in VaD patients. As this and another large-scale trial with an identical design have shown,²⁸ donepezil is an effective symptomatic treatment for VaD.

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References

- Dubois MF, Hebert R. The incidence of vascular dementia in Canada: a comparison with Europe and East Asia. *Neuroepidemiology*. 2001;20:179-187.
- Jorm AF. Cross-national comparisons of the occurrence of Alzheimer's and vascular dementias. *Eur Arch Psychiatry Clin Neurosci*. 1991;240:218-222.
- Román GC. Vascular dementia revisited: diagnosis, pathogenesis, treatment, and prevention. *Med Clin North Am*. 2002;86:477-499.
- Tohgi H, Abe T, Kimura M, Saheki M, Takahashi S. Cerebrospinal fluid acetylcholine and choline in vascular dementia of Binswanger and multiple small infarct types as compared with Alzheimer-type dementia. *J Neural Transm*. 1996;103:1211-1220.
- Swartz RH, Sahlas DJ, Black SE. Strategic involvement of cholinergic pathways and executive dysfunction: does location of white matter signal hyperintensities matter? *J Stroke Cerebrovasc Dis*. 2003;12:29-36.
- Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry*. 1999;66:137-147.
- Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology*. 1998;50:136-145.
- Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, Rogers SL, Friedhoff LT. The effects of donepezil in Alzheimer's disease: results from a multinational trial. *Dement Geriatr Cogn Disord*. 1999;10:237-244.
- Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, Wetterholm AL, Zhang R, Haglund A, Subbiah P. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology*. 2001;57:489-495.
- Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, Pratt RD. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology*. 2001;57:481-488.
- McRae T, Knopman D, Duttagupta S, Ieni J, Provenzano G. Donepezil delays time to nursing home placement in patients with Alzheimer's disease. *J Am Geriatr Soc*. 2001;49:S132(P385). Abstract.
- Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology*. 2001;57:613-620.
- Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet*. 2002;359:1283-1290.
- Hénon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. Post-stroke dementia: incidence and relationship to prestroke cognitive decline. *Neurology*. 2001;57:1216-1222.
- Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250-260.
- Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
- Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356-1364.
- Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg B, Schmitt FA, Grundman M, Thomas RG, Ferris SH. Validity and reliability of the Alzheimer's Disease Cooperative Study: clinical global impression of change. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 2):S22-S32.
- Berg L. Clinical Dementia Rating (CDR). *Psychopharmacol Bull*. 1988;24:637-639.
- Boyle PA, Cohen RA, Paul R, Moser D, Gordon N. Cognitive and motor impairments predict functional declines in patients with vascular dementia. *Int J Geriatr Psychiatry*. 2002;17:164-169.
- Schneider LS. Galantamine for vascular dementia: some answers, some questions. *Lancet*. 2002;359:1265-1266.
- Kittner B, De Deyn PP, Erkinjuntti T. Investigating the natural course and treatment of vascular dementia and Alzheimer's disease: parallel study populations in two randomized, placebo-controlled trials. *Ann N Y Acad Sci*. 2000;903:535-541.
- Orgogozo JM, Rigaud AS, Stoffler A, Mobius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). *Stroke*. 2002;33:1834-1839.
- Pratt RD. Patient populations in clinical trials of the efficacy and tolerability of donepezil in patients with vascular dementia. *J Neurol Sci*. 2002;203-204:57-65.
- Ballard C, O'Brien J, Morris CM, Barber R, Swann A, Neill D, McKeith I. The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia and Alzheimer's disease. *Int J Geriatr Psychiatry*. 2001;16:499-503.
- Small BJ, Viitanen M, Winblad B, Backman L. Cognitive changes in very old persons with dementia: the influence of demographic, psychometric, and biological variables. *J Clin Exp Neuropsychol*. 1997;19:245-260.
- Román GC, Royall DR. Executive control function: a rational basis for the diagnosis of vascular dementia. *Alzheimer Dis Assoc Disord*. 1999;13(suppl 3):S69-S80.
- Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, Kertesz A, Pratt RD. Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology*. 2003;61:479-486.
- Salloway S, Pratt R, Perdomo C. Donepezil improves cognition both in patients with probable and those with possible vascular dementia. *Eur J Neurol*. 2002;9(suppl 2):192(P3114). Abstract.
- Desmond DW, Moroney JT, Sano M, Stern Y. Mortality in patients with dementia after ischemic stroke. *Neurology*. 2002;59:537-543.

Editorial Comment

How to Treat Vascular Dementia?

In clinical practice, we deal with a great proportion of elderly people. Many times, we are able to identify cognitive deficits (although not too scarce, we overlook dementia in our patients). However, the further division into the several subtypes of dementing disorders may be complicated and laborious for patients, caregivers, and physicians due to noncompliance, incomplete clinical history, or missing medical equipment. Moreover, considerable clinical overlap makes treatment decisions difficult. So the good news, presented by Black et al in this issue,¹ is that the 3 most common forms of dementia—Alzheimer's disease (AD), vascular dementia (VaD), and dementia with Lewy bodies—do have a common effective treatment schedule: acetylcholinesterase inhibitors (ACEI). Although their efficacy is, indeed, not overwhelming and a considerable proportion of patients will not profit by this medication, they still represent a ray of hope in the sad story of dementia treatment.

In the 1960s, it was widely recognized that AD was responsible for most cases of dementia in the elderly and that cerebral arteriosclerosis was a rare cause of dementia.² A decade later, research found out that some people develop dementia not due to arteriosclerosis of brain vasculature but rather as a consequence of a series of strokes, affecting different brain regions, and the term *multi-infarct dementia* was introduced.³ In the 1990s, it also became clear that several other mechanisms (ischemic white matter lesions, lacunes) may underlie vascular damage to the brain, which culminates in cognitive decline; therefore, the broader term *vascular dementia* was accepted⁴ and recognized as the second most common cause of dementia. However, as things are going on, separate paths merge sometimes later on. The association between AD and VaD has recently turned out to be more complex. Both AD and VaD increase in prevalence with age; they frequently occur concomitantly; and considerable overlaps are seen in their symptomatology, pathophysiology, and comorbidity.⁵ Many patients show a combination of degenerative brain changes of the AD type along with evidence of strokes. One or two lacunes in elderly subjects with AD changes in the brain increase 20 times the risk of clinical expression of dementia.⁶ Moreover, MRI scans show the high frequency of vascular changes in older people with all forms of dementia. These similarities can on the one hand give reason to some (rather courageous) authors to propose that AD should be classified as a vascular disorder,⁷ and on the other hand explain somehow that AD and VaD both respond to ACEI.

Interestingly, there is growing evidence for the involvement of the cholinergic system in VaD, as is the case in AD. Spontaneously hypertensive stroke-prone rats display a number of symptoms characteristic of patients with VaD, such as cognitive impairment and marked behavioral changes.⁸ Studies in this animal model for VaD demonstrated significant

reductions in the levels of acetylcholine and choline in the cortex, hippocampus, and CSF.⁹ In humans, postmortem studies have shown that compared with controls, patients with VaD have decreased brain choline acetyltransferase activity (a marker of acetylcholine synthesis) in the cortex, hippocampus, and striatum.¹⁰ This suggests that there is a general degeneration of cholinergic neurotransmission in VaD and would explain the therapeutic effect of ACEI. Compared with controls, patients with VaD have significantly lower postmortem CSF acetylcholine concentrations.¹¹

Black and colleagues present a well-designed study of 603 patients with VaD (70% probable, 30% possible VaD) treated with 5 or 10 mg donepezil or placebo for 6 months,¹ most of them (>80%) in combination with antithrombotics for stroke prevention. A total of 478 patients completed the study, thus representing the largest clinical trial on VaD so far. Five cognitive tests were performed on 5 different study points, analyzed in 2 different modes. The results are no reason to get euphoric. The authors found improvement in some items of cognition and global function after half a year of treatment, whereas other items did not improve (interestingly, some items improved with 5 mg but failed to do so with the double dose). Anyway, no item deteriorated under donepezil, but this may be explained by the antithrombotic medication, as deterioration is lacking in the placebo group as well. It has to be counted as shortcoming of the study that the study was not powered for a subgroup analysis. It would be essential to know which subtype of VaD responds to inhibition of the acetylcholinesterase (not solely, but also from an economic point of view), and this question should be clarified by the next trials to reduce the immense number needed to treat.

Donepezil, rivastigmine, and galantamine are the first-line choices in the treatment of mild to moderate AD and dementia with Lewy bodies, although the treatment is only effective in about half of the patients for whom it is prescribed. This might be due to their lack of hepatotoxicity, ease of administration, few significant drug-drug interactions, and mild to moderate side effects. Moreover, there are few contraindications to the use of ACEI. For this reason, they have the potential to evolve to the first-line treatment in VaD as well (in combination with antithrombotics), as comparable results to Black's data were published for galantamine in a similarly designed trial,^{12,13} and there are positive open-label data available on rivastigmine.¹⁴ After analyzing the available randomized, double-blind, placebo-controlled trials, most other treatment options available today show a clearly lower level of evidence: a potential therapeutic role for pentoxifylline,¹⁵ posatirelin,¹⁶ vincamine,¹⁷ naftidrofuryl,¹⁸ and propentofylline¹⁹ in VaD cannot be ruled out; the evidence for a beneficial effect of vinpocetine,²⁰ denbufylline,²¹ sulodexide,²² nicergoline,²³ and nimodipine²⁴ is inconclusive and

does not support clinical use; and there seems to be no therapeutic effect of *Ginkgo biloba* on VaD.²⁵

So how to treat our patients with VaD? There definitely seems to be benefit with the *N*-methyl-D-aspartate receptor antagonist memantine^{26,27}—a drug that acts on the glutamatergic system rather than the cholinergic system. Its benefit seems to be at least comparable to the effect of ACEI. No study ever has combined those 2 substances in VaD, although the mechanism of action is very different, but—wouldn't some of us treat our relatives with this combination, if they turned out to suffer from VaD?

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References

- Black S, Roman G, Geldmacher DS, Salloway S, Hecker J, Burns A, Perdomo CA, Kumar D, Pratt RD. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke*. 2003;34:2323–2332.
- Korczyn AD, Roman GC, Bornstein NM. Vascular dementia. *J Neurol Sci*. 2002;1:203–204.
- Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia: a cause of mental deterioration in the elderly. *Lancet*. 1974;2:207–210.
- Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250–260.
- Kalaria R. Similarities between Alzheimer's disease and vascular dementia. *J Neurol Sci*. 2002;203–204:29–34.
- Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. *JAMA*. 1997;277:813–817.
- de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. *Stroke*. 2002;33:1152–1162.
- Grantham C, Geerts H. The rationale behind cholinergic drug treatment for dementia related to cerebrovascular disease. *J Neurol Sci*. 2002;203–204:131–136.
- Kimura S, Saito H, Minami M, Togashi H, Nakamura N, Nemoto M, Parvez HS. Pathogenesis of vascular dementia in stroke-prone spontaneously hypertensive rats. *Toxicology*. 2000;153:167–178.
- Gottfries CG, Blennow K, Karlsson I, Wallin A. The neurochemistry of vascular dementia. *Dementia*. 1994;5:163–167.
- Tohgi H, Abe T, Kimura M, Saheki M, Takahashi S. Cerebrospinal fluid acetylcholine and choline in vascular dementia of Binswanger and multiple small infarct types as compared with Alzheimer-type dementia. *J Neural Transm*. 1996;103:1211–1220.
- Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet*. 2002;359:1283–1290.
- Erkinjuntti T, Kurz A, Small GW, Bullock R, Lilienfeld S, Damaraju CV. An open-label extension trial of galantamine in patients with probable dementia and mixed dementia. *Clin Ther*. 2003;25:1765–1782.
- Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia: an open 22-month study. *J Neurol Sci*. 2002;203–204:141–146.
- Sha MC, Callahan CM. The efficacy of pentoxifylline in the treatment of vascular dementia: a systematic review. *Alzheimer Dis Assoc Disord*. 2003;17:46–54.
- Parnetti L, Ambrosoli L, Agliati G, Caratozzolo P, Fossati L, Frattola L, Martucci N, Murri L, Nappi G, Puca FM, et al. Posatirelin in the treatment of vascular dementia: a double-blind multicentre study vs placebo. *Acta Neurol Scand*. 1996;93:456–463.
- Fischhof PK, Moslinger-Gehmayr R, Herrmann WM, Friedmann A, Russmann DL. Therapeutic efficacy of vincamine in dementia. *Neuropsychobiology*. 1996;34:29–35.
- Moller HJ, Hartmann A, Kessler C, Rainer M, Brown T, Gamand S, Leher P. Naftidrofuryl in the treatment of vascular dementia. *Eur Arch Psychiatry Clin Neurosci*. 2001;251:247–254.
- Frampton M, Harvey RJ, Kirchner V. Propentofylline for dementia. *Cochrane Database Syst Rev*. 2003;CD002853.
- Szatmari SZ, Whitehouse PJ. Vinpocetine for cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2003;CD003119.
- Treves TA, Korczyn AD. Denbufylline in dementia: a double-blind controlled study. *Dement Geriatr Cogn Disord*. 1999;10:505–510.
- Parnetti L, Mari D, Abate G, Balestreri R, Cucinotta D, Coppola R, Cherubini A, Ferrari P, Senin U. Vascular Dementia Italian Sulodexide Study (V.A.D.I.S.S.): clinical and biological results. *Thromb Res*. 1997;87:225–233.
- Saletu B, Paulus E, Linzmayer L, Anderer P, Semlitsch HV, Grunberger J, Wicke L, Neuhold A, Podreka I. Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: a double-blind, placebo-controlled, clinical and EEG/ERP mapping study. *Psychopharmacology (Berl)*. 1995;117:385–395.
- Lopez A, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. *Cochrane Database Syst Rev*. 2001;1.
- van Dongen M, van Rossum E, Kessels A, Sielhorst H, Knipschild P. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. *J Clin Epidemiol*. 2003;56:367–376.
- Wilcock G, Mobius HJ, Stoffler A. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *Int Clin Psychopharmacol*. 2002;17:297–305.
- Orgogozo JM, Rigaud AS, Stoffler A, Mobius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). *Stroke*. 2002;33:1834–1839.