Mixed Dementia
Emerging Concepts and Therapeutic Implications

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Context The prevalence of mixed dementia, defined as the coexistence of Alzheimer disease (AD) and vascular dementia (VaD), is likely to increase as the population ages.

Objectives To provide an overview of the diagnosis, pathophysiology, and interaction of AD and VaD in mixed dementia, and to provide a systematic literature review of the current evidence for the pharmacologic therapy of mixed dementia.

Data Sources, Study Selection, and Data Extraction The Cochrane Database of Systematic Reviews was searched using the keyword *dementia*. MEDLINE was searched for English-language articles published within the last 10 years using the keywords *mixed dementia*, the combination of keywords *Alzheimer disease*, *cerebrovascular disorders*, and *drug therapy*, and the combination of keywords *vascular dementia* and *drug therapy*.

Evidence Synthesis Dementia is more likely to be present when vascular and AD lesions coexist, a situation that is especially common with increasing age. The measured benefits in clinical trials for the treatment of mixed dementia are best described as statistically significant differences in cognitive test scores and clinician and caregiver impressions of change. In these studies, the control groups' scores typically decline while the treatment groups improve slightly or decline to a lesser degree over the study period. Nevertheless, even the patients who experience treatment benefits eventually decline. Cholinesterase inhibitor (ChI) therapy for mixed dementia shows modest clinical benefits that are similar to those found for ChI treatment of AD. The *N*-methyl-D-aspartate (NMDA) antagonist memantine also shows modest clinical benefits for the treatment of moderate to severe AD and mild to moderate VaD, but it has not been studied specifically in mixed dementia. The treatment of cardiovascular risk factors, especially hypertension, may be a more effective way to protect brain function as primary, secondary, and tertiary prevention for mixed dementia.

Conclusions Currently available medications provide only modest clinical benefits once a patient has developed mixed dementia. Cardiovascular risk factor control, especially for hypertension and hyperlipidemia, as well as other interventions to prevent recurrent stroke, likely represent important strategies for preventing or slowing the progression of mixed dementia. Additional research is needed to define better what individuals and families hope to achieve from dementia treatment and to determine the most appropriate use of medication to achieve these goals.

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Alzheimer disease (AD) and vascular dementia (VaD) are common causes of dementia in the United States and will likely affect an increasing number of patients in the coming decades.[1] Most reports focus on AD and VaD as separate uncomplicated clinical entities, yet there is increasing evidence that, particularly in older patients, the brain lesions associated with each pathological process often occur together[2] and that AD and VaD brain lesions interact in important ways to increase the likelihood of clinically significant cognitive decline.[3,4] This coexistence of AD and VaD pathology is often termed mixed dementia.[2]

We sought to systematically assemble information on the emerging diagnostic, clinical, and pathological issues related to AD, VaD, and their coexistence, and on the implications for treatment. We then present the results of a systematic literature review of the pharmacologic treatments for mixed dementia.

DEFINING *MIXED DEMENTIA*

Pathology and Clinical Criteria

The brain lesions of AD—namely, extracellular amyloid plaques and intracellular neurofibrillary tangles—and VaD—namely, cerebral infarctions, multiple lacunar infarctions, and ischemic periventricular leukoencephalopathy[5]—often occur together.[6-8] Autopsy series from dementia clinics report that coexisting vascular pathology occurs in 24% to 28% of AD cases.[7,9] Community-based autopsy studies consistently find higher proportions of both VaD and mixed dementia, probably because individuals who are older and have more medical comorbidities are less likely to be referred to academic centers. One such autopsy study of pa-

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tients diagnosed clinically with AD found that 42 (45%) of the 94 cases that met the accepted neuropathological criteria for AD also had significant cerebrovascular pathology.[6] A community-based autopsy study in the United Kingdom found that the primary pathological diagnosis in those with dementia was AD in 59% of cases and VaD in 16%. However, when findings were reconsidered without a primary diagnosis, AD pathology was present in 61% of cases and cerebrovascular pathology was present in 54%, with clinical dementia most often associated with the coexistence of both AD and cerebrovascular pathology.[8] As with other aspects of geriatric practice,[10] the search for a single unifying diagnosis to explain symptoms and signs, also known as the Occam's razor rule, likely does not apply to older patients who are at-risk for neurodegeneration from both AD and cerebrovascular disease.

The diagnosis and treatment of patients with both AD and VaD brain pathology is made more complex by the current lack of consensus on appropriate clinical criteria and terminology.[2] The National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) diagnostic criteria for VaD do not include a category for mixed dementia, recommending instead the term *AD with cerebrovascular disease*.[5] Alternatively, the Hachinski Ischemic Score,[11] the *International Classification of Diseases, 10th Revision (ICD-10)*,[12] and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*[13] all include a mixed dementia category although the specific diagnostic criteria differ.[2]

Other coexisting pathologies are also common in dementia. Pathological Parkinson disease is present in about 20% of patients with AD, and about 50% of cases of dementia with Lewy bodies are associated with AD pathology.[9,14] Nevertheless, the term *mixed dementia* is widely recognized and is the most commonly used term for the AD and VaD combination.

Interaction of AD and VaD

Alzheimer disease pathology occurs frequently in asymptomatic elderly individuals and clinical dementia is more likely to be present when AD is accompanied by strokes and cerebrovascular-related brain changes.[3,15] The cognitive consequences of vascular lesions are cumulative,[16] so VaD and perhaps also mixed dementia are potentially preventable if vascular risk factors are controlled and strokes do not recur.[17]

There is also emerging evidence that the cascade of events leading to the development of AD brain plaques and tangles may be due to ischemia resulting from cerebrovascular disease.[4,18,19] The association of the apolipoprotein E (*APOE*) ε4 genotype with an increased risk for both AD and cardiovascular disease further suggests a potential link between atherosclerosis, cerebrovascular disease, and AD.[19,20] Conversely, amyloid deposition in cerebral blood vessels due to AD increases the risk for hemorrhagic strokes and subsequent VaD.[21] These common pathways leading from cerebrovascular disease to both AD and VaD support the notion that when there is evidence of both cerebrovascular disease and a gradual progressive dementia, the illness should be conceptualized as the coexistence of interacting pathological processes resulting in mixed dementia.

We define mixed dementia as cognitive decline sufficient to impair independent functioning in daily life resulting from the coexistence of AD and cerebrovascular pathology, documented either by clinical criteria or by neuroimaging findings.

Evidence Acquisition

We first searched the Cochrane Database of Systematic Reviews using the keyword *dementia*. The title and abstracts of the 134 systematic reviews identified by this search were assessed for relevance to this review. Any review of medication therapy for Alzheimer disease, vascular dementia, mixed dementia, cognitive impairment, or cognition (N=34 reviews) was retained. We searched MEDLINE for English-language articles published within the last 10 years. We reviewed the title and abstracts of all 107 articles identified using the keywords *mixed dementia*; 31 articles identified using the combined keywords *Alzheimer disease*, *cerebrovascular disorders*, and *drug therapy*; and 28 articles identified using the combined keywords *vascular dementia* and *drug therapy*. We then performed a manual search of the reference lists of the relevant retrieved articles. We did not include publications that were judged to be irrelevant to this review based on the title and abstract. Randomized, double-blind, placebo-controlled trials (RCTs) with results reported as intention-to-treat analyses were considered to be the highest quality data and are the focus of this review. Large prospective cohort studies, meta-analyses, and systematic literature reviews were also included, as deemed appropriate, to supplement the RCT results.

EVIDENCE SYNTHESIS

Cholinesterase Inhibitors

Galantamine. An RCT of galantamine for patients with either probable VaD or AD with coexisting cerebrovascular disease showed treatment benefits for cognitive and functional outcomes (TABLE).[22] Patients with baseline scores of 10 to 25 on the 30-point Mini-Mental State Examination (MMSE) treated with 24 mg/d of galantamine showed a small improvement (−1.7; 95% CI, −0.9 to −2.5) over 6 months on the 11-item (70-point) Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog) while those in the placebo group showed a small decline (1.0; 95% CI, 0.5-1.5; $P<.001$). A subgroup analysis of only those patients with mixed dementia (AD with coexisting cerebrovascular disease) showed similar outcomes to those of the subsample of patients with probable VaD.

Rivastigmine. An RCT of rivastigmine showed treatment benefits similar to the galantamine trial.[23] A clinical scale—the Modified Hachinski Ischemic Score[40]—was used to iden-

Table. Randomized Controlled Trials of Medication Treatment for Mixed Dementia, Alzheimer Disease, and Vascular Dementia Included in This Review

Source	Patients	Medication	Trial Length, d	Primary Outcomes
			Mixed Dementia	
Erkinjuntti et al,[22] 2002	592	Galantamine	180	1.7-Point improvement on the ADAS-cog among treated patients vs a 1.0-point decline for those receiving placebo (2.7-point treatment difference, *P*<.001); 74% of treated patients remained stable or showed improvement on the CIBIC-plus vs 59% of those receiving placebo (*P* = .001)
Kumar et al,[23] 2000	699	Rivastigmine	180	0.4-Point decline on the ADAS-cog among treated patients vs a 3.7-point decline for those receiving placebo (3.3-point treatment difference, *P*<.001); mean CIBIC-plus score in the 1-4 mg/d treatment group was 4.2 vs 4.5 in the placebo group (*P* = .023), suggesting less clinical deterioration in treated patients; no significant difference was found for the 6-12 mg/d treatment group vs placebo
			Alzheimer Disease	
Rogers et al,[24] 1998	473	Donepezil	168	1.1-Point improvement on the ADAS-cog among treated patients (10 mg dose) vs a 1.8-point decline for those receiving placebo (2.9-point treatment difference, *P*<.0001); mean CIBIC-plus score in the treatment group was 4.1 at the end of the trial vs 4.5 in the placebo group (*P*<.001) suggesting less clinical deterioration in treated patients
Courtney et al,[25] 2004	486	Donepezil	1005 (3 y)	No significant treatment difference in institutionalization or progression of disability in ADLs; mean MMSE scores were 0.8 points higher (*P*<.001) and mean BADL scores were 1.0 point higher (*P* = .0004) among treated patients over 2 y of follow-up
Reisberg et al,[26] 2003	252	Memantine	196	CIBIC-plus showed trend toward less clinical deterioration in the treatment group (*P* = .06); 3.1-point decline on the ADCS-ADLsev in the treatment group vs a 5.2-point decline in the placebo group (2.2 point treatment difference, *P* = .003)
Tariot et al,[27] 2004	404	Memantine (in patients already receiving donepezil)	168	0.9-Point improvement on the SIB in the treatment group vs a 2.5-point decline in the placebo group (*P*<.001); 2.0-point decline on the ADCS-ADLsev in the treatment group vs a 3.4-point decline in the placebo group (1.4-point treatment difference, *P* = .03)
Sano et al,[28] 1997	341	Vitamin E	730 (2 y)	230-d Delay in median time to death, institutionalization, loss of ability to perform 2 of 3 ADLs, or progression to severe dementia (*P* = .001); no significant treatment difference in the MMSE or ADAS-cog
			Vascular Dementia	
Wilkinson et al,[29] 2003	616	Donepezil	168	2.2-Point improvement on the ADAS-cog among treated patients (10-mg dose) vs a 0.1-point improvement for those receiving placebo (2.1-point treatment difference, *P*<.001); 39% of patients treated with 5 mg and 32% treated with 10 mg showed improvement on the CIBIC-plus vs 25% of those receiving placebo (*P* = .004 for 5 mg comparison, and *P* = .047 for 10 mg)
Orgogozo et al,[30] 2002	321	Memantine	196	0.4-Point improvement on the ADAS-cog among treated patients vs a 1.6 point decline for those receiving placebo (2.0-point treatment difference, *P* = .0016); no significant difference in the CIBIC-plus
			All-Cause Dementia	
Winblad and Portis,[31] 1999	166	Memantine	84	73% Of treated patients showed improvement on the CGI-C vs 45% of those receiving placebo (*P*<.001)
Kanowski and Hoerr,[32] 2003	205	Ginkgo biloba	168	2.1-Point improvement on the SKT among treated patients vs a 1.0-point improvement for those receiving placebo (1.1-point treatment difference, *P* = .01)
Van Dongen et al,[33] 2003*	214	Ginkgo biloba	168	No significant treatment differences on the SKT, CGI-2, or the NAI-NAA.
Le Bars et al,[34] 1997†	309	Ginkgo biloba	365	0.1-Point decline in the ADAS-cog among treated patients vs a 1.5-point decline for those receiving placebo (1.4-point treatment difference, *P* = .04); 0.06-point improvement in the GERRI among treated patients vs 0.08-point decline in the placebo group (0.14-point treatment difference, *P* = .04)

(continued)

Table. Randomized Controlled Trials of Medication Treatment for Mixed Dementia, Alzheimer Disease, and Vascular Dementia Included in This Review (cont)

Source	Patients	Medication	Trial Length, d	Primary Outcomes
			Cardiovascular Trials	
Forette et al,[35,36] 1998, 2002	2418	Nitrendipine	730 (2 y‡)	50% Decrease in the incidence of new dementia in the treatment group (3.8 cases per 1000 patient-years vs 7.7 in the placebo group, $P = .05$)
Shepherd et al,[37] 2002	5,804	Pravastatin	1005 (3 y)	No significant treatment differences on the MMSE or other cognitive tests
Heart Protection Study Collaborative Group,[38,39] 2002, 2004	20,536	Simvastatin	1825 (5 y)	No significant treatment differences on the TICS-m or the incidence of a new clinical diagnosis of dementia

Abbreviations: ADAS-Cog, 11-item (70-point) Alzheimer Disease Assessment Scale-cognitive subscale; ADCS-ADLsev, Alzheimer Disease Cooperative Study Activities of Daily Living Inventory modified for more severe dementia; BADL, Bristol Activities of Daily Living Scale; CGI-2, Clinical Global Impression, Item 2; CGI-C, Clinical Global Impression of Change; CIBIC-plus, Clinician's Interview-based Impression of Change Plus Caregiver Input; GERRI, Geriatric Evaluation by Relative's Rating Instrument; MMSE, Mini-Mental State Examination; NAI-NAA, Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living; SIB, Severe Impairment Battery; SKT, Syndrom Kurz Test; TICS-m, modified Telephone Interview for Cognitive Status.

*The trial included patients with Alzheimer disease, VaD, mixed dementia, and age-associated memory impairment. The number of patients included in each of the dementia subgroups was not reported.

†The trial included 236 patients with Alzheimer disease and 73 patients with vascular dementia. The values reported in the table are for all patients combined. A subgroup analysis of only patients with Alzheimer disease showed similar results.

‡The trial was stopped early because of a significant treatment benefit for stroke. Median follow-up for the dementia study was 2 y.

tify patients with AD who also had concurrent vascular risk factors, focal neurological symptoms or signs suggestive of prior stroke, or a history of strokes. Patients with an MMSE score from 10 to 26 were randomly assigned to high-dose rivastigmine (6-12 mg/d), low-dose rivastigmine (1-4 mg/d), or placebo and were followed-up for 26 weeks. Among the observed cases (ie, "randomized patients with at least one evaluation while on study medication at designated assessment times"[23]), patients treated with 6 to 12 mg/d of rivastigmine showed significantly less decline in their ADAS-cog than those taking placebo ($P<.001$). An intention-to-treat analysis was not reported.

Donepezil. Randomized controlled trials of donepezil have shown treatment benefits for patients with mild to moderate AD[24] and for patients with VaD,[29] but we found no donepezil trials specifically for patients with mixed dementia or AD with concurrent cerebrovascular disease. Both AD and VaD trials showed similar modest treatment benefits (Table 1). A Cochrane review of donepezil for VaD concluded that it is safe and that it has some efficacy.[41]

The recently published AD2000 trial also found statistically significant benefits of donepezil treatment (5 or 10 mg/d) for cognitive function and independent performance of activities of daily living (ADLs) in a sample of patients with mild to moderate AD.[25] However, there were no treatment benefits after 3 years of follow-up for the study's 2 primary outcomes—institutionalization and progression of disability in ADLs, leading the authors to conclude that the small but statistically significant benefits in cognition and ADL performance associated with donepezil treatment did not lead to clinically meaningful benefits for patients or their caregivers, and therefore that donepzil did not reach conventional levels of cost-effectiveness. Sixteen percent of AD patients included in the study also had VaD (ie, mixed dementia); a subgroup analysis suggested more significant cognitive improvement among those with mixed dementia treated with donepezil compared with those lacking VaD ($P=.02$).

NMDA Antagonists

Memantine. Memantine—an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor—has a different mechanism of action than the cholinesterase inhibitors (ChIs) raising the possibility of an additive or even synergistic treatment effect for this class of medications.[27] We found separate RCTs of memantine for patients with AD[26,27] and VaD,[30] as well as a trial that included patients with either AD or VaD,[31] but none specifically for patients with mixed dementia. Two 28-week RCTs found a beneficial treatment effect for memantine (20 mg/d) in patients with moderate to severe AD (MMSE scores of 3-14), when used alone[26] or in combination with donepezil.[27] In patients with mild to moderate VaD (MMSE scores 12-20), memantine treatment was associated with a beneficial 2-point treatment difference on the ADAS-cog ($P<.01$) but no significant difference in the Clinician's Interview Based Impression of Change plus Caregiver Input (CIBIC-plus) rating scale. A trial that included severely demented nursing home patients with either AD or VaD (MMSE scores <10) also found a benefit after 12 weeks of memantine treatment.[31] A subgroup analysis found a similar treatment response for patients with either AD or VaD.

Cardiovascular and Other Agents

Antihypertensives. A number of observational studies have shown a relationship between hypertension and an increased risk for cognitive impairment,[42,43] as well as a protective effect of antihypertensive therapy for preventing cognitive decline.[44] Consistent with these observations, the Systolic Hypertension in Europe (Syst-Eur) RCT found the incidence of dementia decreased 50% from 7.7 to 3.8 cases per 1000 patient-years during 2 years of observation ($P=.05$) in patients treated with the long-acting calcium-channel blocker nitrendipine.[35] A 2-year open-label extension of the trial showed similar results, with a 55% reduction in dementia incidence for those receiving long-term therapy ($P<.001$).[36] Antihypertensive treatment was associated with a decrease in the incidence of AD as well as VaD or mixed dementia.

Statins. Observational studies have found an association between elevated serum cholesterol at middle age and increased risk of mild cognitive impairment[45] and AD.[43] Some observational studies also have shown that statin therapy is associated with a decreased risk for cognitive impairment[46] and dementia[47-49] although more recent studies have not.[50] The *APOE* ε4 genotype may modulate the impact of hypercholesterolemia on cognitive decline, as individuals with evidence of atherosclerosis and the *APOE* ε4 allele showed more significant cognitive decline than those without the allele over 5 to 7 years of follow-up in the Cardiovascular Health Study.[20] One study has suggested that persons with the *APOE* ε4 allele may be the subgroup that receives a cognitive protective benefit from statins.[50]

Randomized controlled trials have not confirmed that statin therapy reduces the incidence of cognitive decline[37-39] or AD.[51] In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial,[37] individuals aged 70 to 82 years at risk for vascular disease with MMSE scores of at least 24 at baseline were randomized to receive either 40 mg/d of pravastatin or placebo and were followed up for an average of 3.2 years. Although there were significant cardiovascular benefits for treated patients, there were no significant differences in cognitive decline during the 3-year follow-up as measured by the MMSE and other cognitive tests. Similarly, the Heart Protection Study[38] found significant cardiovascular and cerebrovascular benefits over 5 years of follow-up for patients with a history of, or risk factors for, coronary or cerebrovascular disease who were treated with 40 mg/d of simvastatin, but no evidence for a decreased incidence of cognitive impairment or dementia.[38,39] The relatively short follow-up period of these 2 trials may have limited their power to detect significant beneficial cognitive outcomes.[19]

Aspirin. An observational study of elderly individuals in Sweden showed an association between aspirin use and a decreased risk of AD and all-cause dementia,[52] but no RCTs of aspirin have been reported for the treatment of mixed dementia, AD, or VaD. A Cochrane review of aspirin for VaD also found no eligible RCTs.[53] The AD2000 RCT of donepezil[25] included an assessment of the potential benefits of aspirin for AD, but these results for aspirin have not been published yet.

Vitamin E. An RCT of vitamin E, selegeline, or both, for patients with moderate AD found a treatment benefit associated with 2000 IU per day of vitamin E.[28] After adjusting for a significant baseline difference in MMSE score across the vitamin E and placebo groups, those taking vitamin E had a significant delay to the combined end point of death, institutionalization, loss of ability to perform at least 2 of 3 ADLs, or progression to severe dementia. The median time to this end point was 670 days in the vitamin E group vs 440 days in the placebo group ($P=.001$). Therefore the estimated increase in median time to end point was 230 days (RR, .47). Significantly fewer patients taking vitamin E were institutionalized during the study period (26% vs 39%, $P=.003$; RR, .42). However, no benefit from vitamin E was found for cognitive function as measured by the MMSE, the ADAS-Cog, or the Blessed Dementia Scale (BDS). Although some reviews have interpreted these results as supporting vitamin E treatment to slow institutionalization in AD patients,[54] a Cochrane systematic review concluded that there is currently insufficient evidence to recommend vitamin E treatment.[55]

Ginkgo Biloba. Evidence of benefit for the use of the plant extract of the Ginkgo biloba tree (EGb 761) for treatment of cognitive impairment and dementia has been mixed. While we found no RCTs specifically testing ginkgo in patients with mixed dementia, 2 trials that included patients with AD and VaD ("multi-infarct dementia"),[32,34] and 1 trial that included patients with AD, VaD, and mixed dementia[33] were identified. The former RCTs found statistically significant improvements in measures of cognition and global clinical impression among patients with AD or VaD who took 120 mg/d[53] or 240 mg/d[54] of EGb 761. The latter RCT found no benefits from treatment with 160 or 240 mg/d.[33] This conflicting evidence, as well as concerns with how one of the positive trials[34] accounted for patients who did not complete the trial, led a recent Cochrane review to conclude that while there is "promising evidence" of benefit from ginkgo, further trials are required before a treatment benefit can be confirmed.[56]

Clinical Significance and Appropriate Treatment Goals for Mixed Dementia

Our literature review found evidence from RCTs that treatment with the ChIs galantamine and rivastigmine has modest beneficial effects on cognitive and functional outcomes in patients with mixed dementia. In addition, memantine has shown modest treatment benefits in separate trials for patients with AD and VaD, suggesting that this agent would also prove beneficial for mixed dementia.

Do the statistically significant differences in the measures of cognition and function found in these trials translate into clinically meaningful results for patients and caregivers? There continue to be differing interpretations of these medication trial results, with some clinicians interpreting them as showing clinical benefit and recommending treatment for all patients with dementia, and other clinicians interpreting them much more cautiously.[57] A 2001 evidenced-based review on the management of dementia from the American Academy of Neurology stopped short of recommending treatment with ChIs, instead recommending that the medications be "considered in pa-

Box. Information and Counseling for Patients With a Recent Diagnosis of Dementia and Their Families

Prognosis regarding expected time course of cognitive decline and life expectancy[66]

Patient and family preferences for specific goals of treatment tailored to patient's current level of cognitive and physical impairment

Medical advance directives, including living will, durable power of attorney for health care, and preferences for end-of-life interventions such as "do not attempt resuscitation" orders and hospice care

Review of finances and powers of attorney

Driving safety and eventual need for driving cessation

Recommendations for social engagement and physical activity

Home safety issues including kitchen safety, firearms, poisons, and potential fall risks

Potential for wandering and the availability of the Safe Return Program through the Alzheimer's Association (information available at: www.alz.org/Services/SafeReturn.asp)

Potential need for long-term care (LTC) services and financial issues surrounding LTC

Identifying family resources for caregiving

Resources for patient and caregiver information and support including the Alzheimer's Association, Alzheimer Disease Education and Referral Center, American Bar Association Commission on Legal Problems of the Elderly[63]

Plan for follow-up and assurance that physician and other members of health care team will be available to provide education and information during the course of illness

tients with mild to moderate AD, although studies suggest a small average degree of benefit."[54] On the other hand, some observers have interpreted the recent negative findings of the AD2000 trial involving more "typical" patients as calling into question any meaningful clinical benefit from ChI treatment, and have recommended additional placebo-controlled trials of ChIs to better inform future treatment of patients with dementia.[58]

One reason for the continued controversy among physicians in defining the clinical significance of dementia treatments is likely the simple fact that desired treatment goals vary significantly across families and likely continue to change as the severity of the patient's cognitive impairment increases. Additional complexity arises because both the patients and the caregivers may derive benefit (and potential harm) from treatment and because caregivers may be the primary decision makers due to the patients' declining cognitive abilities.[59] Clinicians, therefore, often need to solicit, interpret, and synthesize the treatment preferences of multiple individuals who may have very different assessments of: (1) the patient's current severity of cognitive impairment, (2) the potential benefits and harms of treatment, and (3) the most important treatment goals (eg, improved patient quality of life, decreased caregiver burden, delay to nursing home placement, or, as dementia severity advances, achieving a peaceful death[60]).

CONCLUSIONS AND PERSONAL PERSPECTIVES

What Should Clinicians Do For Patients With Mixed Dementia?

Medications to Treat Mixed Dementia. Our review of medication therapy for mixed dementia shows that the cognitive and functional treatment benefits of ChIs and memantine in patients with mixed dementia or VaD are of a similar magnitude to those previously reported for the treatment of AD. Regarding cognitive function, the mean treatment effect across ChI studies for both AD and mixed dementia (about 3 points on the ADAS-Cog) has been described as equivalent to a 4- to 6-month delay in cognitive decline.[61] However, clinicians should discuss with patients and families that current evidence suggests that response to ChIs may be quite variable, with a significant number of treated individuals (30% to 50%[61,62]) showing no improvement, and a smaller proportion (perhaps up to 20%[63]) showing a greater than average response (≥7-point ADAS-cog improvement). Given this significant variability in response to ChIs, clinicians, patients, and caregivers should monitor for either treatment-related improvement, or stabilization of the patient's decline, in cognitive, ADL, and behavioral domains over the initial 8 to 12 weeks of treatment and should discuss the appropriate definition of a meaningful benefit (eg, increased independence, alertness, or the ability to communicate with family members) from ChI treatment.[62] Given that the current monthly out-of-pocket cost of ChI therapy is approximately $150 and combination ChI and memantine treatment is approximately $300, discussions with patients and caregivers regarding concerns about out-of-pocket costs and the value of treatment benefits, while often uncomfortable, are likely to be appreciated by families.[64]

Cardiovascular Risk Factor Control and Stroke Prevention. Given the growing epidemiological[6] and clinical[3] evidence for the coexistence of AD and VaD and the potential common pathway leading from cerebral ischemia to both conditions,[4,19,65] aggressive identification and treatment of cardiovascular risk factors in middle-aged and older individuals may represent an important strategy for decreasing the incidence of dementia and for slowing the progression of cognitive decline.[43,65] Clinicians should address treatment and/or lifestyle changes for the risk factors of hypertension, hyperlipidemia, diabetes, and physical inactivity for patients with early AD, VaD, or mixed dementia as a potential strategy for improving quality of life and delaying the progression of cognitive decline. Even though the Heart Protection Study did not show a statistically significant effect of statins on cognitive decline (perhaps due to a limited follow-up period), the strong evidence for statin-related stroke prevention at least suggests that statin therapy may reduce the incidence and progression of VaD and mixed dementia.[39] In addition, prevention of recurrent strokes through the identification and treatment of atrial fibrillation and carotid vascular occlusive disease, as well as the appropriate use of anticoagulation for thromboembolic disease, will also likely reduce the incidence or progression of VaD and mixed dementia.

Additional Considerations

In addition to discussions of medications and their usage, we believe it is important to address a range of consequential medical, financial, legal, long-term care, and prognosis issues early in a patient's course (BOX). Seeking assistance from social workers, home care services, support groups, and community-based services can help patients and families access the wide range of information and counseling available and can help develop an "activated" family that can proactively address issues as they arise over the progressive course of the disease. In addition, continuing physician care can aid in the early recognition and treatment of the complications often seen in mixed dementia, such as behavioral disturbances and delirium from medical illnesses. Because, as noted above, the definition of therapeutic success may change from both the patient's and family's perspective as dementia progresses, clinicians should discuss treatment goals with patients and families at the time of diagnosis and periodically thereafter.[67]

Current Deficiencies in Knowledge

The growing evidence that AD and cerebrovascular disease commonly coexist and interact in the brains of older individuals is an example of how Occam's razor, or parsimony of diagnosis, may lead clinicians astray when evaluating and treating older patients.[68,69] An inclusive clinical perspective that considers both AD pathology and VaD pathology as causes for cognitive decline will become increasingly appropriate as physicians see proportionately more older patients at higher risk for multiple coexisting chronic conditions in the coming decades.

To better guide the treatment of patients with mixed dementia, future studies should similarly broaden their criteria to include patients with evidence for mixed causes of dementia, rather than identifying only pure AD and VaD. Similarly, population-based studies that can provide more generalizable information on real-world patients—including better identification of the risk factors, prevalence, trajectory of cognitive decline, and survival in patients with mixed dementia—will be important for informing clinicians, patients, and families. However, even given better information on the clinical course of patients with coexisting AD and VaD, the difficult family decisions regarding appropriate treatment goals for patients with dementia, and how these goals should change as cognitive decline progresses, will remain. Additional research into patient and family attitudes will help physicians better use medications to meet realistic treatment goals in mixed dementia.

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Study concept and design: Langa, Foster, Larson.
Acquisition of data: Langa.
Analysis and interpretation of data: Langa, Foster.
Drafting of the manuscript: Langa.
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