REVIEW

Use of Antidementia Agents in Vascular Dementia: Beyond Alzheimer Disease

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Vascular dementia (VaD) is the second leading cause of dementia and is often underdiagnosed. Stroke is the leading cause of VaD, although it may also develop secondary to a variety of other cerebrovascular or cardiovascular conditions. Currently, no drugs are approved for the treatment of VaD. However, because cholinergic deficits have been found in patients with VaD, similar to those found in patients with Alzheimer disease (AD), it is believed that cholinesterase inhibitors, which are indicated for the treatment of mild to moderate AD, may also provide benefit for patients with VaD. Clinical trials of donepezil, galantamine, and rivastigmine have supported this idea, although as yet, large-scale, prospective studies in VaD have only been reported for donepezil. Donepezil was shown to provide benefits in cognition, global function, and activities of daily living compared with placebo. The N-methyl-D-aspartate receptor antagonist memantine may also provide some cognitive benefit in VaD, particularly in patients with more advanced disease. These data suggest that antidementia drugs currently used for treatment of AD should be considered for treatment of VaD as well.

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AD = Alzheimer disease; ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADL = activities of daily living; ChEI = cholinesterase inhibitor; CIBIC-Plus = Clinician's Interview–Based Impression of Change–Plus caregiver input; CVD = cerebrovascular disease; IADL = instrumental activities of daily living; NINDS-AIREN = National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences; OL = open-label; VaD = vascular dementia

Vascular dementia (VaD) is the second most common form of dementia after Alzheimer disease (AD) and accounts for approximately 10% to 20% of dementia cases worldwide. Together AD, VaD, or a combination of both may account for up to 90% of all diagnosed dementia cases,[1] whereas Lewy body dementia alone or in combination with AD may be responsible for up to 15% to 25% of cases.[2]

Vascular dementia is a clinical syndrome of cognitive decline caused by ischemic, hemorrhagic, or oligemic injury to the brain as a consequence of cardiovascular disease or cerebrovascular disease (CVD).[3] Subcortical ischemic VaD is a common form caused by small-vessel occlusions with multiple lacunas and by hypoperfusive lesions from resultant stenosis of medullary arterioles. Vascular dementia forms part of a spectrum of vascular cognitive impairment that also includes cognitive impairment with no dementia and mixed AD with vascular disease.[4] Thus, vascular conditions may be the primary factor in the development of dementia but can also exacerbate existing dementia.[5]

Age is the predominant risk factor for poststroke VaD, the most common form of VaD.[6,7] Each year, approximately 750,000 Americans, most of whom are older than 65 years, experience a stroke (Figure 1)[8]; between 35% and 62% of the survivors develop some level of cognitive impairment within 3 months.[6,9]

Approximately 125,000 new cases of VaD occur after ischemic stroke each year in the United States.[3] Another 26% of patients may develop at least some degree of cognitive impairment after heart failure.[10] More than 1 million elderly people in the United States may be affected by VaD, many cases of which go undiagnosed.[3] Thus, VaD may be the most underrecognized and undertreated form of dementia in elderly patients.[11]

Although the loss of brain tissue after recurrent stroke has long been recognized as a causative factor, it has become apparent that the once common description of VaD as multi-infarct dementia is an oversimplification. In fact, VaD can result from a variety of conditions that compromise the cerebral vasculature, including multiple large infarcts, single strategic infarcts, small vessel disease, hypoperfusion, and hemorrhage. Thus, VaD has a diverse and complex pathology, which is aggravated by the effects of aging, hypertension, diabetes, cardiac arrhythmias, or congestive heart failure, all of which can weaken vascular integrity and increase the likelihood of cognitive loss.[3,11,12]

CLINICAL DIAGNOSTIC FEATURES OF VAD

Both VaD and AD share many similarities in symptoms, risk factors, and pathologic features, which can make differential diagnosis difficult (Table 1).[13] To date, effective clinical criteria for diagnosis of VaD remain elusive. This limita-

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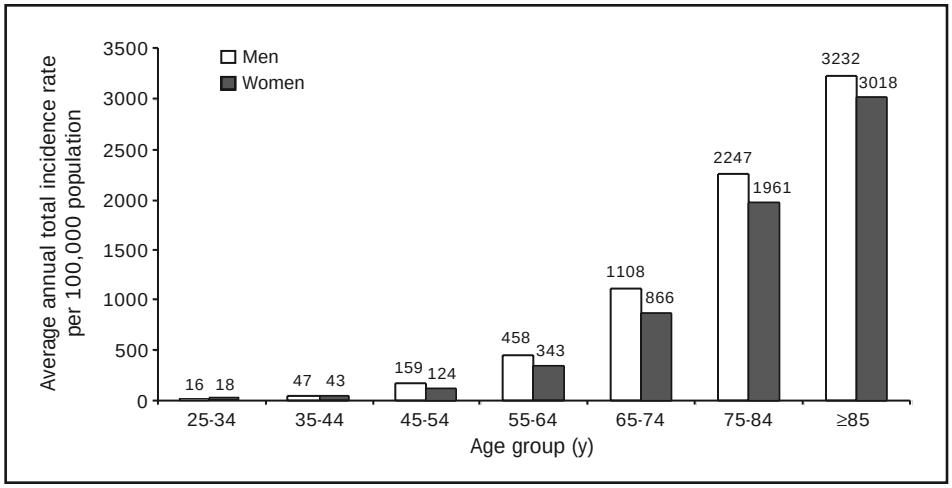

FIGURE 1. Increasing incidence of stroke with age. From *Stroke*,[8] with permission from Lippincott Williams and Wilkins.

tion clearly impedes clinical progress and affects accurate interpretation of reported clinical findings. However, dementia after stroke is common and has proved to be valid as a diagnostic marker.[9] According to the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, developed at a workshop that involved an international panel of neurologists and neuroscientists,[14] a diagnosis of probable VaD is made if dementia is associated with focal neurologic signs and imaging evidence of CVD is present (Table 2).

Some key differences exist between dementia of vascular origin and that of AD. The onset of VaD is often sudden, occurring after a transient ischemic attack or a stroke, after which the clinical course may be static, remitting, or progressive, often with a fluctuating or stepwise deterioration.[12] In contrast, the onset of AD is invariably gradual and typically affects memory to a greater extent in early stages.[13] On the other hand, whereas multiple strokes that affect the large cerebral arteries or single strategic strokes that affect a crucial part of the brain (eg, the thalamus or angular gyrus) usually result in the acute onset of symptoms in VaD, ministrokes that affect the small vessels in the subcortical regions of the brain can produce gradual onset and slower progression of symptoms, reminiscent of AD.[3,12] Nevertheless, the possibility of VaD should be considered in any patient who presents with recent-onset dementia and a history of risk factors for CVD.

TABLE 1. **Key Differential Diagnostic Features of Vascular Dementia (VaD)[12-14]**

Features typical of a classic presentation of VaD
Nocturnal confusion and wandering
Preservation of emotional responsiveness and personality
Depression
Emotional lability
Incontinence
Somatic symptoms
Visuospatial dysfunction
Dysphasia
Cognitive slowing
Impairment of executive function
Focal neurologic symptoms (eg, visual disturbances, brainstem abnormalities, sensory or motor symptoms) and signs (eg, hemiparesis, visual field defects, pseudobulbar palsy, extrapyramidal signs)
Features that exclude a diagnosis of VaD
Early onset of memory deficit
Progressive decline of memory deficit and other cognitive functions (eg, language, motor skills, and perception) without focal lesions
Absence of cerebrovascular lesions on brain imaging

VaD AND AD: DEFINING OVERLAPS AND DISTINCTIONS

Both VaD and AD share certain vascular risk factors (hypertension, peripheral artery disease, some cardiovascular disorders, diabetes mellitus, and smoking), indicating that similar mechanisms may be involved in disease pathogenesis. Potential mechanisms include breach of the blood-brain barrier, apolipoprotein E polymorphism, oxidative stress, angiotensin derangements, apoptosis, neurotransmitter abnormalities, and psychological stress.[13]

It is well established that the progression of AD is accompanied by a decline in cholinergic neurotransmission.[15-17] The extent of cholinergic dysfunction in patients with AD is correlated with the level of cognitive impairment,[18,19] and this is the rationale behind the use of cho-

TABLE 2. **Features Required for a Diagnosis of Vascular Dementia[3,13,14]**

Clinical feature	Test
Dementia, defined as decline in cognitive functioning that causes impaired functioning in daily life in ≥2 cognitive domains (eg, orientation, attention, language, visuospatial functions, executive functions, motor control, praxis)	Clinical examination Neuropsychological testing
Cerebrovascular disease, defined by the presence of focal signs on examination (eg, weakness, sensory loss, exaggerated reflexes, Babinski sign, visual field defects, pseudobulbar palsy, incontinence) *and* evidence of cerebrovascular disease on brain imaging	Neurologic examination Computed tomography or magnetic resonance imaging
Relationship between the onset of dementia and cerebrovascular disease, inferred by onset of dementia within 3 mo of a recognized stroke and/or abrupt deterioration in cognitive functions or fluctuating stepwise progression of cognitive deficits	Thorough and careful history taking The view of someone close to the patient can be helpful

linesterase inhibitors (ChEIs) to improve cognitive function in patients with AD.

Similar neurotransmitter deficits have been found in patients with VaD. Low levels of acetylcholine have been found in the cerebrospinal fluid of patients with VaD, and the levels are inversely correlated with the severity of dementia.[20] Lesions of cholinergic pathways have also been observed in VaD.[21] Therefore cholinergic deficits may be a common feature of the cognitive impairment seen in both AD and VaD.

Beyond the stated similarities, VaD and AD are conditions that are distinguishable in the clinic based on inherent differences in onset and progression.[13] Main points of differentiation include memory, executive function, and gait.[13]

MANAGEMENT AND PREVENTION OF VaD: A ROLE FOR ChEIs?

There are currently no agents licensed in the United States for the treatment of the symptoms of VaD. Management of VaD focuses on preventing strokes by reducing cerebrovascular risk factors, especially among patients in high-risk groups such as elderly patients; those with hypertension, diabetes, atrial fibrillation, previous transient ischemic attack, or stroke; and smokers (Table 3).[12]

The possibility that a cholinergic deficit may contribute to the cognitive symptoms seen in VaD has prompted the investigation of antidementia agents such as ChEIs as potential symptomatic treatments for patients with this type of dementia. Important measures of the clinical effectiveness of an antidementia drug in AD or VaD are its effects on cognition and global functioning. In addition, VaD often affects executive functioning (an interrelated set of abilities that includes cognitive flexibility, concept formation, and self-monitoring) early in the disease[13]; thus, in studies of patients with VaD, their ability to perform everyday tasks dependent on executive functioning is monitored.

Substantial clinical evidence exists regarding risk factors for the prevention of VaD. The main modifiable risk factors for VaD are hypertension, cardiac abnormalities, smoking, lipid abnormalities, diabetes mellitus, and elevated homocysteine levels.[13]

The potential of the ChEIs donepezil, rivastigmine, and galantamine and of the N-methyl-D-aspartate receptor antagonist memantine for improving symptoms has been investigated in a number of studies in populations of patients with pure VaD and also in studies including those with AD and CVD.[22-34] The strength of the conclusions that can be drawn from these studies varies with several factors that will be discussed herein.

FACTORS THAT AFFECT CLINICAL TRIALS

Study design is a major factor that influences the results of clinical trials. Randomized, double-blind, placebo-controlled trials are considered to produce the highest standard of evidence. In contrast, nonrandomized or open-label (OL) studies may be subject to bias and may lack appropriate comparators.

Another factor to consider is the measures used for comparison. The use of more widely accepted measures, and even multiple tests evaluating the same modality, maximizes the chance of a valid measurement and enhances the possibility for comparisons with other studies.

The analytical techniques in clinical studies are also important. For example, last observation carried forward

TABLE 3. **Typical Strategies for Primary Prevention of Vascular Dementia Through Reduction of Cerebrovascular Risk Factors**

Treat hypertension and diabetes optimally
Control hyperlipidemia with statins
Persuade patients to stop smoking and reduce alcohol consumption
Prescribe anticoagulants for atrial fibrillation
Prescribe antiplatelet therapy and aspirin to reduce the risk of recurrent stroke and ischemic attack
Perform carotid endarterectomy for severe (>70%) carotid stenosis
Use dietary control for diabetes, obesity, and hyperlipidemia
Recommend lifestyle changes (eg, weight loss, exercise, stress reduction, decreased salt intake)
Provide intensive rehabilitation after stroke

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analysis is a technique that replaces missing patient values at a given time point with the most recent available value. Thus, any measured improvements attributed to a drug at a given time point are likely to be conservatively estimated. In contrast, observed case analyses omit data from patients who are not participating at the end of the assessment period and may selectively omit patients who withdrew from the study because of a lack of response.

COMMONLY USED INSTRUMENTS IN CLINICAL TRIALS

The Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog),[35] or variations of this instrument, is widely used to detect improvements in cognitive function in clinical trials of dementia.[36] The Mini-Mental State Examination[37] is used most frequently in inclusion criteria and secondarily as a measure of cognitive change.

The overall clinical response to treatment is commonly evaluated using the Clinician's Interview–Based Impression of Change–Plus caregiver input (CIBIC-Plus). This global function instrument assesses cognition, function, behavior, and activities of daily living (ADL) in general by patient and caregiver interviews.[36] Another commonly used test is the Clinical Dementia Rating–Sum of the Boxes,[38] which sums the ratings from 6 boxes of the Clinical Dementia Rating (memory, orientation, judgment, community affairs, home/hobbies, and personal care).

The ADL are often categorized into basic, such as dressing, washing, and personal grooming, or instrumental (IADL), such as telephoning, shopping, food preparation, and housekeeping. These are usually assessed by a caregiver using one of a number of available scoring systems that assign points to specific tasks. Some instruments, such as the Alzheimer's Disease Functional Assessment and Change Scale[39] and the Disability Assessment for Dementia,[40] have scales that include basic and instrumental ADL, thus allowing their use across a spectrum of disease severity. In these scales, IADL measures are reasonable indicators of the level of executive function.

DONEPEZIL

Donepezil is a piperidine-class compound that selectively inhibits acetylcholinesterase in the brain.[41] It is well tolerated and, in patients with AD, has been shown to produce significant benefits in cognition, global function, behavior, and ADL across the continuum of disease severity.[39,42-46]

Donepezil at dosages of 5 or 10 mg/d has been investigated for the treatment of VaD in 2 randomized, double-blind, placebo-controlled, 6-month trials that involved more than 600 patients each.[22,23] Stringent criteria were used in these studies, with all patients having probable or possible VaD meeting NINDS-AIREN criteria[14] of more than 3 months' duration and radiologic or clinical evidence of CVD; patients with a diagnosis of mixed dementia or of AD dementia were excluded.

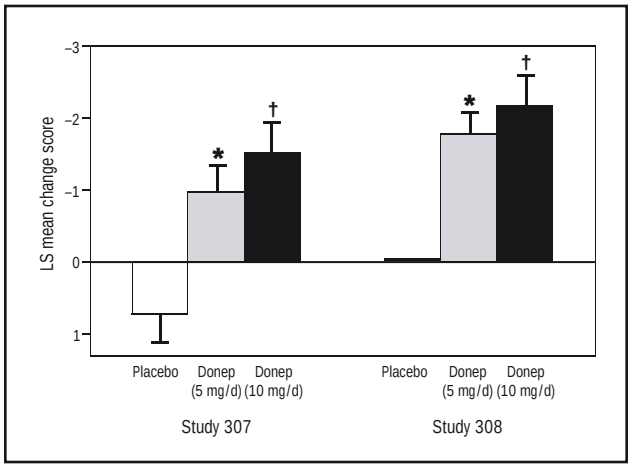

FIGURE 2. Least squares (LS) mean change scores (last observation carried forward) at week 24 on the Alzheimer's Disease Assessment Scale–cognitive subscale in studies 307 and 308.[22,23] Error bars indicate 95% confidence intervals. Donep = donepezil; * = $P<.01$; † = $P<.001$.

Both studies showed that, compared with placebo-treated patients, donepezil-treated patients had statistically significant dose-related improvements in cognitive function, as measured by change in the ADAS-cog score (Figure 2).[22,23] Wilkinson et al[23] also found that a significantly greater proportion of patients in both donepezil-treated groups showed improvements on the CIBIC-Plus than in the placebo group. A similar trend was found on the CIBIC-Plus in the study reported by Black et al[22] but was statistically significant only for the 5-mg/d group. In addition, both studies found that scores on the Clinical Dementia Rating–Sum of the Boxes were significantly improved in the 10-mg/d group compared with the placebo group.

Furthermore, both studies found that donepezil preserved the ability of patients with VaD to perform basic and instrumental tasks.[22,23] The Alzheimer's Disease Functional Assessment and Change Scale scores showed that patients treated with donepezil for 6 months maintained a level of function close to that at baseline, whereas the scores in the placebo-treated patients deteriorated. Although these differences were not statistically significant at study end point, similar trends were also apparent in analyses of the IADL subscale in both studies and were statistically significant for the 5-mg/d group in one study.[22] This finding suggests that executive function was preserved in donepezil-treated patients.

Donepezil was well tolerated, with approximately the same proportion of patients in each group reporting adverse

events in one study[23] and a slightly higher proportion in the 10-mg/d group in the other study.[22] A relatively low proportion of patients in each group withdrew because of adverse events, despite the frequency of comorbid vascular risk factors such as hypertension and diabetes.

Although statistically significant differences at the end point of these studies (week 24 last observation carried forward) were not always realized, this may have been a result of underpowering for some analyses; however, the identical design of these studies has allowed a combined analysis of treatment groups from both studies, and a preliminary report indicated that differences were statistically significant for cognition, global function, and ADL in both donepezil treatment groups compared with placebo.[47]

GALANTAMINE

Galantamine is a ChEI that has demonstrated beneficial effects on cognition, global function, ADL, and behavior in mild to moderate AD.[48-51] Galantamine (24 mg/d) has been evaluated for symptomatic treatment of VaD and AD plus CVD in a 6-month, double-blind, randomized, placebo-controlled study[24] that was followed by a second-phase 6-month OL extension study.[25,26] An interim report of another 24-month extension of this study has been published.[27]

This study had less stringent inclusion criteria and included patients with features of both VaD and AD.[24] Of the 592 patients randomized (galantamine, n=396; placebo, n=196), approximately half were diagnosed as having AD plus CVD and half as having probable or possible VaD only. Two versions of the ADAS-cog were used, including a standard 11-item version (ADAS-cog/11) and a 13-item version also containing comprehension and concentration/distractibility (ADAS-cog/13). At the end of the 6-month, double-blind phase, galantamine-treated patients showed a significant improvement in cognitive function, as measured by both versions of the ADAS-cog, compared with baseline and placebo ($P<.001$).[24] Significantly more galantamine-treated patients than placebo-treated patients also showed improvements in global function as assessed using the CIBIC-Plus ($P=.001$). However, subgroup analyses showed that differences on the ADAS-cog/11 and the CIBIC-Plus were not statistically significant for patients with VaD, and greater treatment differences were seen in the AD plus CVD subgroup, raising the possibility that some of the effects of galantamine in the whole study population resulted from improvements in the AD dementia component. Galantamine treatment was also associated with significant benefits on measures of ADL (Disability Assessment for Dementia, $P=.002$) and behavior (Neuropsychiatric Inventory, $P=.16$). Eight percent of patients given placebo and 20% of patients given galantamine discontinued participation in the study during the double-blind phase of the trial because of adverse events.

After completion of the double-blind phase, 459 patients from both groups (galantamine, n=295; placebo, n=164) entered an OL galantamine treatment phase. After 6 months of OL treatment, initiation of galantamine treatment in the former placebo group raised their ADAS-cog/11 scores to baseline levels.[25] Scores for the continuous galantamine treatment group remained above baseline but were no longer significantly different from those for the former placebo group. The between-group difference in scores on the Disability Assessment for Dementia observed in the double-blind phase was preserved after 6 months of OL treatment,[25] whereas the difference on the Neuropsychiatric Inventory was no longer apparent. Subgroup analyses showed that scores on the ADAS-cog, which had remained at baseline in the former placebo group after 6 months of double-blind treatment, improved to similar levels above baseline at the end of 6 months of OL treatment.[26] In contrast, scores for the group with AD plus CVD, which had significantly declined with placebo treatment and improved with galantamine treatment, were at or below baseline levels at the end of the 6-month OL phase.

These observations have been extended in another 12-month OL extension of the study (18 months total OL treatment).[27] Subanalyses of ADAS-cog scores again confirmed the greater extent of cognitive decline in the AD plus CVD group than in the VaD group, although treatment differences were no longer apparent 18 months after initiation of galantamine treatment in the former placebo group.

Although that study suggests possible benefits of galantamine in VaD, the inclusion of patients with AD plus CVD excluded a prospective analysis of its effects in pure VaD. In fact, the differences found in the subanalyses clearly indicate the importance of distinguishing between these disorders. In addition, no subgroup analyses assessing the efficacy of galantamine on ADL and behavior in the VaD subgroup have yet been reported.

RIVASTIGMINE

Rivastigmine has been found to provide benefits in cognition, global functioning, and ADL in mild to moderate AD.[52,53] Moretti et al[28-32] investigated the effects of rivastigmine in patients with subcortical VaD. A pilot study of 16 patients with subcortical VaD treated with either rivastigmine (3-6 mg/d; n=8) or low-dose aspirin (100 mg/d; n=8) for up to 22 months suggested that rivastigmine provides functional and behavioral benefits.[29,30]

Two larger studies have since reported results in 208 patients followed up for 12 months (rivastigmine vs aspi-

rin[31]) and in 64 patients followed up for 16 months (rivastigmine vs aspirin plus nimodipine[32]). Rivastigmine did not significantly attenuate the cognitive decline observed in the aspirin groups in either study.

A battery of functional ability tests yielded mixed results. For example, rivastigmine-treated patients in both studies showed less deterioration on the Ten Point Clock Drawing test than patients receiving aspirin but no differences on the Phonological Fluency tests.[31,32] The rivastigmine-treated patients in the smaller study showed less deterioration in IADL than those receiving aspirin and nimodipine.[32] Behavioral measures, such as the Behavior Pathology in AD Rating scale,[54] the Geriatric Depression Scale,[55] and the Ryden Aggression Scale,[56] consistently showed improvements in rivastigmine-treated patients compared with declines for the control groups.[31,32]

In these studies, the use of rarely used tests and the omission of more widely accepted tests make it difficult to compare the relative effects of rivastigmine and other ChEIs or to compare the effects of rivastigmine in VaD vs AD. In addition, it is possible that some benefit was conferred by aspirin treatment, thus masking any differences that might have been apparent with a placebo group comparison. These studies were focused on subcortical VaD, and it is unknown whether rivastigmine might provide benefits for patients with cortical VaD, as have been included in trials with other agents.

MEMANTINE

Memantine is an N-methyl-D-aspartate antagonist that has been shown to slow clinical decline in moderate to severe AD,[57] perhaps by inhibiting this glutamate receptor subtype in the brain. The efficacy of memantine, 10 mg/d, on global functioning and cognition was evaluated in a 28-week, randomized, double-blind study of 288 patients with probable VaD defined by the NINDS-AIREN criteria.[33] Although statistically significant drug-placebo differences were not observed for global functioning (CIBIC-Plus scores), differences that favored memantine were observed on the ADAS-cog (P=.002). The effects of memantine on ADAS-cog scores were found to be more pronounced in the more severely afflicted patients. In AD, this may be analogous to the effects of memantine, which is approved for moderate to severe disease but for which no data have been published on milder AD.

Among secondary end points, only the Mini-Mental State Examination showed statistically significant improvement for the memantine group compared with the placebo group. Scores on global assessments, including the Clinical Global Impression of Change and Gottfries-Brane-Steen[58] scales, were not different. Scores for the Nurses Observation Scale for Geriatric Patients,[59] an instrument that measures memory, IADL, self-care, mood, social behavior, and disturbing behavior ratings, also showed no difference between groups.

In a separate 28-week study that involved 579 patients,[34] differences favoring memantine were also found on the ADAS-cog, whereas no difference was found on the Clinical Global Impression of Change scale. No significant differences between groups were found on the Gottfries-Brane-Steen scale or the Nurses Observation Scale for Geriatric Patients, although a difference favoring memantine was found on the memory component of the Nurses Observation Scale for Geriatric Patients. Memantine was well tolerated in both studies, with a frequency of adverse events similar to that associated with placebo.

CONCLUSION

Despite being the second most common form of dementia after AD, with which it shares important pathologic features and symptoms, VaD frequently goes undiagnosed. Although no treatments are currently licensed for the symptomatic treatment of VaD, various antidementia drugs used to treat the symptoms of AD have been evaluated in VaD. The class of agents for which the best evidence exists for therapeutic efficacy is the ChEIs, which target the underlying cholinergic deficit that has been found to be as prominent in VaD as in AD. Donepezil, galantamine, and rivastigmine are ChEIs that have been investigated in patients with VaD or in those with AD and features of VaD. Memantine has also been investigated in patients with VaD, with demonstrated improvement in cognition and no deterioration in global functioning and behavior. Direct comparison of treatment efficacy is not possible because of the different patient populations and different outcome measures in these studies. (See Table 4 for a listing of the most relevant articles.) Of these potential drugs, donepezil has the most compelling efficacy data for ChEI-based treatment in VaD. Studies have demonstrated donepezil's efficacy in improving cognition and global function as well as ADL in patients with pure VaD. Overall, ChEIs appear to be well tolerated in patients with VaD, an important factor for these patients who are often frail and usually require concomitant medications. Although more studies are needed to further define the role of ChEIs in treating symptoms of VaD in patients who meet NINDS/AIREN criteria, it is clear that strategies for prevention should include targeting underlying CVD risk factors.

TABLE 4. **Double-Blind Trials of Cholinesterase Inhibitors in Vascular Dementia**

Reference	Trial
	With donepezil
Black et al,[22] 2003	Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial
Goldsmith & Scott,[60] 2003	Donepezil: in vascular dementia
Johnson,[61] 2004	Donepezil minimally effective for patients with vascular dementia
Malouf & Birks,[62] 2004	Donepezil for vascular cognitive impairment
Mobius et al,[63] 2004	Memantine hydrochloride: pharmacological and clinical profile
Olsen et al,[64] 2005	Drug therapy of dementia in elderly patients: a review
Pratt,[65] 2003	Patient populations in clinical studies of donepezil in vascular dementia
Pratt,[66] 2002	Patient populations in clinical trials of the efficacy and tolerability of donepezil in patients with vascular dementia
Roman et al,[67] 2005	Donepezil in vascular dementia: combined analysis of two large-scale clinical trials
Rossom et al,[68] 2004	Efficacy and tolerability of memantine in the treatment of dementia
Doody,[69] 2003	Update on Alzheimer drugs (donepezil)
Wilkinson et al,[23] 2003	Donepezil in vascular dementia: a randomized, placebo-controlled study
	With galantamine
Bullock et al,[70] 2004	Management of patients with Alzheimer's disease plus cerebrovascular disease: 12-month treatment with galantamine
Bullock,[71] 2004	Galantamine: use in Alzheimer's disease and related disorders
Craig & Birks,[72] 2006	Galantamine for vascular cognitive impairment
Erkinjuntti et al,[25] 2003	An open-label extension trial of galantamine in patients with probable vascular dementia and mixed dementia
Erkinjuntti et al,[24] 2002	Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial
Kertesz,[73] 2002	Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomized trial
Kurz,[74] 2002	Non-cognitive benefits of galantamine (Reminyl) treatment in vascular dementia
Kurz et al,[27] 2003	Long-term safety and cognitive effects of galantamine in the treatment of probable vascular dementia or Alzheimer's disease with cerebrovascular disease
Marder,[75] 2002	Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomized trial
Olsen et al,[64] 2005	Drug therapy of dementia in elderly patients: a review
Small et al,[26] 2003	Galantamine in the treatment of cognitive decline in patients with vascular dementia or Alzheimer's disease with cerebrovascular disease
	With rivastigmine
Craig & Birks,[76] 2005	Rivastigmine for vascular cognitive impairment
Moretti et al,[77] 2004	Rivastigmine in vascular dementia
Moretti et al,[30] 2002	Rivastigmine in subcortical vascular dementia: an open 22-month study
Roman,[78] 2005	Rivastigmine for subcortical vascular dementia
Vincent & Lane,[79] 2003	Rivastigmine in vascular dementia
Wezenberg et al,[80] 2005	Modulation of memory and visuospatial processes by biperiden and rivastigmine in elderly healthy subjects

REFERENCES

1. Fratiglioni L, De Ronchi D, Agüero-Torres H. Worldwide prevalence and incidence of dementia. *Drugs Aging*. 1999;15:365-375.

2. Perry RH, Irving D, Blessed G, Fairbairn A, Perry EK. Senile dementia of Lewy body type: a clinically and neuropathologically distinct form of Lewy body dementia in the elderly. *J Neurol Sci*. 1990;95:119-139.

3. Román GC. Vascular dementia revisited: diagnosis, pathogenesis, treatment, and prevention. *Med Clin North Am*. 2002;86:477-499.

4. Rockwood K, Howard K, MacKnight C, Darvesh S. Spectrum of disease in vascular cognitive impairment. *Neuroepidemiology*. 1999;18:248-254.

5. 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.

6. Pohjasvaara T, Erkinjuntti T, Vataja R, Kaste M. Dementia three months after stroke: baseline frequency and effect of different definitions of dementia in the Helsinki Stroke Aging Memory Study (SAM) cohort. *Stroke*. 1997; 28:785-792.

7. Breteler MM, Ott A, Hofman A. The new epidemic: frequency of dementia in the Rotterdam Study. *Haemostasis*. 1998;28:117-123.

8. Williams GR, Jiang JG, Matchar DB, Samsa GP. Incidence and occurrence of total (first-ever and recurrent) stroke. *Stroke*. 1999;30:2523-2528.

9. Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. *J Neurol Neurosurg Psychiatry*. 1994;57:202-207.

10. Zuccalà G, Onder G, Pedone C, et al, GIFA-ONLUS Study Group. Hypotension and cognitive impairment: selective association in patients with heart failure. *Neurology*. 2001;57:1986-1992.

11. Román GC. Vascular dementia may be the most common form of dementia in the elderly. *J Neurol Sci*. 2002;203-204:7-10.

12. Sachdev PS, Brodaty H, Looi JC. Vascular dementia: diagnosis, management and possible prevention. *Med J Aust*. 1999;170:81-85.

13. Román GC. Vascular dementia: distinguishing characteristics, treatment, and prevention. *J Am Geriatr Soc*. 2003;51(5, suppl dementia):S296-S304.

14. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250-260.

15. Bartus RT, Dean RL III, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. *Science*. 1982;217:408-414.

16. 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.

17. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann Neurol*. 1981;10:122-126.

18. Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH, Perry RH. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *BMJ*. 1978;2:1457-1459.

19. Shinotoh H, Namba H, Fukushi K, et al. Progressive loss of cortical acetylcholinesterase activity in association with cognitive decline in Alzheimer's disease: a positron emission tomography study. *Ann Neurol*. 2000;48:194-200.

20. 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.

21. 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.

22. Black S, Román GC, Geldmacher DS, et al, Donepezil 307 Vascular Dementia Study Group. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke*. 2003 Oct;34:2323-2330. Epub 2003 Sep 11.

23. Wilkinson D, Doody R, Helme R, et al, Donepezil 308 Study Group. Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology*. 2003;61:479-486.

24. 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.

25. Erkinjuntti T, Kurz A, Small GW, Bullock R, Lilienfeld S, Damaraju CV, GAL-INT-6 Study Group. An open-label extension trial of galantamine in patients with probable vascular dementia and mixed dementia [published correction appears in *Clin Ther*. 2003;25:2336]. *Clin Ther*. 2003;25:1765-1782.

26. Small G, Erkinjuntti T, Kurz A, Lilienfeld S. Galantamine in the treatment of cognitive decline in patients with vascular dementia or Alzheimer's disease with cerebrovascular disease. *CNS Drugs*. 2003;17:905-914.

27. Kurz AF, Erkinjuntti T, Small GW, Lilienfeld S, Damaraju CR. Long-term safety and cognitive effects of galantamine in the treatment of probable vascular dementia or Alzheimer's disease with cerebrovascular disease. *Eur J Neurol*. 2003;10:633-640.

28. Moretti R, Torre P, Antonello RM, Cazzato G. Rivastigmine in subcortical vascular dementia: a comparison trial on efficacy and tolerability for 12 months follow-up [letter]. *Eur J Neurol*. 2001;8:361-362.

29. Moretti R, Torre P, Antonello RM, Cazzato G, Griggio S, Bava A. An open-label pilot study comparing rivastigmine and low-dose aspirin for the treatment of symptoms specific to patients with subcortical vascular dementia. *Curr Therapeut Res*. 2002;63:443-458.

30. 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.

31. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia: a randomized, controlled, open 12-month study in 208 patients. *Am J Alzheimers Dis Other Demen*. 2003;18:265-272.

32. Moretti R, Torre P, Antonello RM, et al. Rivastigmine superior to aspirin plus nimodipine in subcortical vascular dementia: an open, 16-month, comparative study. *Int J Clin Pract*. 2004;58:346-353.

33. Orgogozo J-M, Rigaud A-S, Stöffler A, Möbius H-J, 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.

34. Wilcock G, Möbius HJ, Stöffler A, MMM 500 group. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *Int Clin Psychopharmacol*. 2002;17:297-305.

35. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356-1364.

36. Schneider LS. An overview of rating scales used in dementia research. *Alzheimer Insights* [serial online]. October 1996;2(3):1-7.

37. 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.

38. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140:566-572.

39. Mohs RC, Doody RS, Morris JC, et al, "312" Study Group. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients [published correction appears in *Neurology*. 2001;57:1942]. *Neurology*. 2001;57:481-488.

40. Gélinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: the Disability Assessment for Dementia. *Am J Occup Ther*. 1999;53:471-481.

41. Sugimoto H, Iimura Y, Yamanishi Y, Yamatsu K. Synthesis and structure-activity relationships of acetylcholinesterase inhibitors: 1-benzyl-4-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidine hydrochloride and related compounds. *J Med Chem*. 1995;38:4821-4829.

42. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, Donepezil Study Group. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology*. 1998;50:136-145.

43. Burns A, Rossor M, Hecker J, et al, International Donepezil Study Group. The effects of donepezil in Alzheimer's disease—results from a multinational trial. *Dement Geriatr Cogn Disord*. 1999;10:237-244.

44. Winblad B, Engedal K, Soininen H, et al, Donepezil Nordic Study Group. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology*. 2001;57:489-495.

45. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E, Donepezil MSAD Study Investigators Group. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease [published correction appears in *Neurology*. 2001;57:2153]. *Neurology*. 2001; 57:613-620.

46. Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology*. 2004;63:214-219.

47. Farcnik K, Pratt RD, Perdomo CA, Donepezil 307 and 309 VaD Study Groups. Donepezil provides significant benefits on cognition, global function, and activities of daily living in patients with vascular dementia [abstract]. *Int Psychogeriatr*. 2003;15(suppl 2):256.

48. Raskind MA, Peskind ER, Wessel T, Yuan W, Galantamine USA-1 Study Group. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. *Neurology*. 2000;54:2261-2268.

49. Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C, Galantamine USA-10 Study Group. A 5-month, randomized, placebo-controlled trial of galantamine in AD. *Neurology*. 2000;54:2269-2276.

50. Wilcock GK, Lilienfeld S, Gaens E, Galantamine International-1 Study Group. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial [published correction appears in *BMJ*. 2001;322:405]. *BMJ*. 2000;321:1445-1449.

51. Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D. Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. 2001;71:589-595.

52. Rosler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial [published correction appears in *BMJ*. 2001;322:1456]. *BMJ*. 1999;318:633-638.

53. Farlow M, Potkin S, Koumaras B, Veach J, Mirski D. Analysis of outcome in retrieved dropout patients in a rivastigmine vs placebo, 26-week, Alzheimer disease trial. *Arch Neurol*. 2003;60:843-848.

54. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J Clin Psychiatry*. 1987;48(suppl):9-15.

55. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982-1983;17:37-49.

56. Ryden MB. Aggressive behavior in persons with dementia who live in the community. *Alzheimer Dis Assoc Disord*. 1988;2:342-355.

57. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ, Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348:1333-1341.

58. Gottfries CG, Brane G, Gullberg B, Steen G. A new rating scale for dementia syndromes. *Arch Gerontol Geriatr*. 1982;1:311-330.

59. Spiegel R, Brunner C, Ermini-Fünfschilling D, et al. A new behavioral assessment scale for geriatric out- and in-patients: the NOSGER (Nurses' Observation Scale for Geriatric Patients). *J Am Geriatr Soc*. 1991;39:339-347.

60. Goldsmith DR, Scott LJ. Donepezil: in vascular dementia. *Drugs Aging*. 2003;20:1127-1136.

61. Johnson KD. Donepezil minimally effective for patients with vascular dementia. *J Fam Pract*. 2004;53:181-182.

62. Malouf R, Birks J. Donepezil for vascular cognitive impairment. *Cochrane Database Syst Rev*. 2004;1:CD004395.

63. Mobius HJ, Stoffler A, Graham SM. Memantine hydrochloride: pharmacological and clinical profile. *Drugs Today (Barc)*. 2004;40:685-695.

64. Olsen CE, Poulsen HD, Lublin HK. Drug therapy of dementia in elderly patients: a review. *Nord J Psychiatry*. 2005;59:71-77.

65. Pratt RD. Patient populations in clinical studies of donepezil in vascular dementia. *Int Psychogeriatr*. 2003;15(suppl 1):195-200.

66. 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.

67. Roman GC, Wilkinson DG, Doody RS, Black SE, Salloway SP, Schindler RJ. Donepezil in vascular dementia: combined analysis of two large-scale clinical trials. *Dement Geriatr Cogn Disord*. 2005;20:338-344. Epub 2005 Sep 23.

68. Rossom R, Adityanjee, Dysken M. Efficacy and tolerability of memantine in the treatment of dementia. *Am J Geriatr Pharmacother*. 2004; 2:303-312.

69. Doody RS. Update on Alzheimer drugs (donepezil). *Neurologist*. 2003; 9:225-229.

70. Bullock R, Erkinjuntti T, Lilienfeld S, GAL-INT-6 Study Group. Management of patients with Alzheimer's disease plus cerebrovascular disease: 12-month treatment with galantamine. *Dement Geriatr Cogn Disord*. 2004;17:29-34.

71. Bullock R. Galantamine: use in Alzheimer's disease and related disorders. *Expert Rev Neurother*. 2004;4:153-163.

72. Craig D, Birks J. Galantamine for vascular cognitive impairment. *Cochrane Database Syst. Rev*. 2006;1:CD004746.

73. Kertesz A. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomized trial. *Curr Neurol Neurosci Rep*. 2002;2:503-504.

74. Kurz A. Non-cognitive benefits of galantamine (Reminyl) treatment in vascular dementia. *Acta Neurol Scand Suppl*. 2002;178:19-24.

75. Marder K. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomized trial [editorial]. *Curr Neurol Neurosci Rep*. 2002;2:389-390.

76. Craig D, Birks J. Rivastigmine for vascular cognitive impairment. *Cochrane Database Syst Rev*. 2005 Apr 18;2:CD004744.

77. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in vascular dementia. *Expert Opin Pharmacother*. 2004;5:1399-1410.

78. Roman GC. Rivastigmine for subcortical vascular dementia. *Expert Rev Neurother*. 2005;5:309-313.

79. Vincent S, Lane R. Rivastigmine in vascular dementia. *Int Psychogeriatr*. 2003;15(suppl 1):201-205.

80. Wezenberg E, Verkes RJ, Sabbe BG, Ruigt GS, Hulstijn W. Modulation of memory and visuospatial processes by biperiden and rivastigmine in elderly healthy subjects. *Psychopharmacology (Berl)*. 2005 Sep;181:582-594. Epub 2005 Oct 12.