Alzheimer's Disease: Translating Neurochemical Insights Into Clinical Benefits

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *summarizes the highlights of a Continuing Medical Education (CME) accredited satellite symposium approved at the World Alzheimer's Congress 2000–Pivotal Research, held July 8, 2000, Washington, D.C.*

Participants were Changiz Geula, Ph.D., Director of the Laboratory for Neurodegeneration and Aging Research, Department of Medicine, Harvard Medical School, Boston, Mass. (co-chair); Martin Farlow, M.D., Professor and Vice-Chairman of Research, Department of Neurology, Indiana University School of Medicine, Indianapolis (co-chair); Jeffrey Cummings, M.D., Director of the University of California at Los Angeles (UCLA) Alzheimer's Disease Research Center, UCLA School of Medicine, Los Angeles; John Morris, M.D., Director of the Memory and Aging Project, Washington University School of Medicine, St. Louis, Mo.; Philip Scheltens, M.D., Ph.D., Professor of Cognitive Neurology, Research Institute Vrije Universeit, Amsterdam, the Netherlands; and Ravi Anand, M.D., Executive Director and Global Head of CNS Medical Affairs, Novartis Pharmaceuticals Corporation, East Hanover, N.J.

The symposium was jointly sponsored by the Dannemiller Memorial Educational Foundation and Gardiner-Caldwell SynerMed and supported by an unrestricted educational grant from Novartis Pharma AG.

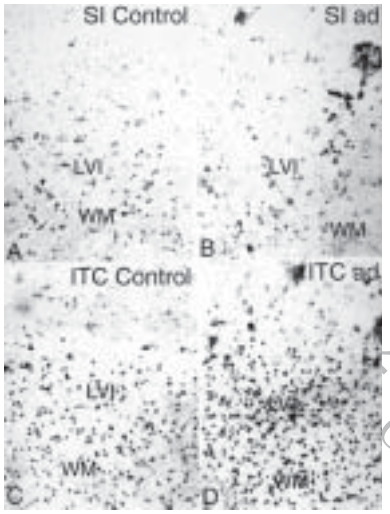
New Perspectives on the Neurochemical Changes of Alzheimer's Disease

Dr. Changiz Geula reviewed recent evidence that updates the "cholinergic hypothesis" and provides insights into the clinical efficacy of cholinesterase (ChE) inhibitors. Alzheimer's disease is widely acknowledged to involve characteristic morphologic brain lesions and neurochemical changes particularly within cortical cholinergic systems.[1] Pathologic lesions in the brains of Alzheimer's disease patients at postmortem consist of extracellular plaques formed primarily of the amyloid-β protein and intraneuronal neurofibrillary tangles, stated Dr. Geula. Mature (compact) plaques appear to evolve from diffuse plaques via transformation of amyloid-β protein into fibrils with an abnormal protein conformation. Fibrillar amyloid-β protein is neurotoxic, and neuritic (compact) plaques formed as fragments of damaged neurons become incorporated into amyloid-β protein deposits.[2] Dr. Geula noted that compact plaques are additionally associated with glial cell proliferation, producing further damage. Plaque maturation and resulting neurotoxicity are specific to Alzheimer's disease and are likely contributors to the substantial cholinergic neuronal loss and clinical dementia characteristic of the disorder.[3,4] Dr. Geula stated that in Alzheimer's disease, there is a marked loss of cortical cholinergic axons, which leads to a progressive decrease in available acetylcholine (ACh) and accounts, at least in part, for impairments in activities of daily living (ADL), behavior, and cognition seen in Alzheimer's disease. This cholinergic deficit has led to the development of the "cholinergic hypothesis" and over the last 25 years has formed the logical basis for ChE inhibitor therapy in Alzheimer's disease.[3,4]

In the Alzheimer's diseased brain, acetylcholinesterase (AChE) activity falls progressively over the course of the disease, and in the Lewy body variant of Alzheimer's disease, in which cholinergic loss is most profound, levels of AChE assessed at autopsy may be undetectable.[5,6] In contrast, postmortem studies indicate significantly elevated levels of butyrylcholinesterase (BuChE) in brains of Alzheimer's disease patients.[7,8] BuChE activity is low in normal brains and increases substantially with increasing severity of Alzheimer's disease and is correlated with an increase in plaque maturation.[9]

Dr. Geula observed that BuChE activity is present in many plaques and tangles,[10] and histochemical studies indicate proliferating glial cells to be the source (Figure 1).[7] This glial cell ChE activity shows biochemical properties identical to those associated with plaques and tangles from Alzheimer's diseased brains. Additionally, ChE enzymes associated with plaques and tangles may function as peptidases, cleaving amyloid-β from the amyloid precursor protein (APP), and thus may contribute to the formation of plaques. Dr. Geula argued that these findings suggest a direct role for BuChE in the

Figure 1. Glial Cells Containing BuChE Proliferate in Alzheimer's Disease[a]



[a]Abbreviations: ad = Alzheimer's disease, BuChE = butyrylcholinesterase, ITC = inferotemporal cortex, LVI = layer b of cortex, SI = somatosensory cortex, WM = cortical white matter.

Table 1. Characteristics of Different Cholinesterase Inhibitors[a]

Characteristic	Tacrine	Donepezil	Rivastigmine	Galantamine
Year available	1993	1996	2000	NDA filed 9/99
Brain selectivity	No	Yes	Yes (brain region selectivity)	Yes
Reversibility	Reversible	Reversible	Reversible	Reversible
Chemical class	Acridine	Piperidine	Carbamate	Phenanthrene alkaloid
Enzymes inhibited				
AChE	Yes	Yes	Yes	Yes
BuChE	Yes	Negligible	Yes	Negligible

[a]Abbreviations: AChE = acetylcholinesterase, BuChE = butyrylcholinesterase, NDA = New Drug Application.

generation of the neurotoxic plaques characterizing Alzheimer's disease.

According to Dr. Geula, as Alzheimer's disease progresses from mild to severe stages and levels of AChE fall, it is likely that BuChE assumes a more important role in regulating ACh in the Alzheimer's diseased brain. Dr. Geula suggested, therefore, that an ability to inhibit BuChE would also be an asset in helping to increase functional levels of ACh over the course of disease severity and in slowing plaque maturation.

Demonstrating that available ChE inhibitors differ in their chemical structures and pharmacologic effects (Table 1), Dr. Geula noted that certain ChE inhibitors have an ability to inhibit both AChE and BuChE while others do not. Dr. Geula concluded by recognizing that sustained efficacy over the course of disease severity, as observed with the ChE inhibitor rivastigmine, may be a result of this dual-inhibition action. ❑

Assessing and Treating Behavioral Symptoms in Alzheimer's Disease

The neurochemical changes that are characteristic of Alzheimer's disease result in symptomatology that includes behavioral disturbances in greater than 80% of cases.[11] Behavioral abnormalities exacerbate patient disability, greatly increase caregiver distress, and are often the single largest factor in the decision to institutionalize an Alzheimer's disease sufferer.[12]

Dr. Cummings discussed behavioral assessment instruments used in Alzheimer's disease studies. The instrumentation must reflect the presence of behavioral changes, be reliable and reproducible across examiners, and be sensitive to changes resulting from disease progression and/or changes induced by treatment. Dr. Cummings noted that, in general, 2 classes of instruments are used. Multidimensional instruments assess multiple symptoms, but do so in somewhat less depth than unidimensional instruments, he explained. Such instruments include the Neuropsychiatric Inventory (NPI), developed by Dr. Cummings' group and used widely; the Behavioral Pathology in Alzheimer's Disease Scale (BEHAVE-AD); the Behavior Rating Scale for Dementia (BRSD); and the Alzheimer's Disease Assessment Scale, noncognitive portion (ADAS-noncog), used in much of the early work on Alzheimer's disease. Alternatively, unidimensional instruments, which assess one core or interesting symptom in greater depth, are available. Examples include the Cornell Scale for Depression in Dementia or the Cohen-Mansfield Agitation Inventory. Dr. Cummings stated that his group favors the multidimensional approach.

The NPI is based on a caregiver interview and assesses behaviors present in the preceding 4 weeks.[13] Dr. Cummings reported the NPI to be valid, reliable, and sensitive to change. The NPI assesses delusions, depression, agitation, disinhibition, euphoria, hallucinations, anxiety, irritability, apathy, and aberrant motor behaviors. These 10 dimensions were chosen because they are common in Alzheimer's disease or other dementia syndromes, he explained. In general, behavioral symptoms tend to increase with disease progression. Additionally, behavioral abnormalities fluctuate and may spontaneously show remission and recurrence.[14] Symptoms increase with the progression of Alzheimer's disease and produce a tremendous amount of caregiver distress.[12,15] Using the NPI again, Dr. Cummings reported that almost 20% of caregivers rated delusions, hallucinations, agitation, depression, and irritability as causing great

distress.[16] Dr. Cummings emphasized that if clinicians can manage (clinically) behavioral symptoms, they will greatly improve the life of both patient and caregiver.

There are currently no U.S. Food and Drug Administration (FDA)-approved pharmacologic treatments for behavioral symptoms in Alzheimer's disease, although medications for schizophrenia and idiopathic depression have found use in treating behavioral disorders in Alzheimer's disease. However, the FDA now requires that drugs claiming efficacy in treating behavioral abnormalities in Alzheimer's disease must be shown to do so in adequate and well-controlled clinical trials. This is a great step forward for the Alzheimer's community, stated Dr. Cummings. Studies of the effects of psychotropic, antipsychotic, antidepressant, anticonvulsant, mood-stabilizing, and ChE-inhibitor therapies on behavioral symptoms in Alzheimer's disease patients are now emerging.

In nursing home Alzheimer's disease patients treated with the antipsychotic risperidone, 25% to 45% of patients' delusional symptomatology resolved with treatment.[17] In this study, as in all others published to date, the placebo response was quite robust, probably reflecting the involvement and engagement of both patients and caregivers in the trial's process and making it more difficult to show drug effectiveness. With olanzapine therapy, there appears to be a low-to-moderate dose window (5–10 mg) within which psychotic symptoms can be reduced in Alzheimer's disease patients.[18] Furthermore, at these doses, olanzapine treatment of the Alzheimer's disease patient may result in improvements in the occupational disruptiveness reported by caregivers, as measured by the Occupational Disruptiveness Scale (part of the NPI-Nursing Home Assessment [NPI-NH]).[18] Citalopram treatment of Alzheimer's disease patients who had preexisting depressive symptoms showed significant improvements after 6 weeks of therapy, assessed by the Montgomery-Asberg Depression Rating Scale.[19] Dr. Cummings stated this to be preliminary evidence of the utility of antidepressants in reducing mood disturbance in Alzheimer's disease.

Dr. Cummings also considered the role of ChE inhibitors in modifying behavioral disturbances in Alzheimer's disease. Rivastigmine, tacrine, and donepezil were developed as antidementia agents, with FDA-required outcomes of improving global functioning and cognition. It has now become clear that these agents also provide benefits in the behavioral domain and may effect a delay in nursing home placement. Tacrine demonstrated a dose-related (40–160 mg) effect of improving Mini-Mental State Examination (MMSE) scores and simultaneously reduced NPI scores in Alzheimer's disease, which prompted other investigations of behavioral benefits with ChE inhibitor treatment.[20] In a retrospective, cost-assessment study of treating Alzheimer's disease with donepezil, a reduction was found in the use of concomitant medications (including antidepressants, antipsychotics, anxiolytics, and sedative hypnotics) in the patients receiving the ChE inhibitor.[21]

A 1-year multicenter U.S. study[22] involving 173 Alzheimer's disease patients with a mean baseline total NPI-NH score of 15.8 investigated behavioral benefits of rivastigmine therapy. More than 85% of patients exhibited at least one behavioral symptom at baseline. After 52 weeks of rivastigmine treatment, many behavioral symptoms showed significant improvement, as measured by the NPI-NH. The most impressive effect was on disinhibition, but improvements were also found in nighttime behavioral disturbances, aberrant motor behavior, anxiety, and irritability. Concurrently, there were significant reductions in concomitant use of antipsychotic medication in this population of patients with severe Alzheimer's disease. While taking rivastigmine, 31% of patients had their antipsychotic medication stopped, 12% had their medication reduced, and only 7% increased use or initiated antipsychotic therapy during the trial[22]—a striking result suggesting behavioral benefits of rivastigmine, commented Dr. Cummings.

In conclusion, Dr. Cummings emphasized the progressive and fluctuating nature of behavioral symptoms and reminded the audience of the distressing impact of behavioral abnormalities on caregivers. He looked forward to the more widespread use of ChE inhibitors and FDA-approved psychotropic medications in managing behavioral symptoms in Alzheimer's disease. ❑

Mild Cognitive Impairment: An Early Stage of Alzheimer's Disease?

Recent evidence suggests that substantial cognitive decline is not part of normal aging. Consequently, even relatively mild cognitive decline may be an early sign of the onset of Alzheimer's disease. Dr. John Morris reviewed the clinical assessment of mild cognitive impairment, which allows the possible distinction of a pre-Alzheimer's condition en route to the development of more profound dementia. Dr. Morris stated that, in many instances, mild cognitive impairment does represent an early stage of Alzheimer's disease.

Dr. Morris outlined the criteria adopted by the Alzheimer's Disease

Table 2. Mild Cognitive Impairment: Definition and Criteria for Inclusion in an Antioxidant Study[a]

Definition of mild cognitive impairment
A transitional phase between nondemented aging and clinically overt dementia
Heterogeneous: not all individuals eventually progress to dementia
Operationalization of mild cognitive impairment[b]
Memory complaints
Memory deficit (eg, score ≤ 4 on paragraph recall [8–15 y of education])
Mini-Mental State Examination score ≥ 24
Clinical Dementia Rating score = 0.5
Not sufficiently impaired for diagnosis of Alzheimer's disease or other dementia

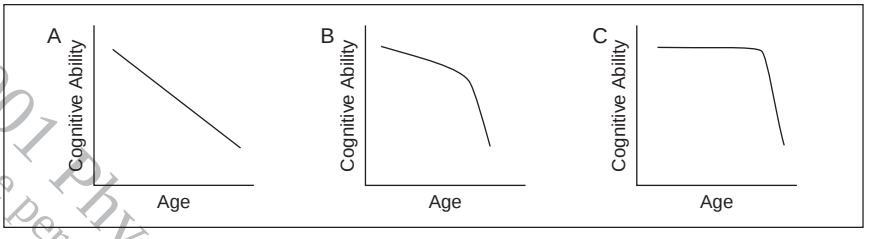
[a]Adapted from Petersen et al.[23]
[b]Inclusion criteria adopted by the Alzheimer's Disease Co-operative Study.

Table 3. Difficulties in Discriminating Very Mild Alzheimer's Disease[a]

	Dementia Severity[b]		
Rating Scale	CDR = 0 (no impairment)	CDR = 0.5 (very mild)	CDR = 1 (mild)
MMSE (range, 30–0)	29 (23–30)	24 (19–28)	20 (4–28)
Blessed Scale-cognitive (range, 0–17)	0.2 (0–6)	1.0 (0–6)	4.0 (0.5–9.5)

[a]J.M., unpublished data, 2000. Abbreviations: MMSE = Mini-Mental State Examination, CDR = Clinical Dementia Rating.
[b]Rating scale scores shown as mean (range).

Figure 2. Patterns of Cognitive Decline in Aging



Cooperative Study (ADCS) for inclusion of individuals in trials assessing whether ChE inhibitors and/or antioxidants may delay the progression from mild cognitive impairment to more overt dementia (Table 2).

The Investigation into the Delay to Diagnosis of Alzheimer's disease with Exelon (InDDEx) study addresses the same question of the ChE inhibitor rivastigmine (S. Ferris, Ph.D., unpublished data, May 2000). The InDDEx multicenter study is prospective, randomized, and placebo-controlled and will extend up to 36 months. The study has recruited 1018 individuals meeting criteria for mild cognitive impairment as defined by the ADCS (e.g., Clinical Dementia Rating [CDR] score = 0.5; see Table 2), of whom 526 patients are undergoing assessments of structural brain changes by magnetic resonance imaging (MRI).

Discussing standard diagnostic criteria, Dr. Morris defined dementia as multiple acquired cognitive deficits that are sufficient to interfere with everyday activities, that is, the social and occupational function of the individual. Although the criteria for diagnosis of dementia are generally well accepted, he expressed concern over inconsistencies relating to their implementation. Utilizing principally neuropsychological tests would, in Dr. Morris's view, probably miss a number of people who might be experiencing interference with their usual functions while still performing well enough that they would remain unrecognized. Dr. Morris highlighted the need to look at an interference threshold, beyond which the clinical picture would be changed. This information is often best available from someone who knows the patient well and may have observed a decline in the patient's ability to carry out accustomed activities. Clinicians need to talk to someone who knows the patient well, Dr. Morris emphasized.

In assessing cognitive function, Dr. Morris noted that the range of scores on the MMSE[24] and the Blessed Scale-cognitive portion[25] overlap between nondemented aging and very mild and mild Alzheimer's disease (Table 3) when compared with the more sensitive CDR.[26] Scores on any instrument cannot define a state of cognitive decline; for example, a score of 24 on the MMSE does not necessarily mean that a patient is experiencing dementia if there is no decline from previous level of function.

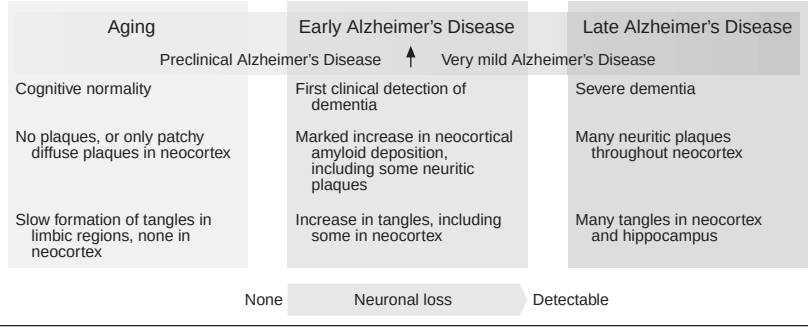
Data for 3 healthy control subjects from a cohort of 82 initially healthy, elderly individuals assessed annually with both clinical and psychometric measures showed that in the absence of disease, cognitive function can be maintained for 15-year periods between ages 60 and 90 years.[27] This finding suggests that normal cognitive changes with age might be viewed as in panel C of Figure 2. Dr. Morris does not consider cognitive decline to be synonymous with aging. He adds that data suggest that there is not an inevitable slow preclinical decline, but rather that cognitive function may be maintained even with increasing age until such time as disease manifests, and then there is a sharp drop in cognitive abilities. It is important to emphasize that informant-based assessments are sufficiently sensitive to detect this threshold of cognitive decline (see earlier discussion by Morris and colleagues[28]). Dr. Morris conceded that in the general population, there might be some cognitive change with age (see Figure 2, panel B), but not nearly so severe as many might consider (see Figure 2, panel A).

In this same cohort, some of the 82 individuals developed dementia, as would be expected in an aged patient sample. Again, the data on cognitive changes matched very closely the pattern modeled in Figure 2, panel C. Moreover, when individuals did progress from a CDR score of 0 to 0.5, 80% went on to more severe dementia (CDR score ≥ 1) within 6 years. These data suggest that mild cognitive impairment (CDR score = 0.5) does represent an early stage of Alzheimer's disease from which there is a predictable progression over time to the onset of overt dementia. Further supporting the notion that mild cognitive impairment represents early Alzheimer's disease are autopsy results which show that patients with a CDR score of 0.5 have tangles and amyloid plaques in the brain, therefore meeting the neuropathologic criteria for Alzheimer's disease.

Why tell somebody that he or she has early-stage Alzheimer's disease? Dr. Morris asked. His view is that many patients and families have an interest in knowing, and for many, removing a degree of uncertainty about the cause of cognitive problems is helpful. Additionally, in this very mild disease stage, patients retain significant function and can play an active role in planning and preparing for the future. Most importantly, the option of treatment with ChE inhibitors, antioxidants, or similar compounds in this early stage of Alzheimer's disease is now available. Trials with certain ChE inhibitors suggest that early treatment may retard progression of the disease,[29] although conclusive evidence for this must await the results of clinical trials now in progress.

Dr. Morris closed by discussing a hypothetical sequence of clinicopathologic events in aging and Alzheimer's disease (Figure 3). From the studies of his group, all individuals studied at autopsy who had died at later than 50 years of age without even mild Alzheimer's disease would be expected to show at least minimal evidence of entorhinal and hippocampal neurofibrillary tangles but few, if any, neocortical abnormalities.[31] Medial temporal lobe tangles may be a part of normal aging, Dr. Morris suggested. Early Alzheimer's disease is marked by increases in neocortical amyloid-β deposition and ultimately the development of the neuritic pathology of neocortical plaques and tangles. This pathologic transformation is associated with neuronal loss and, in Dr. Morris's view, is concurrent with the transition from a preclinical condition to one in which very mild Alzheimer's disease (mild cognitive impairment) is clinically detectable and decisions are required concerning referral and/or pharmacologic intervention. ❑

Figure 3. Hypothetical Sequence of Clinicopathologic Events in Aging and Alzheimer's Disease[a]



[a]Reprinted, with permission, from Morris.[30]

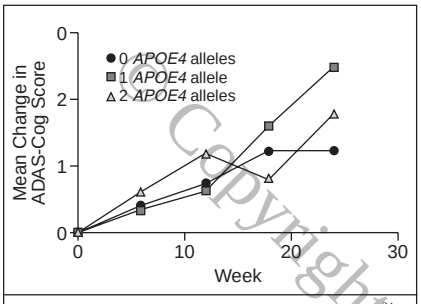
New Approaches in Assessing Delay of Progression of Alzheimer's Disease

There is widespread clinical interest in predictors of Alzheimer's disease severity and assessment of how well patients might be expected to respond to pharmacologic intervention. Dr. Martin Farlow reported briefly on genetic risk factors for Alzheimer's disease and continued with an examination of the severity of disease at diagnosis as a predictor for the magnitude of patients' response to ChE inhibition and the ability of ChE inhibitors to slow the progression of the disease.

APOE genotype was among the first genetic factors to be strongly associated with Alzheimer's disease, and it was hoped to provide a possible predictor of response. In early studies examining the efficacy of tacrine, patients with *APOE4* allele appeared less responsive to therapy than non-*E4* patients.[32,33] Further studies with ChE inhibitors produced equivocal results relating *APOE* genotype to therapeutic response. Currently, the data suggest that a similar response rate should be expected for *APOE4* carriers and noncarriers alike (Figure 4).[34] Dr. Farlow noted that research is not at the point at which the decision of whether or not to provide pharmacologic treatment can be based on a patient's genotype.

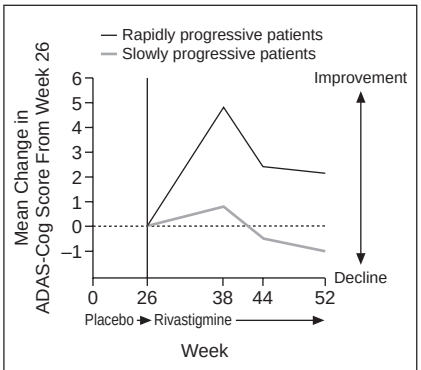
In contrast, clinical trials of the ChE inhibitor rivastigmine have indicated that disease stage at presentation is a

Figure 4. Influence of *APOE* Genotype on Disease Progression in Patients Receiving Metrifonate[a]



[a]Reprinted, with permission, from Farlow et al.[34] Abbreviation: ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive portion.

Figure 5. Response to Rivastigmine Treatment by Disease Progression Rate[a]



[a]Data from Farlow et al.[29] Abbreviation: ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive portion.

clear predictor of responsiveness to therapy as well as Alzheimer's disease progression. Patients with moderate Alzheimer's disease (MMSE score of 10–17, Global Deterioration Scale score of 5–6) tended to deteriorate more rapidly if untreated and, paradoxically, tended to show larger responses to ChE inhibitor therapy than individuals with less severe symptoms—as much as an 8-point improvement in ADAS, cognitive portion (ADAS-cog) scores compared with placebo, Dr. Farlow confirmed.[35] He then asked if it is really the disease stage that matters, or if response has more to do with how fast the patient is progressing. Data from a large, multicenter, double-blind, randomized, placebo-controlled trial of rivastigmine (and open-label extension),[29] in which 82% of patients continued into the open-label phase of the trial, enabled Dr. Farlow to address this question.

At 26 weeks, placebo patients were dichotomized on the basis of their rates of decline during the double-blind phase. Rapidly progressive (ADAS-cog score > 4 and a > 10% decline in Progressive Deterioration Scale [PDS] score while on placebo treatment) and slowly progressive (ADAS-cog score < 4 and a < 10% decline in PDS score while on placebo treatment) patients were started on rivastigmine treatment at 26 weeks and then assessed at 38, 44, and 52 weeks. After 12 weeks of receiving rivastigmine, patients that were previously rapidly progressive showed a 5-point improvement in ADAS-cog score from their week 26 baseline (Figure 5).[29] The slowly progressive patients showed a smaller magnitude of improvement (see Figure 5).[29] Dr. Farlow noted that this effect persists irrespective of initial disease severity and is also seen in assessments of ADL (i.e., via PDS scores).

While ChE inhibitors are FDA-approved as symptomatic therapy for Alzheimer's disease, increasing evidence supports a role for these drugs in altering the course of the disease and especially in slowing the rate of symptomatic decline.

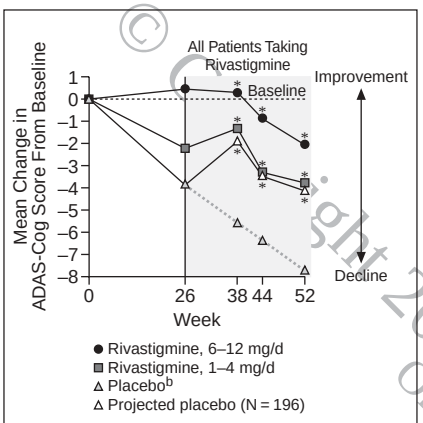
Dr. Farlow described preclinical studies that suggest ChE inhibitors modify the metabolism of the amyloid-β precursor protein, with some evidence of a reduction in secretion of Aβ42.[36] Furthermore, the increasing presence of BuChE, associated with the development of cortical and neocortical neuritic plaques, is concurrent with declines in AChE activity.[37] This finding suggests that ChE inhibitors with a dual inhibition action for both AChE and BuChE might provide therapeutic benefit by reducing neurotoxic plaque formation.

Knopman et al.[38] initially assessed the long-term effects of ChE inhibitors, reporting a 9-month delay in the likelihood of entering nursing home care for Alzheimer's disease patients treated with tacrine (120 or 160 mg/day). Long-term follow-up data after the donepezil trials indicated a far smaller cognitive decline (as determined by ADAS-cog scores) over 2 years in donepezil-treated patients as compared with predicted declines based on the natural history of untreated patients with moderate Alzheimer's disease.[39,40] While the tacrine result is more impressive, both data sets support the ability of ChE inhibitors to slow disease progression.

Dr. Farlow noted methodological difficulties in assessing long-term changes in disease progression, including large numbers of discontinuations and ethical concerns associated with long-term placebo-controlled studies and delayed-start, delayed-withdrawal designs. The U.S. B352 rivastigmine trial and B353 open-label extension[41] did approximate a delayed-start design. Six months of double-blind data were combined with an extension of 6 months of open-label treatment. Patients receiving placebo for the first 6 months were then given rivastigmine (2–12 mg/day) and showed a good initial symptomatic response to the drug. Responses in this group did not, however, match the response (in any assessed domain) of those receiving rivastigmine (6–12 mg/day) from day 1 (Figure 6). The data suggest that placebo patients experienced a loss during the first 6 months that could not be restored. Patients still have a good response to rivastigmine therapy, said Dr. Farlow, but they cannot get back what they have lost.

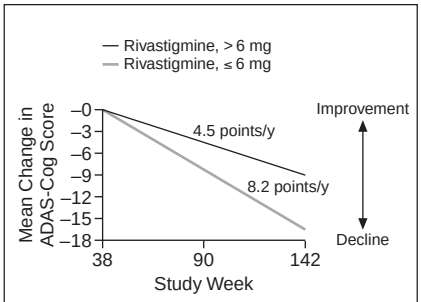
If rivastigmine can modify the rate of disease progression, it seems reasonable to postulate that there should be a dose-response effect. Using data

Figure 6. Effects of Rivastigmine on Mean Change From Baseline ADAS-Cog Score in Patients With Mild to Moderately Severe Alzheimer's Disease[a]



[a]Reprinted, with permission, from Farlow et al.[41] Abbreviation: ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive portion.
[b]Patients treated for 6 months with placebo and then treated for 6 months with rivastigmine, 2–12 mg/day.
*p = .05 vs. projected placebo.

Figure 7. Effects of Rivastigmine Dose on Rate of Cognitive Decline Measured by Mean Change in ADAS-Cog Score[a]



[a]Reprinted, with permission, from Farlow et al.[29] Abbreviation: ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive portion.

Table 4. Suitability of Brain Imaging Techniques for Use as a Surrogate Marker to Follow Disease Progression[a]

Characteristic	MTA	VBM	Reg	fMRI
Specific for disease	?	–	–	–
Specific for progression	–	±	+	±
Sensitive to change	–	+	+	+
Small measurement error	–	+	+	±
Widely applicable	+	±	±	–
Biological validity	+	–	+	–

[a]Abbreviations: fMRI = functional magnetic resonance imaging, MTA = medial temporal lobe atrophy, Reg = registration, VBM = voxel-based morphometry. Symbols: + = applicable to characteristic, ± = somewhat applicable to characteristic, – = not applicable to characteristic, ? = applicability unknown.

from the rivastigmine trials extending to 3 years and not beginning analysis until week 38, beyond the time of initial symptomatic response, Dr. Farlow and colleagues[29] were able to assess the long-term, dose-related effect on disease progression. Using regression analyses, annualized rates of decline in ADAS-cog scores were calculated for patients receiving ≤ 6 mg/day and > 6 mg/day. Scores for patients receiving ≤ 6 mg/day of rivastigmine declined by 8.2 points per year (95% confidence interval [CI] = 9.1 to 7.3) compared with only 4.5 points per year for patients receiving higher doses (95% CI = 5.1 to 3.9; Figure 7). The analyses considered dropouts, the numbers of which were no different between groups and therefore did not bias the results. Using all data available over the 3-year period, Dr. Farlow and colleagues[29] reported estimated rates of decline to be decreased by 1 point per year for each 3-mg/day increase in rivastigmine dose.

On the basis of the findings from the rivastigmine trials, Dr. Farlow presented 2 primary conclusions. First, patients who prior to treatment have very rapid rates of disease progression, rather than being poor candidates for ChE inhibitor therapy, are actually those who have the most dramatic response to drug intervention. Second, a growing body of evidence suggests that ChE inhibitors, and rivastigmine in particular, may have an effect on delaying disease progression. ❑

Magnetic Resonance Imaging in Measuring Progression of Alzheimer's Disease

Dr. Philip Scheltens presented information on newer brain MRI techniques, both quantitative (medial temporal lobe atrophy [MTA] volumetry, voxel-based morphometry [VBM], and registration) and qualitative (functional MRI [fMRI]), which appear to improve the accuracy and reproducibility of traditional MRI techniques and may allow the assessment of changes in brain morphology over the course of Alzheimer's disease with greater certainty. These refinements of MRI techniques may allow more widespread use in evaluating the need for pharmacologic intervention and assessing therapeutic benefits of agents such as ChE inhibitors.

Dr. Scheltens considered the suitability of MTA, VBM, registration, and fMRI as surrogate markers for following the progression of Alzheimer's disease (Table 4). A marker should be specific for the disease, specific for disease progression, and sensitive enough to detect clinically meaningful changes, with an acceptable measurement error that does not obscure assessment. The parameter should also have biological validity and be measuring a brain change that is causally related to the disease process. Ideally, the marker would also be readily assessed in treatment and testing centers worldwide.

Hippocampal atrophy, as a component of MTA, is clearly distinguished on MRI scans and is considered to be a specific indicator for the presence of Alzheimer's disease.[42] Volume reductions in the hippocampus have also been observed in Lewy body dementia,[43,44] vascular dementia,[44] and Parkinson's dementia,[45] but Dr. Scheltens reasoned that all such disorders contain elements of Alzheimer's pathology. However, with changes in hippocampal volume of the order of 2% to 8% in Alzheimer's disease and MRI measurement

errors averaging 5%, it is difficult to show morphologic changes directly related to the disease process.[46] Morphologic changes in the hippocampus are also considered to occur at such an early stage in disease progression that volume reductions are not as great later in the disease, when it is more likely to be assessed clinically.

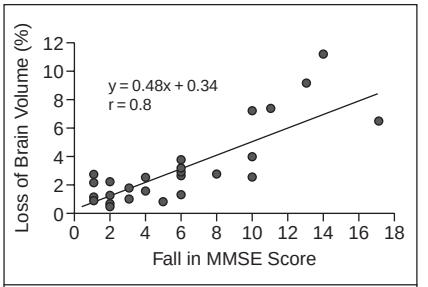
Evidence from postmortem studies has indicated that early neuropathologic changes manifest as atrophy of the entorhinal cortex, continue to the hippocampus before progressing to the association cortices, and finally involve the whole brain.[47] It can therefore be argued that assessing whole brain volume may be a more appropriate means of assessing disease progression. VBM and registration allow this assessment.

VBM utilizes statistical analyses of MRI scans partitioned into gray matter, white matter, and cerebrospinal fluid. Dr. Scheltens presented data indicating gray matter loss in a group of 7 patients with mild-to-moderate Alzheimer's disease as compared with healthy elderly controls.[48]

Registration, as developed by Fox et al.[49] from the Dementia Research Group in London, U.K., utilizes 2 consecutive MRI scans of the same individual made at a 1-year interval. The 2 scans are then "subtracted" by computer to allow any changes in brain volume over the 12-month period to be assessed. Registration has the advantage over VBM of allowing the quantification of changes and has a longitudinal measurement error of ≤ 1%. Healthy individuals are likely to experience a loss of brain volume of approximately 0.2% per year, as compared with around 3% per year in Alzheimer's disease patients. Ideally, a good drug would reverse that cascade of pathologic events and have the volume loss over time reduced from 3% to 0%, Dr. Scheltens suggested. Data were then presented showing a correlation of cerebral atrophy with cognitive decline as measured by change in MMSE scores (Figure 8).[49] Registration is currently being used by the InDDEx study to assess longitudinal morphologic changes in patients as they progress from mild cognitive impairment to Alzheimer's disease.

In fMRI, MRI scans are viewed while the patient is inside the scanner and performs set cognitive tasks. Small and colleagues[50] have reported decreased hippocampal activation in Alzheimer's disease patients and decreased entorhinal activation in one third of a patient group with mild cognitive impairment. Furthermore, in follow-up, all patients in the mild cognitive impairment group showing decreased entorhinal activation progressed to overt Alzheimer's disease within 2 years. From his own work, Dr. Scheltens described studies to investigate the consistency and reproducibility of fMRI. In healthy individuals, he and his colleagues[51] assessed whether the same brain regions were activated and visualized by fMRI if the same cognitive tasks were performed on consecutive occasions. In a qualitative assessment, it appeared that similar regions (occipital lobe, ventromedial stream, and hippocampus) were activated on both occasions, but quantitative analyses (count of active voxels) showed incomplete correspondence.[51] Dr. Scheltens noted that fMRI is less than perfect, especially not perfect enough yet to follow patients over time.

Figure 8. Cognitive Decline in Alzheimer's Disease Correlates With Rate of Cerebral Atrophy[a]



[a]Reprinted, with permission, from Fox et al.[49]

Dr. Scheltens concluded with 5 main points:

1. MRI is a tool with great potential to aid diagnosis and measure disease progression in patients with Alzheimer's disease.
2. Hippocampal atrophy is not well suited to show changes over time.
3. VBM could be used to monitor groups of patients in an unbiased way, but is probably not effective within single patients.
4. Registration has proved to be reliable and valid.
5. fMRI is currently a research tool with limited availability, but has a promising future. ❑

Response to Cholinesterase Inhibitor Treatment Along the Continuum of Alzheimer's Disease

As Alzheimer's disease progresses from mild to severe stages, patients experience deterioration in ADL, behavior, and cognition and become increasingly dependent on caregivers. Therefore, it is essential that clinicians are able to treat patients with agents that provide symptomatic benefits over the course of disease severity. Dr. Ravi Anand presented a review of ChE inhibitor therapies with emphasis on treatment options throughout the stages of the disease.

Deterioration in ADL severely impacts both patient and caregiver. Dr. Anand reported that rivastigmine,[52] tacrine,[53] and donepezil[54] have all been shown to significantly benefit perfor-

mance of ADL. In trials ranging in duration from 26 to 52 weeks, all 3 agents have demonstrated the ability to produce statistically and clinically significant improvements in PDS scores. Data from the rivastigmine study further demonstrated that beneficial effects on ADL are related to disease severity and are observed throughout the progression of the disease.[55] In patients with mild Alzheimer's disease (Global Deterioration Scale score ≤ 3), clinical benefits with rivastigmine are observed on the PDS for high-level ADL such as ability to handle money and tell time. In moderate Alzheimer's disease (Global Deterioration Scale score = 4), rivastigmine improves the activities most impaired at this stage such as ability to dress properly. In more severe patients (Global Deterioration Scale score ≥ 5), rivastigmine benefits basic ADL such as the ability to feed and bathe oneself. The overall pattern of ADL benefit with rivastigmine appears to vary at different stages of disease severity, since at any given disease stage the most pronounced effects will be seen in those activities that are deteriorating or being lost at that stage. For example, an activity lost in the mild stage such as balancing a checkbook is unlikely to be regained by a severe-stage patient during therapy, whereas an activity that has been newly lost, such as dressing independently, may be regained. These findings are crucial in establishing realistic treatment expectations for both patients and caregivers.

Dr. Anand noted that behavior has become the forgotten domain of Alzheimer's disease. However, recent data from trials with ChE inhibitors specifically investigating the behavioral domain have reported clinically significant benefits (see Dr. Cummings' presentation described above). Dr. Anand noted the benefit of the newer ChE inhibitor rivastigmine for patients with Lewy body dementia, an Alzheimer's disease variant characterized by the most profound cholinergic loss. These patients have prominent behavioral symptoms and cannot receive classical antipsychotic therapies due to serious and potentially life-threatening adverse reactions, Dr. Anand explained.[56]

Table 5. Effect of Rivastigmine on Behavioral Symptoms[a]

Variable	Mild/ Moderate[b]	Moderate/ Severe[c]
Mean baseline Neuropsychiatric Inventory score	17.8	24.4
Mean change in Neuropsychiatric Inventory score	–3.2[d]	–7.3[e]

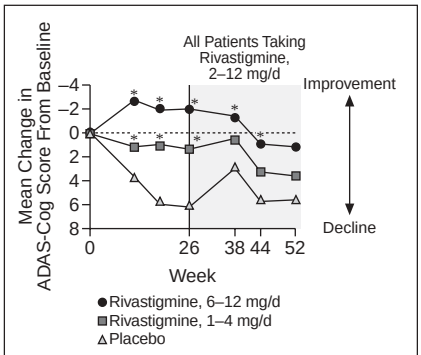
[a]Data from Anand et al.[57]
[b]92 patients from nursing homes.
[c]59 patients with Lewy body dementia.
[d]18% reduction at week 26.
[e]30% reduction at week 20.

Reviewing treatment effects in mild, moderate, and severe dementia, Dr. Anand noted with interest that behavioral benefits of rivastigmine therapy are not only seen in severe Alzheimer's disease patients in a nursing home setting, but are evident in patients at all stages of the disease. (Table 5).[57] Furthermore, the magnitude of behavioral benefit increases with increasing severity of behavioral dysfunction.

Cognition has been extensively studied with all ChE inhibitors. In mild-to-moderate Alzheimer's disease, rivastigmine,[41,52] tacrine,[58] and donepezil[39] all produce improvements in ADAS-cog scores, with somewhat larger drug-placebo differences reported for rivastigmine and tacrine compared with donepezil, in similarly designed 24- to 30-week trials. However, are the cognitive benefits maintained across the spectrum of disease severity? Dr. Anand asked.

Dr. Anand presented data from moderately severe and severe Alzheimer's disease (Global Deterioration Scale score ≥ 5). Following 6 months of treatment with 6 to 12 mg/day of rivastigmine, Alzheimer's disease patients showed an 8-point improvement in ADAS-cog scores relative to placebo (Figure 9).[35] During a further 26-week open-label phase (all patients receiving 2–12 mg/day of rivastigmine), the former placebo-treated patients showed a marked improvement in ADAS-cog scores, particularly during the first 12 weeks of receiving rivastigmine.[35] At no point did the former placebo group attain the same cognitive benefit as those patients who had received 6 to 12 mg/day of rivastigmine throughout. According to Dr. Anand, this indicates that the delay in start of rivastigmine in the placebo-treated patients reduces their ability to benefit fully from treatment. Furthermore, after 52 weeks of receiving rivastigmine (6–12 mg/day), the cognitive decline of only 1 point on the ADAS-cog was approximately half of that observed in the placebo group at 8 weeks. These data also support the ability of rivastigmine to delay the cognitive deterioration in advanced or more severe Alzheimer's disease by at least 10 months, thus further reinforcing findings of greater benefit through initiating treatment early in the progression of the disease.

Figure 9. Long-Term Effects of Rivastigmine on Cognition in Patients With Moderately Severe to Severe Alzheimer's Disease[a]



[a]Data from Doraiswamy et al.[35] Abbreviation: ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive portion. Moderately severe to severe Alzheimer's disease designated by Global Deterioration Scale score ≥ 5.
*p < .05 vs. placebo.

Table 6. ChAT and AChE Activities by Popular and Baseline Level of Cognition[a]

Activity (nmol ACh/h/mg protein)	Alzheimer's Disease			Lewy Body Dementia
	Mild	Moderate	Severe	
ChAT	14.6 ± 1.4	10.1 ± 1.1	3.1 ± 0.7	2.4 ± 1.9
AChE	390 ± 30	305 ± 10	200 ± 25	ND

[a]Data from Davis et al.[5] and Tiraboschi et al.[6] Abbreviations: ACh = acetylcholine, AChE = acetylcholinesterase, ChAT = choline acetyltransferase, ND = not detectable. All values shown as mean ± SD.

Table 7. Cognitive Change With Rivastigmine Treatment Across the Spectrum of Severity of Cognitive Dysfunction

MMSE[a] Score	Alzheimer's Disease			Lewy Body Dementia
	Mild	Moderate	Severe	
Baseline, mean ± SD	21.6 ± 3.6	15.8 ± 3.9	9.3 ± 5.3	17.9 ± 4.6
Drug-placebo difference	0.7	0.8	0.6	1.7

[a]Data from Tariot et al.[59] Abbreviation: MMSE = Mini-Mental State Examination.

Levels of cholinergic markers correlate with disease severity in Alzheimer's disease patients who have been followed to autopsy (Table 6).[5,6] Levels of choline acetyltransferase and ACh show progressive decline as the severity of Alzheimer's disease increases, with AChE levels being virtually undetectable in patients with Lewy body dementia.[5,6] Furthermore, the greatest cognitive benefit with rivastigmine treatment is also observed for patients with Lewy body dementia (Table 7).[59] Dr. Anand reported that patients with Lewy body dementia also show greater behavioral improvement than patients with less severe Alzheimer's disease. He suggested that the reason why a larger effect is beginning to be seen in more severe patients is perhaps because of the greater cholinergic deficiency in those patients.

Dr. Anand concluded that some ChE inhibitors do appear to be more effective over the course of disease severity. Referring to a hypothesis proposed by Dr. Geula (see above), Dr. Anand suggested that an explanation for these findings may rest in the elevated BuChE activity observed in Alzheimer's diseased brains. As Alzheimer's disease progresses and levels of AChE decline, levels of BuChE are shown to increase. Agents such as rivastigmine and tacrine that have the ability to inhibit both AChE and BuChE demonstrate sustained efficacy over the course of the disease and may show greatest therapeutic benefit in patients with disease of greater severity. ❑

Conclusion

Losses in cholinergic function in the Alzheimer's disease brain, as proposed by the "cholinergic hypothesis," have remained fundamental to our understanding of the etiology of Alzheimer's disease for 25 years. The progressive cognitive decline characteristic of Alzheimer's disease has long been associated with a profound loss of cholinergic function. These neurochemical changes, which form the basis of ChE inhibitor therapy, also result in behavioral disturbances. Given the high levels of patient and caregiver distress associated with behavioral abnormalities, the behavioral domain is now receiving far greater clinical attention. It is important to note that in mild cognitive impairment, which may represent early-stage Alzheimer's disease, clinical symptoms can predate any significant cholinergic deficit, whereas in Lewy body dementia, the cholinergic loss in some areas may be almost complete.

Trials investigating the efficacy of ChE inhibitors in Alzheimer's disease have reported a wide range of clinical benefits over the course of the disease and in all symptomatic domains. Explanation of the therapeutic benefits of ChE inhibitors almost certainly involves the neurochemical changes observed in Alzheimer's disease and their progression. Indeed, recent insights into the pharmacology of the disease reveal that in addition to AChE, BuChE may also be of functional significance, since levels of this enzyme actually increase as Alzheimer's disease progresses. This finding suggests that there may be clinical benefits from inhibiting both enzymes, particularly since levels of AChE are shown to fall as disease severity increases.

Trials have shown that some ChE inhibitors, such as rivastigmine, might also be able to slow the progression of symptomatic decline in Alzheimer's disease, possibly by acting on altered forms of AChE and BuChE associated with neuritic plaques and tangles. Substantial therapeutic benefit may be gained by the earliest intervention with such compounds. Finally, the morphologic changes in the Alzheimer's diseased brain can be assessed using traditional MRI and new MRI techniques with improved accuracy and reproducibility.

In the future, as ChE inhibitors are administered increasingly early in the disease course, significant delays in the decline associated with Alzheimer's disease are likely to become a widespread reality, resulting in improved quality of life for both patient and caregiver. ❑

To cite a section from these symposia, follow the format below:
Geula C. New perspectives on the neurochemical changes of Alzheimer's disease, pp 791–792. In: Geula C, Farlow M, chairs. Alzheimer's Disease: Translating Neurochemical Insights Into Clinical Benefits [ACADEMIC HIGHLIGHTS]. J Clin Psychiatry 2000;61:791–802

REFERENCES

1. Katzman R. Medical progress: Alzheimer's disease. N Engl J Med 1986;314:964–973
2. Geula C, Mesulam MM, Saroff DM, et al. Relationship between plaques, tangles, and loss of cortical cholinergic fibers in Alzheimer disease. J Neuropathol Exp Neurol 1998;57:63–75
3. Geula C, Mesulam MM. Cholinergic systems and related neuropathological predilection patterns in Alzheimer disease. In: Bick KL, Katzman R, Terry RD, eds. Alzheimer Disease. New York, NY: Raven Press; 1994:263–291
4. Whitehouse PJ, Price DL, Clark AW, et al. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. Ann Neurol 1981;10:122–126
5. Davis KL, Mohs RC, Marin D, et al. Cholinergic markers in elderly patients with early signs of Alzheimer disease. JAMA 1999;281:1401–1406
6. Tiraboschi P, Hansed LA, Alford M, et al. Cholinergic dysfunction in diseases with Lewy bodies. Neurology 2000;54:407–411
7. Wright CI, Geula C, Mesulam MM. Neurological cholinesterases in the normal brain and in Alzheimer's disease: relationship to plaques, tangles, and patterns of selective vulnerability. Ann Neurol 1993;34: 373–384
8. Enz A, Amstutz R, Boddeke H, et al. Brain selective inhibition of acetylcholinesterase: a novel approach to therapy for Alzheimer's disease. In: Cuello AC, ed. Progress in Brain Research. New York, NY: Elsevier Science; 1993:431–438
9. Guillozet AJ, Smiley JF, Mash DC, et al. Butyrylcholinesterase in the life cycle of amyloid plaques. Ann Neurol 1997;42: 909–918
10. Mesulam M, Geula C. Butyrylcholinesterase reactivity differentiates the amyloid plaques of aging from those of dementia. Ann Neurol 1994;36:722–727
11. Mega MS, Cummings JL, Fiorello T, et al. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996;46: 130–135
12. O'Donnell BF, Drachman DA, Barnes HJ, et al. Incontinence and troublesome behaviors predict institutionalization in dementia. J Geriatr Psychiatry Neurol 1992;5:45–52
13. Cummings J, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314
14. Levy ML, Cummings JL, Fairbanks LA, et al. Longitudinal assessment of symptoms of depression, agitation and psychosis in 181 patients with Alzheimer's disease. Am J Psychiatry 1996;153:1438–1443
15. Dura JR, Stukenberg KW, Kiecolt-Glaser JK. Anxiety and depressive disorders in adult children caring for demented parents. Psychol Aging 1991;6:467–473
16. Kaufer DI, Cummings JL, Christine D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the neuropsychiatric inventory caregiver distress scale. J Am Geritatr Soc 1998;46: 210–215
17. Katz IR, Jeste DV, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry 1999;60: 107–115
18. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic behavioral symptoms in patients with Alzheimer's disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry. In press
19. Nyth AL, Gottfries CG, Lyby K, et al. A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatr Scand 1992; 86:138–145
20. Kaufer DI, Cummings JL, Christine D. Effect of tacrine on behavioral symptoms in Alzheimer's disease: an open-label study. J Geriatr Psychiatry Neurol 1996; 9:1–6
21. Small GW, Donahue JA, Brooks RL. An economic evaluation of donepezil in the treatment of Alzheimer's disease. Clin Ther 1998;20:838–850
22. Anand R, Koumaras B, Hartman R. The effects of rivastigmine on behavioral symptoms in patients in a nursing home setting. Neurobiol Aging 2000;21:S220
23. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56:303–308
24. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinicians. J Psychiatr Res 1975;12: 189–198
25. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968;114:797–811
26. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414
27. Rubin EH, Storandt M, Miller JP, et al. A prospective study of cognitive function and onset of dementia in cognitively healthy elders. Arch Neurol 1998;55:395–401
28. Morris JC, McKeel DW, Storandt M, et al. Very mild Alzheimer's disease: informant-based clinical, psychometric, and pathologic distinction from normal aging Neurology 1991;41:469–478
29. Farlow MK, Messina J, Anand R, et al. Attenuation in the progression of cognitive deterioration in Alzheimer's disease with rivastigmine: a dose-dependent effect. In: New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association; May 16, 2000; Chicago, Ill. Abstract NR274:130
30. Morris JC. Is Alzheimer's disease inevitable with age? J Clin Invest 1999;104: 1171–1173
31. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol 1999; 45:358–368
32. Farlow MR, Lahiri DK, Poirier J, et al. Apolipoprotein E genotype and gender influence response to tacrine. Ann N Y Acad Sci 1996;802:101–110
33. Poirier J, Delisle MC, Quirion R, et al. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. Proc Natl Acad Sci U S A 1995;92:12260–12264
34. Farlow MK, Cyprus PA, Nadel A, et al. Metrifonate treatment of Alzheimer's disease: influence of APOE genotype. Neurology 1999;53:2010–2016
35. Doraiswamy M, Anand R, Hartman R, et al. Cognitive effect of rivastigmine, a new generation cholinesterase inhibitor in moderately severe to advanced Alzheimer's disease [poster]. Presented at the 13th annual meeting of the American Association for Geriatric Psychiatry; March 2000; Miami, Fla
36. Lahiri D, Farlow M, Numberger JL, et al. Effects of cholinesterase inhibitors on the secretion of beta-amyloid precursor protein in cell cultures. Ann N Y Acad Sci 1997; 826:416–421
37. Perry EK, Tomlinson BE, Blessed G, et al. Correlation of cholinergic abnormalities with senile plaques and mental scores in senile dementia. Br Med J 1978;2: 1457–1459
38. Knopman D, Schneider L, Davis K, et al. Long-term tacrine (Cognex) treatment: effects on nursing home placement and mortality. Neurology 1996;47:166–177
39. Rogers SL. Perspectives in the management of Alzheimer's disease: clinical profile of donepezil. Dement Geriatr Cogn Disord 1998;9(suppl 3):29–42
40. Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiatry 1994; 151:390–396
41. Farlow M, Anand R, Messina J, et al. A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease. Eur Neurol. In press
42. De Leon M, Convit A, Se Santi S, et al. Contribution of structural neuroimaging to the early diagnosis of Alzheimer's disease. Int Psychogeriatr 1997;9:183–190
43. Hashimoto M, Kitagaki H, Imamura T, et al. Medial temporal and whole-brain atrophy in dementia with Lewy bodies: a volumetric MRI study. Neurology 1998;51:

357–362
44. Barber R, Gholkar A, Scheltens P, et al. Apolipoprotein E epsilon4 allele, temporal lobe atrophy, and white matter lesions in late-life dementias. Arch Neurol 1999;56: 961–965
45. Hanyu H, Asano T, Sakamoto S, et al. Is hippocampal atrophy a specific change for Alzheimer's disease? No To Shinkei 1999;51:947–951
46. Jack CR, Petersen RC, Xu YC, et al. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. Neurology 1997;49:786–794
47. Schneider LS. Cholinergic deficiency in Alzheimer's disease: pathogenic model. Am J Geriatr Psychiatry 1998;6:S49–S55
48. Rombouts SA, Barkhof F, Witter MP, et al. Unbiased whole brain analysis of grey matter loss in Alzheimer's disease. Neurosci Lett 2000;285:231–233
49. Fox NC, Scahill RI, Crum WR, et al. Correlation between rates of brain atrophy and cognitive decline in AD. Neurology 1999;52:1687–1689
50. Small SA, Perera GM, DeLaPaz R, et al. Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. Ann Neurol 1999;45:466–472
51. Machielsen WCM, Rombouts SA, Barkof F, et al. FMRI of visual encoding: reproducibility of activation. Hum Brain Mapping 2000;9:1156–1164
52. Corey-Bloom JF, Anand R, Veach J. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharmacol 1998;1:55–65
53. Knapp MJ, Knopman DS, Solomon PR, et al. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. JAMA 1994;271:985–991
54. Winblad B. Long-term therapeutic benefits of acetylcholinesterase inhibitor therapy in patients with Alzheimer's disease. Presented at the Satellite Symposium "Extending the Frontiers of Cholinesterase Therapy in Dementia," the 6th International Stockholm/Springfield Symposium on Advances in Alzheimer's Therapy; April 6, 2000; Stockholm, Sweden
55. Potkin SG, Messina J, Graham S. Spectrum of ADL impairment and response to rivastigmine varies by severity of Alzheimer's disease. Neurobiol Aging 2000;21:S222
56. McKeith I, Fairbairn A, Perry EK, et al. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. Br Med J 1992;305:673–678
57. Anand R, Koumaras B, Hartman R, Study B452 Investigators. The effects of rivastigmine on behavioral symptoms in severe AD patients in a nursing home setting. Presented at the World Alzheimer Congress; July 9–18, 2000; Washington, DC
58. Farlow M, Brashear A, Hui S, et al. The effects of tacrine in patients with mild versus moderate stage Alzheimer's disease. In: Iqbal K, Mortimer JA, Winblad B, et al. Research Advances in Alzheimer's Disease and Related Disorders. London, England: John Wiley & Sons; 1995:283–292
59. Tariot P, Anand R, Loy R. Effect of rivastigmine on behavior may be predicted by the underlying cholinergic deficits. Presented at the annual meeting of the American Association of Geriatric Psychiatry; March 12, 2000; Miami, Fla