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Management of Mixed Dementia

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Abstract

Alzheimer's disease (AD) and vascular dementia (VaD) are the most common causes of dementia in the elderly. Although AD can be diagnosed with a considerable degree of accuracy, the distinction between isolated AD, VaD and mixed dementia (MD) [when both pathologies coexist in the same patient] remains a controversial issue and one of the most difficult diagnostic challenges. MD represents a very common pathology, especially in the elderly, as reported in neuropathological studies. Accurate diagnosis of MD is of crucial significance for epidemiological purposes and for preventive and therapeutic strategies. Until recently, pharmacological studies have generally focused on pure disease, either AD or VaD, and have provided few data on the best therapeutic approach to MD. There is only one original randomized clinical trial on (acetyl)cholinesterase inhibitor therapy (GAL-INT-6, galantamine) for MD; the other studies are *post hoc* analyses of AD trial subgroups (AD2000, donepezil) or of VaD trial subgroups (VantagE, rivastigmine). Cholinesterase inhibitors have reproducible beneficial effects on cognitive and functional outcomes in patients with MD. These benefits are of a similar magnitude to those previously reported for the treatment of AD. It is likely that the beneficial effects of memantine (an NMDA receptor antagonist) in AD may also

apply to MD, but randomized controlled trials are still lacking. Treatment of cardiovascular risk factors, especially hypertension, may protect brain function and should be included in prevention strategies for MD.

1. Introduction

Alzheimer's disease (AD) and vascular dementia (VaD) are generally recognized as the two most prevalent causes of dementia.[1,2] Less attention has been paid to the co-occurrence of the two disorders referred to as mixed dementia (MD).[3-5] However, the differentiation between AD, VaD and MD is complicated by symptom overlap and lack of well defined diagnostic criteria to aid differentiation in the clinical setting. Despite advances in neuroimaging and the continued development of dementia markers, MD remains a challenging clinical diagnosis. As a result, MD prevalence rates from clinicopathological studies vary widely (2–60%).[6,7] In the literature, authors have defined MD as AD with vascular pathology (either macroscopic infarcts or smaller vascular lesions), AD with vascular risk factors or AD with any other dementing illness such as Lewy body pathology, for example. The concept has greatly evolved as a result of recent clinicopathological studies that have provided a better understanding of the interaction between vascular and degenerative lesions in brain aging and dementia, and have proposed relatively simple neuropathological scoring systems that provide a strong basis for the distinction between MD and pure AD or VaD.[8-13] Based on these reports and general consensus in the field, we considered that MD reflects the co-occurrence of Alzheimer pathology and cerebral vascular lesions, both of which lead to the presence of cognitive impairment.

Although many reviews have addressed diagnostic and therapeutic issues in AD and VaD,[14-20] very few have specifically focused on MD. This paper reviews available data in this field and discusses potential strategies for prevention and pharmacological treatment in the management of MD. Relevant articles were identified through the review of article reference lists and a MEDLINE search for all English language articles using the keywords 'mixed dementia' and combinations of keywords: 'Alzheimer's disease', 'cerebrovascular component' and 'drug therapy'; 'mixed dementia' and 'drug therapy'; and 'vascular dementia' and 'drug therapy'.

2. Prevention

2.1 Risk Factors

Although little is known about specific risk factors for MD, they most likely include the risk factors for both AD and VaD, which have been extensively studied.[21-24] Vascular risk factors appear to be particularly important. Hypertension is one of the most potent risk factors for the development of VaD.[25-35] However, hypertension may also increase AD risk. Skoog et al.[29] reported that elderly individuals who developed dementia (either AD or VaD) had higher blood pressures 10–15 years earlier than those whose cognitive function remained unimpaired.

Randomized controlled trials of primary and secondary prevention of VaD demonstrate a reduction in incidence of disease (disease-modifying treatment).[25-35] These strategies include a reduction in all cerebrovascular risk factors, particularly hypertension. Such treatment may prevent dementia by reducing stroke and possibly by other mechanisms that remain undetermined, such as those involved in neurodegeneration and cell death.[25-35] In the Syst-Eur (Systolic Hypertension in Europe) trial, treatment of isolated systolic hypertension markedly reduced the incidence of both VaD and AD.[36] There is evidence suggesting that AD is also related to other vascular risk factors classically associated with VaD, such as smoking, diabetes mellitus, a history of heart disease, atrial fibrillation and elevated serum homocysteine.[22,37,38] Furthermore, studies have consistently shown that patients with MD have a higher prevalence of cardiovascular risk factors, such as hypertension and stroke, and present more frequently

with cardiovascular disease than patients with AD.[39,40]

Thus, it is reasonable to expect that prevention strategies for VaD also may be effective in the prevention of MD.

2.2 Primary Prevention

One of the most promising lines of research involves trials of preventive treatment in individuals with multiple risk factors: smokers, diabetics and patients with atrial fibrillation, cardiac disease and hypertension. In addition, recent epidemiological studies suggest that primary prevention of dementia in such patients should be implemented from midlife. A retrospective cohort study evaluated 8845 participants aged 40–44 years from a health maintenance organization undergoing health evaluations between 1964 and 1973.[41] Midlife cardiovascular risk factors included high total cholesterol, diabetes, hypertension and smoking. Diagnoses of dementia were ascertained from medical records between January 1994 and April 2003. The authors identified 721 participants (8.2%) with dementia. Smoking, hypertension, high cholesterol and diabetes at midlife were each associated with an increase in risk of dementia of between 20% and 40% (fully adjusted Cox proportional hazards model: hazard ratio [HR] 1.24, 95% CI 1.04, 1.48 for hypertension; HR 1.26, 95% CI 1.08, 1.47 for smoking; HR 1.42, 95% CI 1.22, 1.66 for high cholesterol; and HR 1.46, 95% CI 1.19, 1.79 for diabetes). A composite cardiovascular risk score was created using all four risk factors and was associated with dementia in a dose-dependent fashion. Compared with participants with no risk factors, the risk for dementia increased from 1.27 with one risk factor to 2.37 with all four risk factors.[41] It remains to be shown that interventions targeting these risk factors – giving up smoking; controlling diabetes, hyperlipidaemia and obesity; carotid endarterectomy for symptomatic patients with 70–99% carotid stenosis; anticoagulants for atrial fibrillation; aspirin (acetylsalicylic acid) for patients at high primary risk; and antihypertensives for patients with hypertension – would result in reduction of the risk of later development of dementia.

Only a few intervention studies exist. In the SHEP (Systolic Hypertension in the Elderly Program) study (n = 4736),[42] treatment of isolated systolic hypertension in individuals aged >60 years with chlortalidone followed by atenolol if necessary led to a 36% reduction in the incidence of stroke, with a 5-year absolute benefit of 30 events per 1000 participants. The Syst-Eur trial (n = 4695) reported a 42% reduction in the overall incidence rate for stroke using antihypertensive treatment (nitrendipine followed by enalapril and hydrochlorothiazide) in a similarly aged population.[43] In the same trial, in elderly people with isolated systolic hypertension, antihypertensive treatment was associated with a lower incidence of dementia (VaD but also AD).[44] Treatment of 1000 hypertensive patients with antihypertensive drugs for 5 years prevented 19 cases of dementia. In the SCOPE (Study on Cognition and Prognosis in the Elderly), elderly patients (n = 4937) with mildly to moderately elevated blood pressure who received angiotensin II type 1 receptor antagonist candesartan cilexetil-based therapy had a slightly larger reduction in blood pressure than patients receiving placebo.[45] This was associated with a modest, statistically non-significant reduction in major cardiovascular events and a marked reduction in non-fatal stroke. However, cognitive function was well maintained in both treatment groups in the presence of substantial reductions in blood pressure. More recent analyses suggested that candesartan cilexetil-based treatment improves cognitive function and quality of life in old and very old patients with mild to moderate hypertension.[46,47] In the Rotterdam study, a large, observational, prospective, population-based study, subjects (n = 2015) taking antihypertensive medication at baseline (21.1% took monotherapy, 8.5% took two drugs and 1.7% took three or more drugs: 15.3% diuretics, 14.6% β-adrenoceptor antagonists, 5.9% calcium channel antagonists, 5.7% ACE inhibitors and 1.9% other antihypertensives), who were then followed for a mean of 2.2 years, had a reduced incidence of dementia (adjusted relative risk 0.76; 95% CI 0.52, 1.12).[48] This reduction in risk was most pronounced for VaD (adjusted relative risk 0.30; 95% CI 0.11, 0.99). Thus, there seem to be clear prognostic

benefits of treatment that lowers blood pressure in hypertensive patients.

However, other results were published recently in the HYVET (Hypertension in the Very Elderly Trial).[49-51] This study was a double-blind, placebo-controlled trial of antihypertensive treatment (indapamide sustained release 1.5 mg ± perindopril 2–4 mg) that recruited only hypertensive patients who were aged ≥80 years without a diagnosis of dementia at baseline (n = 3336). Hypertension was defined as systolic blood pressure of 160–199 mmHg and diastolic blood pressure <110 mmHg. In an intent-to-treat analysis, active treatment was associated with a 30% reduction in the rate of fatal or non-fatal stroke, a 39% reduction in the rate of death from stroke, a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from cardiovascular causes and a 64% reduction in the rate of heart failure. There were 263 incident cases of dementia. The rates of incident dementia were 38 per 1000 patient-years in the placebo group and 33 per 1000 patient-years in the treatment group, with no significant difference between treatment and placebo groups (HR 0.86; 95% CI 0.67, 1.09). According to the authors, this negative finding might have been due to the short follow-up; the trial was stopped at the second year, after treatment resulted in a reduction in stroke and total mortality.

Despite these findings, a meta-analysis that included the HYVET and other placebo-controlled trials of antihypertensive treatment reported a decreased dementia risk in the treated group (HR 0.87; 95% CI 0.76, 1.00; p = 0.045). However, a recent update of the Cochrane database that combined results from four hypertension trials (including Syst-Eur[43] and SHEP[42]) involving 15 936 hypertensive subjects with no evidence of previous cerebrovascular disease was unable to provide definitive conclusions regarding the effect of blood pressure lowering on late-life cognitive impairment and dementia, because of methodological heterogeneity between trials, the high number of drop-outs and active treatment of subjects in the control groups.[52]

Randomized controlled trials addressing interventions to minimize other risk factors mentioned previously, such as warfarin treatment in atrial fibrillation or carotid endarterectomy, based their study endpoints on the prevention of strokes and not the prevention of dementia. HMG-CoA reductase inhibitors (statins) have been shown to prevent both incident and recurrent cerebral ischaemic stroke.[53-55] Given the benefits of preventing recurrent stroke, it would seem reasonable to treat VaD patients with statin therapy to prevent stroke. However, to date there is no evidence that statin therapy reduces the risk of incident dementia. A *post hoc* analysis of the Cardiovascular Health Study revealed a trend towards reduced cognitive decline in patients treated with statins, but there was no change in the risk of incident dementia in this cohort.[56,57] Similarly, two other prospective cohort studies also failed to show a reduction in dementia associated with statin use.[58,59] An ongoing, large, randomized, controlled trial in Australia, the ASPREE (ASPirin in Reducing Events in the Elderly) trial is currently investigating the use of aspirin 100 mg for the primary prevention of major adverse cardiovascular events and dementia.[60]

Kivipelto et al.[61] sought to develop a simple method for the prediction of the risk of late-life dementia in people of middle age on the basis of their risk profiles. To this end, the investigators studied 1409 individuals in midlife and re-examined them 20 years later for signs of dementia. Several midlife vascular risk factors were evaluated to create the scoring tool. Occurrence of dementia during the 20 years of follow-up was 4%. Future dementia was significantly predicted by high age (≥47 years), low education (<10 years) and, most importantly, vascular risk factors such as hypertension, hypercholesterolaemia and obesity.[61]

2.3 Secondary Prevention (After Stroke or Silent Cerebral Ischaemia)

Secondary prevention deals with early management of acute stroke, preventing recurrent stroke and reducing the progression of vascular-related changes in the brain by treating vascular risk factors. The PROGRESS (Perindopril Protection Against Recurrent Stroke Study)[62] showed that active treatment with an ACE inhibitor, given

alone or combined with a diuretic, was associated with a reduced risk of dementia and cognitive decline in patients with recurrent stroke. In addition, an active blood pressure-lowering regimen stopped or delayed the progression of white matter hyperintensities detected on cerebral MRI in patients with cerebrovascular disease.[63]

3. Treatment

Evidence supports the involvement of the cholinergic system in VaD, similar to that seen in AD.[64,65] Decreased acetylcholine levels and nicotinic receptor dysfunction have both been implicated in the development and progression of cognitive decline in animal and human studies of not only AD but also of VaD.[66-73] Some studies have been conducted with the aim of determining the effect of (acetyl)cholinesterase inhibitors (ChEIs) in VaD, but their results have been limited and inconsistent. A recent meta-analysis of randomized controlled trials concluded that ChEIs and memantine produce measurable benefits in cognitive function in patients with mild to moderate VaD but found that these agents have no significant effect on functional status, behaviour and global clinical status.[74] According to these authors, there are insufficient data to support widespread use of these drugs in pure VaD. However, several studies suggest that these drugs may be beneficial in the management of patients with MD.

3.1 Cholinesterase Inhibitors (ChEIs)

Clinical and radiological criteria, patients' characteristics and endpoints of trials of ChEIs for MD are described in table I. The results of these trials are summarized in table II.

3.1.1 Galantamine

Galantamine is a ChEI that also modulates central nicotinic receptors to increase cholinergic neurotransmission. In a randomized, double-blind, controlled, multicentre, 6-month trial (GAL-INT-6), patients diagnosed with probable VaD or with AD combined with cerebrovascular disease (considered to be MD) received galantamine 24 mg/day (n = 396) or placebo (n = 196).[75,76,85,86] In analyses of both groups as a whole, galantamine showed greater efficacy than placebo, as manifested by a mean 1.7-point improvement on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)[87] among treated patients versus a mean 1.0-point decline in those receiving placebo (2.7-point treatment difference, $p < 0.001$). In addition, 74% of treated patients remained stable or showed improvement on the Clinicians' Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus)[88] versus 59% of those receiving placebo ($p = 0.001$). Activities of daily living and behavioural symptoms were also significantly improved with galantamine compared with placebo ($p = 0.002$ and $p = 0.016$, respectively).

Although the study was not powered to detect differences between subgroups, the subgroup of patients with MD receiving galantamine showed greater efficacy than the subgroup with MD receiving placebo at 6 months.[86] Mean CIBIC-Plus scores were also significantly better in the galantamine group than in the placebo group; at 6 months, 32% and 19% of patients, respectively, had improved scores ($p = 0.019$) and 75% and 54%, respectively, had improved or unchanged scores ($p = 0.001$). The proportion of responders demonstrating improved or maintained cognition on the 11-item ADAS-cog (ADAS-cog/11) was 60.5% for galantamine versus 46.0% for placebo ($p = 0.013$). The proportion of patients responding by at least 4 points on the ADAS-cog was significantly greater in the galantamine group than in the placebo group (33.6% vs 17.2%; $p = 0.003$). Galantamine also had favourable effects on patients' activities of daily living compared with placebo, as shown by significant improvements on the Disability Assessment for Dementia (DAD) scale.[89] At 6 months, the ability to carry out activities of daily living was maintained in patients assigned galantamine, whereas there was a significant deterioration in patients in the placebo group ($p = 0.0006$).

In the open-label extension of the study,[77,78,90,91] the original galantamine-treated group of patients with probable VaD or MD showed similar sustained benefits in terms of maintenance of or improvement in cognition (ADAS-cog/11), functional ability (DAD) and behaviour (Neuropsychiatric Inventory [NPI])[92] after 12 months. In this extension

Table I. Trials of cholinesterase inhibitors for mixed dementia (MD): trial design, patient (pt) characteristics, clinical and radiological diagnostic criteria and trial endpoints

Trial/centres/ regimens	Design and pts				Criteria for diagnosis of MD and endpoints			
	length; design	no. of pts; sex; age [mean (SD)]	MMSE [mean (SD)]	ADAS-cog/11 [mean (SD)]	clinical	radiological evidence of CeVD (CT scan or MRI)	primary endpoints	secondary endpoints
GAL-INT-6:[75,76] 24 mg/d; 10 centres: Denmark, Canada, Finland, France, Germany, Ireland, Israel, UK, the Netherlands, Poland	24 wk; RCT, mc	592 (239 MD); 53% M; 75.1 (7.00) y	20.5 (3.63)	22.8 (9.18)	Probable VaD by NINDS-AIREN or possible AD by NINCDS-ADRDA	Multiple large-vessel infarcts or a single, strategic infarct (angular gyrus, thalamus, basal forebrain, territory of posterior or anterior cerebral artery), or at least two basal ganglia and WM lacunae, or WM changes involving at least 25% of the total WM	Cognition (ADAS-cog/11), global functioning (CIBIC-Plus)	ADL (PDS), behaviour (NPI)
GAL-INT-6:[77,78] 24 mg/d	24 wk; ol extn	459 (238 MD); 52% M; 75.2 (0.33) y	20.5 (0.17)	22.2 (0.53)	As above	As above	As above	As above
Rivastigmine:[79] low (1–4 mg/d) or high dose (6–12 mg/d); 19 centres in the US	26 wk; RCT, mc	699 (319 AD plus vascular risk factors); 39% M; 74.0 (0.42) y	20.2 (0.22)	21.2 (0.56)	AD by NINCDS-ADRDA and vascular risk factors and MHIS <5	Results consistent with the diagnosis of AD	Cognition (ADAS-cog/11), global functioning (CIBIC-Plus and GDS)	ADL (PDS)
Rivastigmine:[80] low (1–4 mg/d) or high dose (6–12 mg/d); 19 centres in the US	26 wk; ol	119 MD; 53% M; 77.5 (7.2) y	19.1 (4.1)	23.9 (11.8)	NINDS-AIREN and NINCDS-ADRDA and MHIS >0 and vascular risk factors	Multiple large-vessel infarcts or at least one single, strategic infarct, or multiple basal ganglia or WM lacunae, or periventricular WM lesions	Cognition (ADAS-cog/11). global functioning (CIBIC-Plus and GDS)	ADL (PDS), behaviour (NPI)

AD = Alzheimer's disease; **ADAS-cog/11** = Alzheimer's Disease Assessment Scale-Cognitive Subscale (11 items); **ADL** = activities of daily living; **CeVD** = cerebrovascular disease; **CIBIC-Plus** = Clinicians' Interview-Based Impression of Change Plus Caregiver Input; **extn** = extension; **GDS** = Global Deterioration Scale;[81] **M** = male; **mc** = multicentre; **MHIS** = Modified Hachinski Ischemic Scale; **MMSE** = Mini-Mental State Examination; **NINCDS-ADRDA** = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association;[82] **NINDS-AIREN** = National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences;[83] **NPI** = Neuropsychiatric Inventory; **ol** = open-label; **PDS** = Progressive Deterioration Scale;[84] **RCT** = randomized controlled trial; **VaD** = vascular dementia; **WM** = white matter.

Table II. Results of trials of cholinesterase inhibitors for mixed dementia (MD) compared with placebo (PL)[a]

Trial	Outcomes			
	cognition: ADAS-cog	global functioning: CIBIC-Plus; GDS	functionality: DAD for GAL trials; PDS for RIV trials	behavioural symptoms: NPI
GAL-INT-6:[75,76] 6 mo, n = 285 (97 PL; 188 GAL 24 mg/d)	1.0 (0.46)-point improvement among GAL pts vs 1.8 (0.6)-point decline among PL pts; 2.7-point treatment difference (95% CI 1.17, 4.16; p < 0.001)	*CIBIC-Plus:* 49 GAL pts (32%) improved scores vs 16 PL pts (19%) [p = 0.019] 75% of treated pts showed improvement or remained stable vs 54% of those receiving PL (p = 0.001)	*For all pts (MD plus VaD):* 0.2 (0.9)-point improvement among GAL pts vs 4.4 (1.3)-point decline among PL pts; 4.6-point treatment difference (p = 0.0017)	*For all pts (MD plus VaD):* 1.2 (0.6)-point improvement among GAL pts vs 1.0 (0.9)-point decline among PL pts; 2.2-point treatment difference (p = 0.0164)
GAL-INT-6:[77,78] 12 mo, n = 238 (86 PL 6 mo/GAL 24 mg/d 6 mo; 152 GAL 24 mg/d 6 mo/GAL 24 mg/d 6 mo)	0.1 (0.58)-point improvement among GAL/GAL pts (scores remained near baseline) vs 1.0 (0.95)-point decline among PL/GAL pts; 1.1-point treatment difference (p-value not shown)	No data for these outcomes for the 12 mo of follow-up	*For all pts (MD plus VaD):* 3.6 (1.33) [95% CI 0.95, 6.21]-point improvement among GAL/GAL pts vs 7.4 (1.68) [95% CI 4.12, 10.78])-point decline among PL/GAL pts (p ≤ 0.001)	*For all pts (MD plus VaD):* total NPI scores not significantly different from baseline in either GAL/GAL pts [0.2 (0.98)-point improvement] or PL/GAL pts [0.1 (0.70)-point improvement]
RIV:[79] 26 wk; low dose = 1–4 mg/d (n = 90), high dose = 6–12 mg/d (n = 69), PL (n = 85)	1.9 (0.78)-point improvement among high dose-treated pts; 1.4 (0.54)-point decline among low dose-treated pts; 4.2 (0.69)-point decline among PL pts; 6.1-point treatment difference for high dose (p < 0.001); 2.8-point treatment difference for low dose (p < 0.002)	*CIBIC-Plus:* 0.28-point treatment difference for high dose (p = 0.125); 0.17-point treatment difference for low dose (p = 0.315) *GDS:* 0.21 (0.07)-point decline among high dose-treated pts; 0.15 (0.07)-point decline among low dose-treated pts; 0.34 (0.07)-point decline among PL pts; 0.13-point treatment difference for high dose (p = 0.155); 0.19-point treatment difference for low dose (p = 0.028)	2.1 (1.32)-point decline among high dose-treated pts; 6.6 (1.04)-point decline among low dose-treated pts; 5.6 (1.01)-point decline among PL pts; 3.5-point treatment difference for high dose (p = 0.03); 1.0-point treatment difference for low dose (p = 0.468)	No assessment done
RIV:[80] 26 wk; high dose = 6–12 mg/d (n = 119)	0.3-point improvement relative to baseline (p = 0.656); >50% of pts improved or did not decline	*GDS:* 0 (0.9)-point relative to baseline (no change)	0.2 (10.8)-point improvement relative to baseline (no change) [p = NS]	2.5 (11.4)-point improvement relative to baseline (p = 0.043)

a Values are expressed as mean ± SD change in endpoint from baseline ± 95% CI for treatment difference, except where stated otherwise.

ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; **CIBIC-Plus** = Clinicians' Interview-Based Impression of Change Plus Caregiver Input; **DAD** = Disability Assessment in Dementia; **GAL** = galantamine; **GDS** = Global Deterioration Scale;[81] **NPI** = Neuropsychiatric Inventory; **NS** = not significant; **PDS** = Progressive Deterioration Scale;[84] **pts** = patients; **RIV** = rivastigmine; **VaD** = vascular dementia.

phase, patients with MD who were continuously treated with galantamine maintained cognitive abilities at baseline for 12 months (mean change in ADAS-cog/11 score +0.1). The subgroup analysis of only patients with MD showed similar outcomes to those of the subsample of patients with probable VaD. The estimates of the number of patients needed to treat with galantamine to observe improvement compared with placebo were 12 in the VaD group and 6 in the MD group. In contrast to treated patients, cognitive function deteriorated among those in the placebo group (mean change in ADAS-cog/11 score at month 6 +2.0; $p \leq 0.001$ vs baseline). Patients with MD who were switched from placebo to galantamine for the open-label phase of the trial did show an improvement in cognitive function, but they never attained the same cognitive level as patients who had been treated with galantamine for the entire 12 months.

3.1.2 Rivastigmine

Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase. Kumar et al.[79] conducted a randomized controlled clinical trial of rivastigmine in patients with mild to moderately severe AD with or without concurrent vascular risk factors. In this study, the Modified Hachinski Ischemic Score (MHIS)[93] was used to identify patients with AD who also had concurrent vascular risk factors, focal neurological symptoms or signs suggestive of prior stroke, or a history of stroke. Patients were dichotomized as having MHIS = 0 (n = 378) or MHIS >0 (n = 319) at baseline and assigned to high-dose rivastigmine (6–12 mg/day), low-dose rivastigmine (1–4 mg/day) or placebo. For the whole group, patients treated with rivastigmine 6–12 mg/day showed significantly less decline on the ADAS-cog than those taking placebo, i.e. a mean 0.4-point decline on the ADAS-cog among treated patients versus a mean 3.7-point decline among those receiving placebo (3.3-point treatment difference, $p < 0.001$). The mean CIBIC-Plus score in the rivastigmine 1–4 mg/day treatment group was 4.2 versus 4.5 in the placebo group ($p = 0.023$), suggesting less clinical deterioration in treated patients. No significant difference was found for the rivastigmine 6–12 mg/day treatment group versus the placebo group. The treatment effect was generally larger in MHIS >0 patients with vascular risk factors for all of the endpoints. Furthermore, the mean treatment difference at week 26 for patients in this group treated with high doses of rivastigmine versus placebo was 6.15 ADAS-cog points, exceeding results reported previously for AD patients. An intent-to-treat analysis was not conducted. In a *post hoc* analysis of hypertension as a vascular risk factor, patients receiving rivastigmine 6–12 mg/day had better outcomes on the ADAS-cog and CIBIC-Plus than those receiving placebo in both the hypertensive and non-hypertensive subgroups.[94] Hypertensive patients receiving rivastigmine 6–12 mg/day also showed improvement compared with those receiving rivastigmine 1–4 mg/day ($p = 0.023$).

An open-label study (no placebo arm) of rivastigmine 6–12 mg/day in patients with MD was conducted by Potkin et al.[80] The clinical and radiological diagnostic criteria, patients' characteristics and the endpoints of the study are described in table I. An additional inclusion criterion in this study was having three or more of the following vascular risk factors: history of clinically significant hyperlipidaemia, hypertension (currently well controlled), diabetes mellitus, smoking, obesity, heavy alcohol consumption, transient ischaemic attacks or strokes, evidence of peripheral vascular disease, atrial fibrillation or arrhythmias. The primary efficacy measure, ADAS-cog score, showed an improvement relative to baseline at weeks 12 and 26; mean changes of –0.4 ($p = 0.449$) and –0.3 ($p = 0.656$), respectively, were reported. Furthermore, >50% of patients improved or did not decline on the ADAS-cog and NPI, and 74% improved or did not decline on the CIBIC-Plus. The NPI domains that consistently appeared to be significantly improved by treatment with rivastigmine were apathy/indifference and irritability/lability. Assessment of the effects of treatment on activities of daily living revealed no statistically significant change. In a *post hoc* analysis of hypertensive AD patients who received rivastigmine, there was a trend towards better ADAS-cog scores in early starters who were treated for 104 weeks compared with late starters who received rivastigmine for the last 78 weeks only.[95] Significant treatment differences were also observed on global scales. In non-hypertensive patients, these differences were not present, suggesting that apparent benefits on disease progression detected in AD patients with hypertension may be linked to the effects of treatment on cerebrovascular factors.[95]

More recently, the VantagE (Vascular Dementia trial studying Exelon), a randomized controlled clinical trial including 710 patients with probable VaD, showed that rivastigmine was not consistently effective in probable VaD. Exploratory analyses indicated that older patients (aged ≥75 years), who were assumed to be more likely to also have AD pathology, demonstrated significant cognitive responses to rivastigmine and a safety profile similar to that seen in AD patients.[96] Younger patients, who were assumed to be less likely to have concomitant AD pathology, showed no efficacy response and were found to have slightly

increased blood pressure, cerebrovascular accident rates and mortality. Differences between rivastigmine and placebo in patients with, versus those without, medial temporal atrophy (which is also suggestive of concomitant AD) showed a numerical difference similar to that seen between older versus younger patients, but did not attain statistical significance. The efficacy observed in terms of cognitive outcomes was derived from effects in older patients likely to have concomitant Alzheimer pathology. This is supportive of an existing argument that the putative cholinergic deficit in VaD may reflect the presence of concomitant Alzheimer pathology.

3.1.3 Donepezil

Donepezil is a reversible central ChEI. There has been no donepezil trial specifically designed for patients with MD. However, in the AD2000 trial, which was designed to include only AD patients, 16% of the patients also had VaD (i.e. MD).[97] This study showed statistically significant benefits of donepezil treatment (5 or 10 mg/day) on cognitive function and independent performance of activities of daily living, but there was no effect on institutionalization. The subgroup analysis suggested more significant cognitive improvement among patients with MD (AD plus VaD) treated with donepezil than in those without VaD ($p = 0.02$).[97]

3.1.4 Donepezil Plus Galantamine

Recently a unique case report was published of an 84-year-old MD patient who mistakenly took donepezil and galantamine concomitantly and reported subjective improvement, which was followed by a 9-point decrease in Mini-Mental State Examination (MMSE) score upon discontinuation of donepezil.[98] A MEDLINE literature search revealed only one open-label study[99] that has explored the combined use of donepezil and rivastigmine in possible or probable AD. This showed more improvement on the MMSE than has been reported in ChEI monotherapy trials.

3.2 Memantine

A low-affinity antagonist at glutamate NMDA receptors may prevent excitatory neurotoxicity in dementia. Trials of memantine have shown effects on cognition, function, behaviour and global clinical status in AD and a purely cognitive effect in VaD.[100-102] Although it is possible that the beneficial effect of memantine in AD may also be present in MD, there are no available trials to demonstrate this.

3.3 Safety and Tolerability of ChEIs

The incidence of the various adverse events (AEs) reported in the ChEI trials for MD was similar to those reported in the ChEI trials for pure AD.

Acute, centrally mediated gastrointestinal events (mostly nausea and vomiting) are class effects of all ChEIs, and are reported mostly dur ing the dose-escalation phase of therapy. These events have been associated more with the dual acetylcholinesterase/butyrylcholinesterase inhibitor rivastigmine than with the acetylcholinesterase-selective inhibitors donepezil and galantamine. In the study by Kumar et al.,[79] which evaluated the efficacy and safety of rivastigmine in patients with mild to moderately severe AD with or without concurrent vascular risk factors, gastrointestinal AEs (nausea, vomiting, diarrhoea and anorexia) were significantly higher in treated patients than in untreated patients, but the symptoms were mild and transient during the titration phase. Similarly, in the galantamine trials,[75,76,85,86] nausea and vomiting were significantly higher during the dose-escalation phase. However, these events can be minimized using slow dose escalation with small dose graduations and administration with food. Furthermore, the availability of a skin patch delivery system for rivastigmine may decrease gastrointestinal AEs.

Other AEs associated with ChEIs include CNS events, extrapyramidal symptoms and sleep disturbances, which are associated with cholinergic activity in the cortex, caudate nucleus, brainstem and medulla, together with muscle cramps, weakness and cardiac events such as bradycardia and urinary incontinence, which are associated with peripheral cholinergic activity. These symptoms are mostly reported during the maintenance phase of therapy. In the AD2000 trial,[97] the incidence

of bradycardia and syncope in patients taking donepezil was not significantly different to that in the placebo group. A subgroup analysis of AEs in MD patients was not performed.

When dosed with care, ChEIs are well tolerated, and patient compliance and patient and caregiver acceptability are good.

4. Improving Clinical Trials of Mixed Dementia

Several important issues need to be addressed to improve clinical trials of MD.

4.1 Clinical Diagnosis

Further efforts are needed to develop a consensus regarding clinical criteria for MD and to validate these criteria through clinicopathological studies.

4.2 High Prevalence of Mixed Pathology, Especially in the Elderly

Clinical testing, biochemical markers and neuroimaging may fail to distinguish pure AD and VaD from mixed cases, particularly in the presence of microscopic infarcts that cannot be identified prior to autopsy with currently available technology. Such lesions have been shown to have a significant impact on cognition. Kovari et al.,[103] in a series of 43 prospectively evaluated autopsy cases with Braak neurofibrillary tangle stage III but without macroscopic vascular pathology or substantial non-AD, non-vascular microscopic lesions, showed that cortical microinfarcts and periventricular demyelination were significantly associated with Clinical Dementia Rating scale score. Another study of 156 autopsied, elderly individuals with various degrees of AD pathology showed that Braak neurofibrillary tangles, β-amyloid deposition, cortical microinfarcts, and thalamic and basal ganglia lacunes were strong predictors of the presence of dementia.[8] The clinical expression of the vascular component in mixed cases is highly dependent on lesion type and location as well as on severity of concomitant AD-related pathology.

In the same way, advances in neuroimaging techniques have led to a better understanding of the high prevalence and features indicative of MD. Both medial temporal atrophy and large vessel disease contribute to global cognitive impairment, and from a structural radiological perspective, medial temporal atrophy is generally considered to be the best surrogate marker of degenerative pathology in AD. Subcortical ischaemic vascular disease (SIVD) is less well understood, but has been thought to result from direct effects of subcortical lacunes and white matter lesions. The cognitive impairment associated with white matter hyperintensities is restricted to certain tests of executive function and that of multiple lacunar infarcts and thalamic lesions to reductions in verbal fluency.[104] In another large study, lacunes in the thalamus were associated with lower MMSE scores, decreased speed and motor control, and impaired executive function,[105] independently of the extent of white matter hyperintensities. In an MRI study of 157 participants in a multicentre study of SIVD and AD that included cognitively normal, cognitively impaired and demented individuals with and without subcortical lacunar infarcts, cognitive impairment associated with SIVD was primarily a result of associated hippocampal and cortical changes; subcortical lacunes were not related to cognitive measures.[106]

Unfortunately, cortical microinfarcts are not visible with current MRI technology. It is thus likely that a significant portion of clinically diagnosed pure cases are in fact MD. Therapeutic effects in AD trials may thus also reflect an impact on cognitive impairment secondary to vascular lesions. Similarly, small effects in the VaD trials may be related to co-morbid AD pathology.

4.3 Selection of Tools Specific to Vascular Pathology

Outcome measures from AD trials need to be adapted to the VaD and MD populations. For example, the ADAS-cog test used in AD trials essentially provides a composite score of memory, language and orientation. It does not assess attention and the range of executive dysfunction or subcortical impairment often associated with

VaD or MD. Some modifications have been suggested for this purpose such as the Vascular Dementia Assessment Scale-Cognitive Subscale (VaDAS-cog), which includes additional frontal lobe subtests covering attention, working memory, executive function and verbal fluency.[107-109]

5. Conclusions

Recent epidemiological data from both clinical and neuropathological series identify MD (AD plus VaD) as one of the most common causes of dementia. Treatment of cardiovascular risk factors in middle-aged and older individuals represents the best strategy to decrease the incidence of MD and slow its progression. Evidence from randomized clinical trials indicates that treatment with ChEIs has reproducible beneficial effects on cognitive and functional outcomes in patients with MD.[110] These effects are of a similar magnitude to those previously reported in trials of these medications for AD. It is plausible that the beneficial effects of memantine in AD may also apply to MD, but there is no randomized controlled trial to specifically support this. Further studies are needed to improve our ability to diagnose and treat MD. Greater awareness should lead to improved recognition and, possibly, better prevention of this disorder. Careful evaluation of non-pharmacological approaches is also warranted.

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