Emerging Therapies for Vascular Dementia and Vascular Cognitive Impairment

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Background—Cerebrovascular disease (CVD) and ischemic brain injury secondary to cardiovascular disease are common causes of dementia and cognitive decline in the elderly. CVD also contributes to cognitive loss in Alzheimer disease (AD).

Summary—Progress in understanding vascular cognitive impairment (VCI) and vascular dementia (VaD) has resulted in promising symptomatic and preventive treatments. Cholinergic deficits in VaD due to ischemia of basal forebrain nuclei and cholinergic pathways can be treated with cholinesterase inhibitors used in AD. Controlled clinical trials with donepezil and galantamine in patients with VaD, as well as in patients with AD plus CVD, have demonstrated improvement in cognition, behavior, and activities of daily living. The N-methyl-D-aspartate receptor antagonist memantine stabilized progression of VaD compared with placebo. Primary and secondary stroke prevention, in particular with control of hypertension and hyperlipidemia, can decrease VaD incidence.

Conclusions—From a public health viewpoint, recognition of VCI before the development of dementia and correction of vascular burden on the brain may lead to a global decrease of incident dementia.

Key Words: carbamates ■ cognitive disorders ■ dementia ■ galantamine ■ memantine ■ nimodipine ■ piperidines ■ vascular diseases ■ donepezil ■ rivastigmine

Stroke and dementia increase exponentially with aging of the population.1 Less well known is their interplay, whereby stroke may result in vascular cognitive impairment (VCI) and vascular dementia (VaD), but conversely brain ischemia may worsen the cognitive effects of Alzheimer disease (AD) pathology.2–4 Poststroke dementia occurs in up to one third of patients with clinically eloquent ischemic stroke after age 65 years.5 Moreover, MRI-documented silent brain infarcts more than double the risk of dementia in the elderly.6 In addition, in these age groups VCI with no dementia (VCIND) is also common.2–9 With increasing longevity, the damaging effects of cerebrovascular disease (CVD) and heart disease on cognition may become one of the main causes of dementia in the elderly.10

VaD: Terminology and Criteria
Dementia is a syndrome of acquired intellectual deficit resulting in significant impairment of social or occupational functioning. Currently, all diagnostic criteria for dementia are based on AD and require a core amnestic disorder and progressive, irreversible decline, despite the fact that VaD may present with mild memory impairment,11 relatively slow progression, and a subcortical pattern. Historically, VaD is the second most common cause of dementia. Until recently, VaD was termed multi-infarct dementia (MID) or poststroke VaD; it is defined clinically by sudden onset of cognitive decline, stepwise deterioration, and focal neurological findings.12 Hachinski’s ischemic score (HIS)13 is useful in the clinical diagnosis of MID but is less sensitive to VaD and less sensitive still to VCI.13 Not all cases of VaD are represented by MID since subcortical ischemic vascular dementia (SIVD)14 appears to be more common. This subcortical dementia presents with prominent involvement of prefrontal executive functions, apathy, slowing of psychomotor functions, and gait abnormalities; SIVD may result from lacunar strokes and incomplete white matter ischemia.

The concept of VaD has been broadened to encompass all forms of cognitive loss due to CVD, under the nosology of...
The term VCI includes patients with important cognitive and functional impairment without dementia (VCIND), who can have a high rate of adverse outcomes.7,8

**VaD Criteria**

Although their sensitivity and specificity vary, all clinical criteria (HIS, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV], National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l’Enseignement en Neurosciences [NINDS-AIREN], International Statistical Classification of Diseases, 10th Revision [ICD-10], California Alzheimer’s Disease Diagnostic and Treatment Centers [CAD-DTC]) identify patients with VaD.16,19 However, for research or controlled clinical trials in which false-positive cases (usually AD plus CVD) must be excluded, only high-specificity criteria are used, eg, CAD-DTC and NINDS-AIREN. Specificity is usually obtained at the cost of decreased sensitivity18–20 (1) by using a strict diagnosis of dementia and (2) by including brain imaging with confirmation of cerebrovascular pathology. The criteria of the CAD-DTC21 apply exclusively to VaD caused by ischemic CVD, while the criteria of the NINDS-AIREN22 recognize that VaD may result from complete or incomplete brain ischemia, cerebral hemorrhage, and other vascular or circulatory injuries to the brain. Both sets of criteria define dementia following the AD model, and VaD is operationalized following the notion of MID, although the important role of single strategic infarcts is recognized by both sets of criteria. In this way, as argued elsewhere,23 both evolved from the HIS.13 Finally, these 2 sets of VaD criteria rely on neuroimaging by CT or MRI for confirmation of cerebrovascular lesions (although neither requires imaged lesions to correlate with cognitive or functional deficits).

Lesions include both large-vessel and small-vessel ischemia. Large-vessel injuries are multiple either cortical or cortico-subcortical infarcts or single, strategically placed infarcts that occur in areas that are crucial for cognition or behavior (eg, angular gyrus, basal forebrain, thalamus, anterior or posterior cerebral artery strokes). Small-vessel injury is manifested as multiple basal ganglia and white matter lacunae or as extensive white matter lesions or combinations thereof. Patients can have evidence of either large-vessel or small-vessel disease or both.

By excluding cases with prodromal amnestic disorder or mild cognitive impairment before the cerebrovascular injury, the criteria effectively exclude patients with “mixed” dementia, ie, combinations of AD or other degenerative disorders with CVD.24

**Clinical Features and Subtypes of VaD**

**Poststroke VaD**

Poststroke VaD (also termed MID when present after multiple strokes) is characterized by abrupt onset of focal neurological symptoms and signs, along with cortical cognitive impairments such as aphasia, apraxia, or agnosia. MID is relatively uncommon and evolves slowly or in association with silent infarction, with long plateaus between events and day-to-day fluctuations in severity.12 Correlation between infarction and impairment remains imprecise.24

**Single “Strategic” Infarct Dementia**

In 1968, Blessed et al25 concluded that VaD could not occur without <100 cm³ of infarcted brain tissue. However, it is currently recognized that small but strategically located infarcts in thalamus, basal forebrain, or caudate also produce acute-onset VaD.12,17 The clinical features of strategic infarct VaD vary with location of lesions in cortical or subcortical regions. Memory impairment, impaired executive function, confusion, and fluctuating levels of consciousness may occur. Behavioral changes may include apathy, lack of spontaneity, and perseveration.26

**Subcortical Ischemic VaD**

This common form of VaD results from small-vessel disease, causing lacunes and incomplete white matter ischemia.14 Patients with SIVD may respond differently to drug therapy than those with MID; therefore, diagnostic criteria have been proposed.27 Lesions in subcortical VaD tend to injure specific prefrontal subcortical circuits. Clinically, a prominent cognitive feature is the executive dysfunction syndrome, affecting performance in activities of daily living (ADL) as a result of faulty goal formulation, initiation, planning, and organization.28 Abstract thought is also affected, but memory deficits are less severe than in AD. Recognition and cuing effect remain relatively intact. Mood changes with depression, personality changes, and labile emotionality are common. Onset is usually slow and subtle; acute, stroke-like episodes are usually missing. Focal motor signs, gait disorder, urinary urgency, and psychomotor slowing often occur.

**Mixed AD With CVD**

Neuropathological studies indicate that concurrent AD and CVD lesions frequently occur, particularly in the oldest patients.29 This combination is usually termed mixed dementia.30 AD and VaD share risk factors, some clinical features, and pathogenic mechanisms.31,32 CVD appears to play an important role in determining clinical symptoms in AD; for instance, lacunar infarcts reportedly raise the risk of clinical dementia 20-fold in patients with pathology-confirmed AD lesions.2 By damaging frontal circuits, CVD may compound the effect of early hippocampal lesions of AD.32

**Clinical Course**

The cognitive outcome of patients with VaD may be as severe as in AD, but morbidity and mortality are usually worse.33 Survival variability may produce a length bias whereby patients with shorter survival are usually excluded in prevalence surveys.34 However, in clinical trials of VaD the placebo groups have shown little progression of impairment (“stable placebo response”).35 Most likely this is due to exclusion of cases with mixed AD plus CVD. Other explanations include selection bias, placebo effect, and better control of vascular risk factors. Finally, the outcome measures used in VaD trials may be relatively unresponsive to decline.
Primary and Secondary Prevention

Primary prevention aims to reduce incident disease by eliminating its cause or main risk factors. In VaD the target is the person with a “brain at risk” of CVD, before VCI or stroke occurs. The intent is to treat putative vascular risk factors, including arterial hypertension in particular, as well as lipid abnormalities, atrial fibrillation, myocardial infarction, coronary heart disease, diabetes, atherosclerosis, smoking, and hyperhomocysteinemia. Although the effect of primary prevention in populations free of cognitive impairment remains unknown, the Systolic Hypertension in Europe (Syst-Eur) Study demonstrated that treatment of isolated systolic hypertension in the elderly with a calcium channel agent decreased the incidence of dementia significantly.38 Inferences about the positive effects of primary prevention are based on cumulative experience with the treatment of vascular risk factors in the primary prevention of stroke.

In secondary prevention the target is stroke management and prevention,17 including (1) early diagnosis and appropriate treatment of acute stroke; (2) prevention of stroke recurrence; and (3) slowing of progression of brain changes associated with VaD by intensive management of existing risk factors.

Although neuroprotection has been disappointing, there have been significant advances in acute stroke management and in prevention of stroke recurrence. Hypoxic ischemic events during acute stroke (cardiac arrhythmias, congestive heart failure, myocardial infarction, seizures, pneumonia) are important risk factors for incident VaD. However, there is a dearth of knowledge on the effects of secondary prevention of VaD since most trials on acute stroke and secondary stroke prevention studies have failed to evaluate cognition as an end point.

Lipid-lowering agents are important in the secondary prevention of stroke and may protect against dementia. In an animal model, simvastatin inhibited β-secretase and reduced amyloid load. In addition, lovastatin and simvastatin inhibit human butyrylcholinesterase. Further studies and targeted clinical trials will be needed to understand the role of statins in the prevention and treatment of dementia.

In patients with previous stroke, perindopril, an angiotensin-converting enzyme inhibitor, showed a strikingly beneficial effect (usually coupled with the diuretic indapamide) in lowering blood pressure and reducing the risk of dementia and severe cognitive impairment among patients who experienced recurrent stroke.

Treatment Targets and Trial Methods in VaD

Potential targets for treatment of VaD include (1) symptomatic improvement of the core symptoms (cognition, function, and behavior); (2) slowing of progression; and (3) treatment of neuropsychiatric symptoms (eg, depression, anxiety, agitation).88 Current VaD trials have used the same primary outcome measures used in AD trials, as recommended by the US Food and Drug Administration. These instruments include the cognitive portion of the Alzheimer’s Disease Assessment Scale (ADAS-cog), the Clinician’s Interview-Based Impression of Change plus caregiver input (CIBIC-plus), or the Clinical Global Impression of Change (CGIC). The European Commission for Medicinal and Pharmaceutical Compounds (CPMC) also requires positive impact on ADL and a responder analysis. To the extent that ADAS-cog and CIBIC-plus assess the multiple cognitive domains affected in all forms of dementia, including VaD, and have proved to be sensitive in cholinergic AD trials, and since the cholinergic hypothesis is being endorsed in VaD, it is not unreasonable to use the same measures in both patient populations. Recently, Quinn et al51 showed difficulties with CIBIC-plus ratings in instances of clinical improvement. Physicians fail to recognize successful disease treatment beyond reversal of progression. This is likely to be a problem in VaD, as illustrated in a recent memantine trial.52 The ADAS-cog, the primary cognitive outcome measure, was strongly positive, while the CIBIC did not reach significance.

Moreover, current tests are relatively insensitive to frontal/subcortical dysfunction, a key cognitive domain in VaD. Future clinical trials should incorporate tests such as the vascular equivalent of the ADAS-cog, the VaDAS-cog, and others that include formal measurement of executive function. Of interest, ADL are considered a proxy evaluation of executive function. Pohjasvaara et al49 confirmed that executive dysfunction was the main determinant of abnormalities in both basic ADL and instrumental ADL (IADL) in patients with poststroke VaD. Executive function tests, including IADL, may be sensitive tools for the diagnosis of VaD and may accurately measure the effects of potential therapies.

The usefulness of mood and behavioral symptoms and functional abilities as outcome measures in VaD trials remains to be determined. In contrast to AD, in which there are predictable hierarchical losses in ADL in association with cognitive decline, functional losses in VaD may be more discordant. Because of the heterogeneity of subtypes of VaD, functional rates of decline are not well characterized. Separating functional decline due to sequelae of stroke from that evolving from disordered cognitive function may be important. However, the current generation of AD scales does not allow this distinction to be made.

Pharmacotherapy in VaD

Published data on interventions for patients with dementia believed to have a vascular component span several decades. Numerous compounds purported to be useful in the symptomatic treatment of VaD include antithrombotics, ergot alkaloids, nootropics, thyrotropin-releasing hormone analogue, ginkgo biloba extracts, plasma viscosity drugs, hyperbaric oxygen, antioxidants, serotonin and histamine receptor antagonists, vasoactive agents, xanthine derivatives, and calcium antagonists. These studies had mostly negative results, were based on small numbers and short treatment periods, and often included mixed populations and various diagnostic criteria, evaluation tools, and clinical end points. Currently, there is no approved symptomatic treatment of VaD.

The following agents have been studied carefully. Propentofylline, a glial modulator, is no longer under development despite observed beneficial effects on learning and memory in several European and Canadian double-blind,
placebo-controlled, randomized, parallel-group trials\cite{35,59}; most were in patients with mild to moderate VaD according to NINDS-AIREN criteria.\cite{22} Significant symptomatic improvement and long-term efficacy in ADAS-cog and CIBIC-plus were noted up to 48 weeks compared with placebo. In addition, sustained treatment effects for at least 12 weeks after withdrawal suggested an effect on disease progression.\cite{59}

Nimodipine, a dihydropyridine calcium antagonist, has effects on autoregulation of cerebral blood flow, causing vasodilatation without a steal effect, and blocks L-type calcium receptors, providing some degree of neuroprotection. Nimodipine has specific effects on small vessels. A promising open-label trial\cite{60} led to a subgroup analysis of a larger double-blind, placebo-controlled study of nimodipine in VaD.\cite{61,62} Patients were divided between MID and subcortical VaD groups, according to CT findings, and were assessed blindly. Nimodipine had beneficial effects on attention and psychomotor performances in the subcortical group but not in the combined sample.\cite{61,62} Results of an international, multicenter, randomized, double-blind trial in patients with subcortical VaD, defined on a clinical-radiological basis,\cite{27} are awaited with interest. Currently, there is insufficient evidence that nimodipine is a useful symptomatic treatment for VaD.\cite{63}

Memantine is a moderate-affinity, voltage-dependent, non-competitive N-methyl-D-aspartate receptor antagonist with fast receptor kinetics. In a double-blind, placebo-controlled nursing home trial in patients with severe dementia of mixed etiology (51% of patients had VaD), memantine (10 mg/d) was well tolerated, improved function, and reduced care dependency in treated patients compared with placebo.\cite{64} On the basis of the hypothesis of glutamate-induced neurotoxicity in cerebral ischemia, 2 randomized, placebo-controlled 6-month trials (MMM 300/MMM 500)\cite{52,65} studied memantine (20 mg/d) in mild to moderate probable VaD by NINDS-AIREN criteria.\cite{22}

In the MMM 300 study, 147 patients were randomized to memantine and 141 to placebo.\cite{52} After 28 weeks, the mean ADAS-cog scores were significantly improved relative to placebo: the memantine group mean score had gained an average of 0.4 points, whereas the placebo group mean score declined by 1.6, i.e., a difference of 2.0 points ($P=0.0016$). The response rate for CIBIC-plus, defined as improved or stable, was 60% with memantine compared with 52% with placebo ($P=0.227$). The Gottfries-Bråne-Steen (GBS) Scale and the Nurses’ Observation Scale for Geriatric Patients (NOSGER) total scores at week 28 did not differ significantly between the 2 groups. However, the GBS Scale intellectual function subscore and the NOSGER disturbing behavior dimension also showed a difference favoring memantine ($P=0.04$ and $P=0.07$, respectively).\cite{52}

The MMM 500 study randomized 277 patients to memantine and 271 to placebo.\cite{65} At 28 weeks, the active group had gained 0.53 points and the placebo group declined by 2.28 points in ADAS-cog, a significant difference of 1.75 ADAS-cog points between the groups ($P<0.05$). There were no differences in CGIC, Mini–Mental State Examination (MMSE), GBS, or NOSGER scores between groups. Memantine was well tolerated in both studies. In a post hoc pooled subgroup analysis of these 2 studies by baseline severity as assessed by MMSE, the more advanced patients obtained a larger cognitive benefit than did mildly affected patients. Patients with MMSE score $<15$ at baseline showed an ADAS-cog improvement of 3.2 points over placebo.\cite{66} Additionally, the cognitive treatment effect for memantine was more pronounced in the small-vessel type group without cortical infarctions by CT or MRI. In addition, placebo decline of the small-vessel group was clearly more pronounced than in the large-vessel type of VaD.\cite{66}

**Cholinergic Dysfunction and Cholinesterase Inhibitors in VaD**

Cholinergic deficits are well documented in VaD, independently of any concomitant AD pathology.\cite{67} Cholinergic structures are vulnerable to ischemic damage; for instance, basal forebrain cholinergic nuclei are irrigated by penetrating arterioles susceptible to the effects of arterial hypertension; in addition, hippocampal CA1 neurons are particularly vulnerable to experimental ischemia, and hippocampal atrophy is common in patients with VaD in the absence of AD.\cite{66} Selden et al.\cite{69} described 2 highly organized and discrete bundles of cholinergic fibers in human brains that extend from the nucleus basalis to the cerebral cortex and amygdala. Both pathways travel in the white matter and together carry widespread cholinergic input to the neocortex. Localized strokes may interrupt these cholinergic bundles.\cite{70} Mesulam et al.\cite{71} demonstrated cholinergic denervation from pathway lesions, in the absence of AD; in a young patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a pure genetic form of VaD.

In experimental rodent models, such as the spontaneously hypertensive stroke-prone rat, there is a significant reduction in cholinergic markers, including acetylcholine, in the neocortex, hippocampus, and cerebrospinal fluid.\cite{72} In humans, there is loss of cholinergic neurons in 70% of AD cases and in 40% of VaD patients examined neuropathologically, with reduced acetylcholine activity in the cortex, hippocampus, striatum, and cerebrospinal fluid.\cite{73}

Three of the acetylcholinesterase inhibitors approved for use in AD—donepezil, rivastigmine, and galantamine—have also been used in VaD.

**Donepezil**

This piperidine derivative is a reversible central acetylcholinesterase inhibitor currently approved for treatment of mild to moderate AD.\cite{74} The safety and efficacy of donepezil have been studied in the largest clinical trial of pure VaD to date.\cite{75,76} A total of 1219 subjects were recruited for a 24-week, randomized, placebo-controlled, multicenter, multinational study divided into 2 identical trials, 307\cite{77} and 308.\cite{76} The patients were randomized to 1 of 3 groups: placebo, donepezil 5 mg/d, or donepezil 10 mg/d. The group receiving 10 mg/d initially received 5 mg/d for 4 weeks; the dosage was then titrated up to 10 mg/d. Most patients (73%) fulfilled diagnosis of probable VaD according to the NINDS-AIREN criteria.\cite{22} All had brain imaging before enrollment (CT or MRI) with demonstration of cerebrovascular lesions. Patients with preexisting AD and those with mixed dementia (AD plus CVD) were excluded.
Most cases were classified as poststroke VaD, diagnosed by the presence of mild to moderate dementia, clinical and brain imaging evidence of relevant CVD, and a clear temporal relationship between stroke and cognitive decline, with onset of dementia within 3 months of a clinically evident stroke. Possible (subcortical) VaD was diagnosed in cases with indolent onset of the cognitive decline and accounted for 27% of the cases. Possible VaD included patients with silent stroke, extensive white matter disease, or an atypical clinical course. There were no differences in trial results between these 2 subgroups.

The end points included cognition as measured with the ADAS-cog and MMSE, global function as measured with the CIBIC-plus, the Sum of Boxes of the Clinical Dementia Rating (CDR-SB), and ADL as measured with Alzheimer’s Disease Functional Assessment and Change Scale (ADFACS).

In study 307,75 the donepezil treatment group showed statistically significant improvement in cognitive functioning measured with the ADAS-cog; the mean changes from baseline score were as follows: donepezil 5 mg/d, −1.90 (P=0.001); donepezil 10 mg/d, −2.33 (P<0.001). The MMSE also showed statistically significant improvement versus placebo. The treated group also showed significant improvement in global function on the CIBIC-plus in the 5-mg/d group (P=0.014), which did not reach significance in the 10-mg/d group (P=0.27). CDR-SB showed nonsignificant benefit in the 5-mg/d group but was significant in the 10-mg/d group (P=0.007). ADL showed significant benefits in donepezil-treated patients versus placebo with the use of the ADFACS in both treatment groups (P>0.02).

In study 308,76 the donepezil treatment group showed statistically significant improvement in cognitive functioning measured with the ADAS-cog; the mean changes from baseline score were as follows: donepezil 5 mg/d, −1.65 (P=0.003); donepezil 10 mg/d, −2.09 (P=0.0002). The MMSE also showed statistically significant improvement versus placebo. The treated group also showed significant improvement in global function on the CIBIC-plus in the 5-mg/d group (P=0.004), which did not reach significance in the 10-mg/d group (P=0.047). CDR-SB showed nonsignificant benefit in the 5-mg/d group but was significant in the 10-mg/d group (P=0.03). ADL showed superiority in the donepezil-treated patients over placebo with the use of the ADFACS in both treatment groups, which, however, did not reach significance at the end of the study compared with placebo.

Of interest, cognitive decline in untreated patients with VaD in this trial was less severe than in placebo-treated patients with AD during 24 weeks of study, with the use of similar instruments. These differences were also noted for global effects, measured by the CIBIC-plus version; in contrast to AD, patients with VaD showed actual improvement in global function. In contrast to AD trials, these VaD studies enrolled more men than women (58% versus 38%), their mean age was older (74.5±2.0 versus 72±0.2 years), and their HIS score was more elevated (6.6±0.2 versus <4), with higher percentages of subjects with hypertension, cardiovascular disease, diabetes, smoking, hypercholesterolemia, previous stroke, and transient ischemic attacks, suggesting that the 2 populations were clearly different.

Donepezil was generally well tolerated, although more adverse effects were reported in the 10-mg group than in the 5-mg or placebo groups. The adverse effects were assessed as mild to moderate and transient and were typically diarrhea, nausea, arthralgia, leg cramps, anorexia, and headache. The incidence of bradycardia and syncope was not significantly different from that in the placebo group. The discontinuation rates for the groups were 15% for the placebo group, 18% for the 5-mg group, and 28% for the 10-mg group. There was no significant interaction with cardiovascular medications or antithrombotic agents. Donepezil was thus effective and well tolerated in patients with VaD.

Galantamine

Galantamine is an acetylcholinesterase inhibitor that also modulates central nicotinic receptors to increase cholinergic neurotransmission. In a randomized, controlled clinical trial, patients diagnosed with probable VaD or with AD combined with CVD received galantamine 24 mg/d (n=396) or placebo (n=196) in a multicenter, double-blind, 6-month trial.77 Eligible patients met the clinical criteria of probable VaD by NINDS-AD criteria22 or of possible AD according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria. They also showed significant radiological evidence of CVD on CT or MRI (ie, AD plus CVD). Evidence of CVD on a recent (within 12 months) scan included multiple large-vessel infarcts or a single, strategically placed infarct (angular gyrus, thalamus, basal forebrain, territory of the posterior or anterior cerebral artery), or at least 2 basal ganglia and white matter lacunae, or white matter changes involving at least 25% of the total white matter. The MMSE score was 10 to 25, and ADAS-cog/11 score was ≥12; age ranged from 40 to 90 years.

Primary end points were cognition, as measured with the ADAS-cog/11, and global functioning, as measured with the CIBIC-plus. Secondary end points included assessment of ADL according to the Disability Assessment in Dementia (DAD)78 and assessment of behavioral symptoms according to the Neuropsychiatric Inventory (NPI).79

In analyses of both groups as a whole, galantamine demonstrated efficacy on all outcome measures. Galantamine showed greater efficacy than placebo on ADAS-cog (2.7 points; P≤0.001) and CIBIC-plus (74% versus 59% of patients remained stable or improved; P=0.001). ADL and behavioral symptoms were also significantly improved compared with placebo (both P<0.05). Galantamine was well tolerated.77 In an open-label extension,80 the original galantamine group of patients with probable VaD or AD plus CVD showed similar sustained benefits in terms of maintenance of or improvement in cognition (ADS-cog), functional ability (DAD), and behavior (NPI) after 12 months.

Although not designed to detect differences between subgroups, the subgroup of patients with AD plus CVD on galantamine (n=188; 48%) showed greater efficacy than placebo (n=97; 50%) at 6 months on ADAS-cog (P≤0.001)
and CIBIC-plus (P = 0.019).77 In the open-label extension, patients with AD plus CVD continuously treated with galantamine maintained cognitive abilities at baseline for 12 months.80

Probable VaD was diagnosed in 81 (41%) of the placebo patients and in 171 (43%) of those on galantamine. In the probable VaD group, ADAS-cog scores improved significantly (mean change from baseline, 2.4 points; P<0.024) in patients treated with galantamine for 6 months but not in the patients treated with placebo (mean change from baseline, 0.4 point; treatment difference versus galantamine, 1.9: P = 0.06).77 More patients treated with galantamine than with placebo maintained or improved global function (CIBIC-plus, 31% versus 23%); however, this was not statistically significant. In these patients, the cognitive benefits of galantamine were maintained at least up to 12 months, demonstrating a mean change of −0.9 in the ADAS-cog score compared with baseline, and the active group was still close to baseline at 24 months.80

Some inferences about the clinical importance of the trial data on donepezil and galantamine can be made from calculating effect sizes, as discussed elsewhere.81 When one uses the intention-to-treat analyses and calculates Cohen’s d (the difference between active treatment and placebo groups, divided by the pooled baseline standard deviation82), the estimates of the effect size range from 0.16 to 0.29. This is comparable to the effect size estimates seen in the first trials of donepezil and galantamine for AD, in which a dose-response effect also was not clear.83 Treatment effects of this magnitude are considered small but clinically detectable.84 The CIBIC-plus data are harder to interpret, but when one focuses on improvement (compared with no change or worsening), the number needed to treat ranges, for donepezil, from no effect (the 10-mg dose in study 307) to 7, using the estimate of the 5-mg dose in study 308.76 The estimates of the number of patients needed to treat with galantamine77 to observe improvement compared with placebo are 12 in the VaD group and 6 in the mixed AD/VaD group. Thus, the numbers appear to be comparable between compounds but higher than the treatment experience with AD.83,84

Rivastigmine

Rivastigmine is an acetylcholinesterase inhibitor and butyrylcholinesterase inhibitor; its effects in VaD remain to be established. In a small open-label study of patients with subcortical VaD, rivastigmine improved cognition, caregiver stress, and behavior.85–87

Conclusions

Rigorous control of vascular risk factors is important in primary and secondary prevention of VaD and perhaps in ameliorating mild VaD. A number of reasonable studies and controlled clinical trials on VaD using donepezil, galantamine, and memantine have become available. However, despite positive results, none have been approved officially. New randomized studies are under way with these agents in which the best available measurement outcomes are used.

References


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Stroke. published online March 4, 2004;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
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