Understanding Changes in Cholinergic Function: Implications for Treating Dementia

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *summarizes important new clinical data presented during satellite symposia held on June 19, 2001, during the XVII World Congress of Neurology (WCN), at Earl's Court Conference and Exhibition Centre, London, United Kingdom, and on September 10, 2001, 10th Congress of the International Psychogeriatric Association (IPA), at Athéna Auditorium Acropolis Convention and Exhibition Centre, Nice, France. Participants in the WCN symposium were Jeffrey Cummings, M.D., UCLA Alzheimer's Disease Center, Los Angeles, Calif.; Martin Farlow, M.D., Indiana University School of Medicine, Indianapolis, Ind.; Changiz Geula, Ph.D., Harvard Medical School, Boston, Mass.; Amos Korczyn, M.D., Sackler School of Medicine, Tel Aviv University, Israel; Ian McKeith, M.D., University of Newcastle-Upon-Tyne, United Kingdom; Agneta Nordberg, M.D., Karolinska Institute, Stockholm, Sweden. Participants at the IPA were Pierre Tariot, M.D., University of Rochester Medical Center, Rochester, New York; Philippe Robert, M.D., Memory Centre of the University Department of Psychiatry, Nice, France; Ian McKeith, M.D., University of Newcastle-Upon-Tyne, United Kingdom; Alistair Burns, M.D., South Manchester Hospitals' NHS Trust, Manchester, United Kingdom.*

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Functional Brain Activity in Alzheimer's Disease: Effects of Cholinergic Therapy

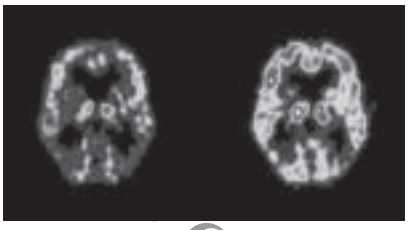
Professor Agneta Nordberg presented data establishing the use of positron emission tomography (PET) imaging to aid the early identification of functional deficits in patients with mild cognitive impairment, which may be an early sign of Alzheimer's disease (AD). Unlike traditional imaging techniques (e.g., X-ray, computerized axial tomography [CAT] scanning), which provide only structural information, PET imaging techniques can identify functional abnormalities in the brains of patients with mild cognitive impairment by measuring deficits in the rate of cerebral glucose metabolism (CMRGlu). Recent data from a 2-year study conducted in 27 patients with mild cognitive impairment have highlighted the possible utility of PET scans to predict clinical outcomes.[1,2] At the end of the study, 20 patients remained stable with mild cognitive impairment, while the remaining 7 patients progressed to AD. The clinical outcome had been accurately predicted by baseline CMRGlu findings in 25 cases out of 27, giving this technique a positive predictive value of 93%.

PET imaging can also measure cerebral activation during tasks of memorization by identifying brain areas of increased blood flow. These are detected on PET scans as changes in the distribution of radiolabeled water ($H_2{}^{15}O$). Professor Nordberg's work has shown that brain activation patterns during attentional task performance differ between patients with mild cognitive impairment and those with AD. Previous work has indicated that treatment with cholinesterase (ChE) inhibitors can lead to improvements in cerebral blood flow and CMRGlu and preservation or increased nicotinic cholinergic receptor function. Professor Nordberg explained that it was of interest to see whether cholinergic therapy could influence the brain activation patterns in AD and if the accurate predictive value of PET imaging techniques could be used to detect any therapeutic benefits in brain function.

Professor Nordberg went on to describe the results of a short-term study in which patients with AD were treated with ChE inhibitors, including the dual ChE inhibitor rivastigmine.[3] After only 3 months of treatment, cerebral perfusion was increased (Figure 1). This was accompanied by an increase in CMRGlu as evaluated by PET imaging and increased numbers of nicotinic cholinergic receptors.

While these results were encouraging for the team, Professor Nordberg explained that they wanted to know if such effects could be sustained over longer treatment periods. She went on to deliver the findings of a longer term study of 11 patients with mild AD (Mini-Mental State Examination [MMSE] score 25 ± 1).[4] These patients were treated with rivastigmine (3–12 mg/day) for a period of 12 months and

Figure 1. Positron Emission Tomography Scans Showing Effect of Rivastigmine on Cerebral Blood Flow in a Patient With Alzheimer's Disease[a]



[a]A. Nordberg, unpublished data, 2000. Left panel = baseline (pretreatment); right panel = increased perfusion (shown as lighter areas) after 3 months' therapy with rivastigmine.

underwent neuropsychological tests of cognition after 3, 6, 9, and 12 months of treatment. In addition, samples of blood and cerebrospinal fluid (CSF) were taken after 3 and 12 months for analysis of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Each patient also underwent PET measurements of CMRGlu, cerebral blood flow, and brain activation during the performance of attentional tasks prior to and after 12 months of treatment.

Inhibition of AChE and BuChE in the CSF increased markedly between 3 and 12 months of rivastigmine therapy.[4] Professor Nordberg noted that the persistent inhibition of AChE activity in the CSF seen at 12 months was in contrast to her previous work with tacrine. The results of neuropsychological testing during the study indicated a beneficial effect on cognitive function at 3 and 6 months, which was sustained at 12 months.

In assessing the utility of PET imaging during the 12-month study, Professor Nordberg noted that treatment with rivastigmine had a protective effect against the deterioration in CMRGlu that was observed in untreated patients. CMRGlu before and after treatment with rivastigmine was significantly improved in the dorsolateral prefrontal cortex—an area of the brain associated with attention. As would be expected with regional increases in CMRGlu, PET scans also revealed increased blood flow.[5]

Professor Nordberg explained that treatment with rivastigmine could change the activation pattern during attentional task performance in patients with AD. After 3 months of rivastigmine therapy, cerebral blood flow during attentional task performance was increased in the left frontal cortex compared with pretreatment measurements. These results in AD patients treated with rivastigmine were very similar to those observed in untreated patients with mild cognitive impairment. Professor Nordberg considered such data to be good evidence of the beneficial effects of rivastigmine therapy in patients with AD and patients with mild cognitive impairment.

In summary, Professor Nordberg presented 4 main conclusions. First, in patients with AD, long-term treatment with rivastigmine causes a persistent and significant inhibition of AChE and BuChE. Second, the inhibition of both ChEs is associated with improvements in attentional task performance and the preservation of CMRGlu in brain regions associated with attention. Third, while there seem to be marked differences in brain activation patterns during attentional task performance between patients with mild cognitive impairment and those with AD, rivastigmine treatment improves cerebral blood flow in patients with AD. Finally, the preemptive use of PET imaging techniques could enable the judicious early initiation of cholinergic therapy in patients with mild cognitive impairment, which could offer the opportunity to delay progression to AD. ❑

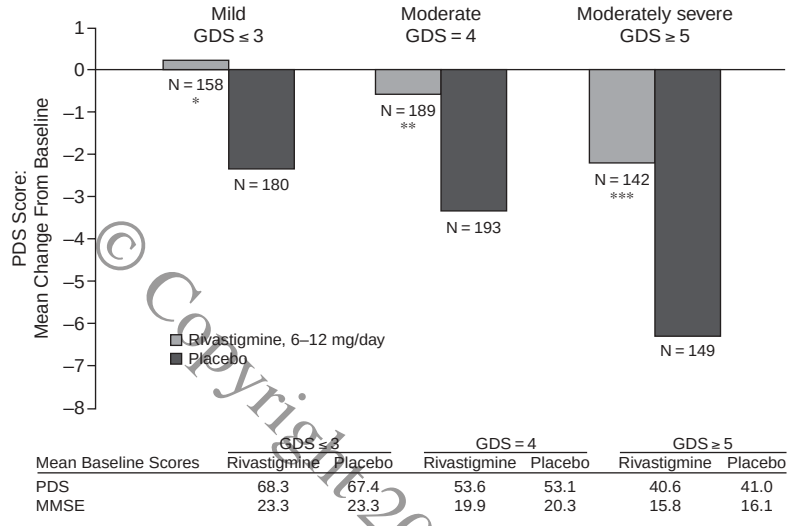
Treating the Cholinergic Deficit in Dementia: A Therapeutic Strategy With Disease-Modifying Potential

Central to the underlying pathophysiology of AD is the cholinergic deficit, manifested by progressive cholinergic nerve degeneration.[6] This correlates with reduced levels of cholinergic enzymes responsible for neurotransmitter synthesis.[7] ChE inhibitors are the only widely prescribed, approved agents for the symptomatic treatment of AD. Previous studies with rivastigmine have demonstrated substantial benefits across the key symptom domains (activities of daily living [ADL], behavior, and cognition) along the continuum of disease severity.

Reviewing the pharmacokinetic profile and clinical efficacy of rivastigmine, Dr. Jeffrey Cummings explained that this agent has a unique pharmacologic profile that distinguishes it from the other widely prescribed ChE inhibitors. Rivastigmine acts by the dual inhibition of AChE and BuChE.[8,9] Both of these enzymes are found in the neuritic plaques that characterize AD. Analysis of brain tissue has shown that ChEs exist in several molecular forms.[10] In healthy human brain, the G4 forms of ChEs are most abundant, while the G1 forms are found in smaller quantities. During aging, and particularly in AD, the amount of the G4 form of AChE declines, while levels of the developmentally primitive G1 form remain stable. In contrast, the G1 form of BuChE increases as AD develops, while the G4 form remains unchanged.[11] Rivastigmine preferentially inhibits the G1 molecular form of AChE, which could prove very relevant in the treatment of AD.

Clinical experience with rivastigmine has demonstrated the value of a simple "one-step" dosing regimen. Patients may obtain clinical benefits at the initial starting dose of 1.5 mg b.i.d., followed by an increase to 3 mg b.i.d. after a minimum of 4 weeks. This dose provides broad and sustained efficacy for many patients, with no further dose increases required. However, if the patient begins to show symptomatic deterioration, clinicians may elect further dose increases, up to a maximum dose of 6 mg twice daily, contingent on patient response and tolerability. Adverse events with rivastigmine tend to be transient and of mild-to-moderate intensity, occurring most frequently during dose escalation. These can be minimized by coadministration with food

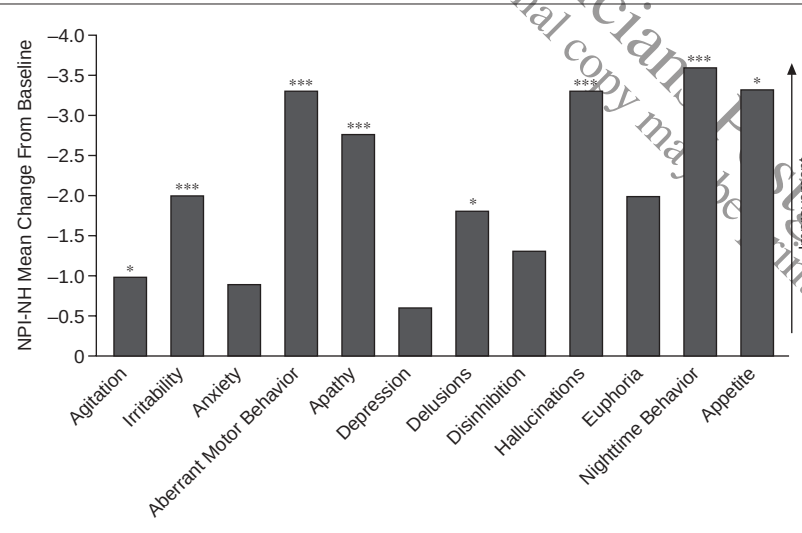
Figure 2. Rivastigmine Treatment Benefits Activities of Daily Living (ADL) Along the Continuum of Disease Severity[a]



Mean Baseline Scores	GDS ≤ 3		GDS = 4		GDS ≥ 5	
	Rivastigmine	Placebo	Rivastigmine	Placebo	Rivastigmine	Placebo
PDS	68.3	67.4	53.6	53.1	40.6	41.0
MMSE	23.3	23.3	19.9	20.3	15.8	16.1

[a]Reprinted with permission from Potkin et al.[14] Pooled 26-week data (observed case data set analysis): *p < .05, **p < .02, ***p = .003. Abbreviations: GDS = Global Deterioration Scale, MMSE = Mini-Mental State Examination, PDS = Progressive Deterioration Scale.

Figure 3. Rivastigmine Treatment Improves Behavioral Symptoms in Nursing-Home Patients With Alzheimer's Disease[a]



[a]Reprinted with permission from Cummings et al.[15] Pooled 26-week data (observed case data set analysis): *p < .05 vs. baseline, ***p < .001 vs. baseline. Mean baseline scores: Neuropsychiatric Inventory-Nursing Home version (NPI-NH) = 15.8, Mini-Mental State Examination = 9.2.

and following the slow, flexible dosing regimen described above.

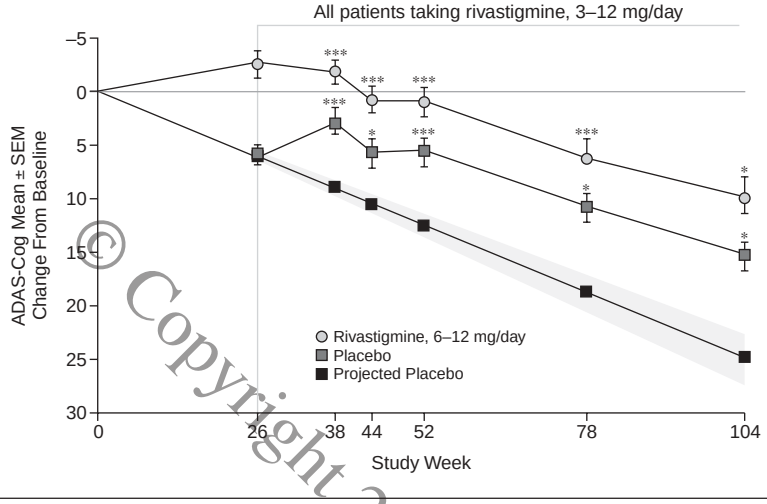
Moving on to discuss the assessment of efficacy in clinical trials of AD, Dr. Cummings stressed that assessment of cognition using only the MMSE was insufficient. Instead, routine evaluation of response to therapy in this disease should take into account the entire global clinical picture, including additional assessments of behavior and ADL.

In clinical trials, the Progressive Deterioration Scale (PDS)[12] has been used to measure the efficacy of rivastigmine on performance of ADL. This scale assesses both instrumental and basic ADL. Rivastigmine significantly delays the loss of ADL, compared with placebo. "This is an important finding," stated Dr. Cummings, "because it is loss of ADL which distresses the patient and caregiver most." Analysis of pooled data showed that, for patients treated with rivastigmine (6–12 mg/day) for 26 weeks, the mean deterioration in PDS score was 0.3 points compared with approximately 4 points in the placebo-treated patients.[13] The improvement was dose-dependent, with patients on higher doses of rivastigmine demonstrating a greater improvement, although a number of patients on lower doses (3 mg/day) also showed therapeutic benefits. In addition, the beneficial effects of rivastigmine treatment on ADL were sustained regardless of disease severity, as assessed by the Global Deterioration Scale (GDS) (Figure 2).[14]

Dr. Cummings also discussed work in which the effects of rivastigmine on behavioral disturbances among institutionalized patients with advanced AD were evaluated. Treatment with rivastigmine (3–12 mg/day) resulted in clinically meaningful improvements in Neuropsychiatric Inventory-Nursing Home version (NPI-NH) scores across multiple behavioral symptoms, compared with placebo. The behavioral features that responded most ($p < .001$) were aberrant motor behavior such as pacing and wandering, apathy, hallucinations, irritability, and abnormal nighttime behavior. Other behaviors significantly ($p < .05$) improved with rivastigmine treatment included agitation, delusions, and disturbed eating behavior (Figure 3).[15] The benefits of rivastigmine across the broad spectrum of behavioral symptoms of AD are probably indicative of the multiple regions of the brain affected by cholinergic loss that are targeted by this brain-region specific agent.

Dr. Martin Farlow discussed the hallmark cognitive changes of AD, as measured by the Alzheimer's Disease Assessment Scale, Cognitive subscale (ADAS-Cog). This 70-point scale, in which the score increases as cognition declines, assesses language, visuospatial skills, and memory.[16] In a clinical trial observing a randomized,

Figure 4. Long-Term Cognitive Benefits of Rivastigmine in Moderately Severe Alzheimer's Disease Patients[a]



[a]Data from Anand.[18] Patients with baseline Global Deterioration Scale scores ≥ 5. Observed case data set. *p < .05; ***p < .001 vs. projected placebo.

placebo-controlled design for the first 26 weeks only, patients who continued to receive rivastigmine remained at above-baseline ADAS-Cog scores for up to 38 weeks.[17] Patients who initially received placebo for 26 weeks subsequently received rivastigmine (3–12 mg/day) for the remainder of the study, constituting a "delayed start" group. Long-term follow-up of these patients for over 2 years revealed that the "delayed start" group failed to show the same level of cognitive stabilization as the patients who had received rivastigmine from the start of the study (Figure 4).[18] Such findings indicate that the early initiation of rivastigmine treatment provides benefits that may not be as large with later initiation of therapy. "These results strongly suggest that rivastigmine possesses disease-modifying potential beyond an initial symptomatic action," said Dr. Farlow.

Multivariate regression analyses revealed that the cognitive benefit was consistently dose-related: patients who received doses of rivastigmine > 6 mg/day showed far less cognitive decline than those receiving doses ≤ 6 mg/day.

Exploring the clinical relevance of BuChE inhibition, Dr. Farlow explained that immunohistochemical studies have shown that BuChE might play a role in the progression of AD by transforming diffuse plaques into more compact forms. The increasing deposition of β-amyloid protein (Aβ) in neuritic plaques is associated with increasing concentrations of plaque-associated AChE and BuChE. Synaptic levels of AChE start to decrease as cholinergic neurons are lost, while concomitantly, there is an increase in the levels of BuChE. Inhibition of BuChE may also reduce abnormal amyloid precursor protein (APP) processing and the metabolism and/or secretion of Aβ.

Dr. Farlow went on to describe experiments performed in rats with lesioned Basalis of Meynert nuclei. These animals generally produce large quantities of APP, and treatment with rivastigmine reduced concentrations of Aβ and APP in CSF (data on file, Novartis AG, Basel, Switzerland). In humans with mild AD, the benefits seen in short-term memory and learning from a single dose of rivastigmine correlate better with the inhibition of BuChE than inhibition of AChE.[19] Results from experiments such as these indicate that BuChE inhibition may be an important factor in mediating the therapeutic effects seen with the dual ChE inhibitor rivastigmine.

Brain imaging techniques such as single photon emission computerized tomography (SPECT) can be used to detect the effect of ChE inhibitors on brain function. Dr. Farlow described a clinical study in which patients who had been taking rivastigmine for 3 months were analyzed by SPECT at the beginning and end of the study.[20] Compared with baseline levels, increased cerebral blood flow was observed in patients who had responded to rivastigmine. This was in contrast to nonresponsive patients, for whom SPECT revealed a decrease in cerebral blood flow compared with baseline levels. While rivastigmine may be responsible for improved cerebral blood flow, Dr. Farlow pointed out that this increase may be a reflection of other positive effects of rivastigmine therapy.

Dr. Farlow concluded that ChE inhibitors such as rivastigmine are likely to have disease-modifying effects and that the early initiation of cholinergic therapy provides the greatest symptomatic benefits. "However, the definitive answers can only be ascertained after carrying out carefully planned, double-blind trials." ❑

Treatment of Dementia in Parkinson's Disease: Results With Rivastigmine

Professor Amos Korczyn discussed the observation that many patients diagnosed with Parkinson's disease develop dementia. In light of this dementia often being profound and resistant to treatment, Professor Korczyn went on to examine the use of the dual ChE inhibitor, rivastigmine, in the treatment of this condition.

Professor Korczyn explained that approximately one third of patients diagnosed with Parkinson's disease develop dementia. Parkinson's disease–associated dementia is not responsive to treatment with dopaminergic agents, indicating that this condition is unlikely to arise as a result of the dopaminergic deficit that underlies the

Table 1. Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) Scores Showing Significant Improvement From Baseline at Week 26 of Rivastigmine Treatment in 19 Patients With Parkinson's Disease–Associated Dementia[a]

Scale	p Value
Total ADAS-Cog	.004
Naming	.05
Recognition	.007
Word finding	.02
Remembering instructions	.008
Concentration	.0005

[a]A. Korczyn, M.D., unpublished data, 2001.

Table 2. Effects of Rivastigmine Treatment on Clinical Global Impression of Change (CGIC) Scores in Patients With Parkinson's Disease–Associated Dementia[a]

Variable	Week 12 (N = 21)	Week 26 (N = 19)	Week 34 (N = 20)
Patient perspective	1.6*	1.5*	–0.3
Caregiver perspective	1.7*	1.3*	–0.5
Neurologist perspective	1.8*	1.7*	0.1
Mean rivastigmine dose (mg/day)	7.3	7.5	None

[a]A. Korczyn, M.D., unpublished data, 2001. CGIC scale: 3 = marked improvement, 2 = moderate improvement, 1 = mild improvement, 0 = no change, –1 = mild worsening, –2 = moderate worsening, –3 = marked worsening. *p < .0001 vs. baseline.

motor disturbances in Parkinson's disease. "Indeed, if these patients are treated with dopaminergic drugs, we frequently observe the development of complications, for example, hallucinations and confusional states, that were not seen during the initial stages of the disease," said Professor Korczyn, emphasizing that effective pharmacologic agents for the treatment of this condition are needed.

It has been observed that some brain lesions in Parkinson's disease–associated dementia are similar to those seen in AD. Prompted by this similarity between the 2 diseases, Professor Korczyn and his group initiated a trial of rivastigmine in patients with relatively severe Parkinson's disease–associated dementia. The trial was a 26-week, open-label pilot study (unpublished data) in which patients were evaluated with multiple batteries of psychometric tests at baseline, throughout the study, and again after washout at 34 weeks. Treatment with rivastigmine was started at the low dose of 3 mg/day and then slowly increased to the maximal tolerated dose. The dose of rivastigmine was then tapered off at week 26, and patients were followed up and reexamined at week 34.

Treatment with rivastigmine (mean dose = 7 mg/day) resulted in significant (p < .0004) improvements in the attention subscore of the MMSE. A similar picture emerged in the ADAS-Cog score compared with baseline, such that significant improvements were demonstrated in many domains including the total score (p = .004) (Table 1). In addition, significant improvements in Clinical Global Impression of Change scores from baseline were observed, as assessed by the caregiver and the neurologist (p < .0001) (Table 2). All of these improvements had regressed when patients were reassessed 8 weeks after the cessation of treatment.

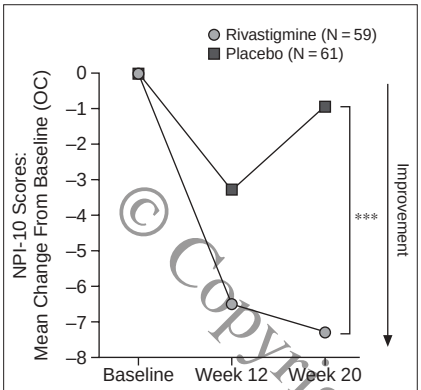
Adverse events were generally cholinergic in nature, of mild-to-moderate severity, and generally ameliorated by brief reduction in the administered dose. Treatment with rivastigmine did not cause these patients to develop motor symptomatology or induce deterioration of extrapyramidal symptoms, except for tremor which was enhanced in some patients. This may be a result of the preferential selectivity of rivastigmine in inhibiting the G1 molecular form of AChE, which is located postsynaptically and predominates in the cortex and hippocampus but is relatively low in the caudate nucleus. In contrast, the G4 membrane-bound form, which is selectively reduced in AD, is more widely distributed throughout brain regions and located presynaptically. Furthermore, in patients who are concomitantly receiving levodopa, dopamine D_2 receptors in the area postrema may become desensitized. As a consequence, these individuals are likely to experience less centrally mediated nausea and vomiting following the rise in brain ACh level induced by rivastigmine. Patients who tolerated the drug demonstrated significant cognitive benefits, particularly in memory and attention. Professor Korczyn remarked that, at the end of the study, caregivers were very disappointed when observing the deterioration that followed cessation of rivastigmine treatment.

Drawing to a close, Professor Korczyn pointed out that in addition to executive functions, concentration needs to be assessed in order to establish fully how these patients respond to pharmacologic agents. Professor Korczyn concluded that rivastigmine has potential in the treatment of Parkinson's disease–associated dementia, but impressed upon the audience the importance of confirming these results in randomized placebo-controlled trials. ❑

Treating Dementia With Lewy Bodies

Continuing the theme introduced by Professor Korczyn, Professor Ian McKeith discussed, at both the London and the Nice symposia, the clinical symptomatology of dementia with Lewy bodies (DLB). DLB represents one of the most common causes of dementia after AD. The clinical course of DLB tends to be quite aggressive, with rapid deterioration toward loss of independent living skills. Patients usually require a great deal of care and may be institutionalized early, with a mixture of psychiatric symptoms, cognitive impairment, and mobility problems.[21] The characteristic neuropathologic lesions of the disease are Lewy bodies, comprised of aggregates of the proteins α-synuclein and ubiquitin. They are similar to the Lewy bodies seen in Parkinson's disease, although their distribution in the brain differs. In

Figure 5. Neuropsychiatric Inventory (NPI) Scores in a Randomized Placebo-Controlled Trial of Rivastigmine in Dementia With Lewy Bodies[a]



Mean Baseline Scores	Rivastigmine	Placebo
NPI-10	23.2	20.2
Mini-Mental State Examination	17.9	17.8

[a]Data on file, Novartis Pharma AG, 2000.
***p < .001 (ANOVA/ANCOVA).
OC = observed case data set.

addition, while the dysregulation of neuronal proteins in DLB lies on a spectrum with Parkinson's disease, there is some additional overlap with the plaque and tangle pathology characteristic of AD.

The 3 key symptomatic features of DLB are cognitive impairment, visual hallucinations, and spontaneous motor features of parkinsonism. The cognitive impairments of DLB are fundamentally different from those seen in AD. Professor McKeith explained that patients with AD show profound deficits in immediate and delayed recall, whereas patients with DLB showed fluctuations in the cognitive state and/or consciousness with pronounced variations in attention and arousal. Patients with DLB experience repetitive and persistent visual hallucinations that can lead to behavioral disturbances. Approximately 75% of patients will go on to develop a parkinsonian syndrome characterized by bradykinesis and body rigidity as opposed to tremor.

Professor McKeith spent a few moments discussing the difficulties of diagnosing DLB. Advances in neuroimaging mean that it is now possible to visualize nigrostriatal dopaminergic integrity in vivo. These neurons undergo degeneration in patients with Parkinson's disease and DLB, but remain unaffected in patients with AD. Such techniques are useful in the differential diagnosis of neurologic diseases.

Turning to the treatment of DLB, Professor McKeith explained that historically, the majority of patients received neuroleptic drugs (generally dopamine receptor antagonists). Unsurprisingly, the use of such drugs in individuals already compromised by limited nigrostriatal dopaminergic function has been shown in over half of DLB patients to result in acute adverse reactions that do not necessarily resolve upon discontinuation.[22] Typically these patients go on to develop secondary complications resulting in a 2-fold to 3-fold increase in mortality rate. The use of neuroleptics is therefore not recommended as a treatment option for DLB.

Professor McKeith explained that there is a greater pathologic degeneration of the cholinergic system in DLB compared with AD. Since cholinergic therapy has been associated with improved cognitive and global function in patients with AD, it may therefore provide similar benefits in DLB. In both DLB and AD, there is a degeneration of cholinergic neurons projecting from the basal forebrain to the frontal and parietal temporal cortex. However, in DLB there is additional degeneration of cholinergic neurons projecting from the brainstem to areas such as the thalamus and occipital cortex. This degeneration may contribute to the occurrence of perceptual disorders. Professor McKeith hypothesized that a combination of an attentional deficit with a perceptual disorder could form the basis of the visual hallucinations often observed in DLB.

Evidence to support the cholinergic deficit model of DLB has emerged from many different sources. Professor McKeith referred to neuroimaging studies utilizing SPECT, which showed good correlation between cerebral blood flow and the differential pathology of AD and DLB.[23] Cerebral blood flow is generally reduced in the brains of patients with AD and DLB. However, in DLB patients, additional perfusion deficits were observed in the occipital areas. Furthermore, neurochemical studies have shown that in DLB, levels of choline acetyltransferase (ChAT) (the enzyme responsible for ACh synthesis) are drastically reduced to 50% or less of the levels observed in AD.[24] Reductions in ChAT activity were particularly apparent in the occipital cortex.

"So, do ChE inhibitors have a role to play in treating DLB?" asked Professor McKeith. He described the findings from his own group, in which 120 patients with DLB were randomly assigned to receive either rivastigmine or placebo for 20 weeks.[25] The primary outcome measure was the NPI score for 4 core symptoms: apathy, hallucinations, delusions, and agitation. At week 20, 63% of patients showed ≥ 30% improvement in NPI-4 score, compared with 30% receiving placebo. For total NPI score (NPI-10), treatment with rivastigmine resulted in a mean reduction of 7.3 points from a mean baseline value of 23 points (Figure 5). When active treatment was stopped, the beneficial effects were largely lost within 3 weeks.

Professor McKeith concurred with the earlier comment by Dr. Korczyn regarding the importance of appropriate cognitive measures for the accurate diagnosis of DLB. In his work with rivastigmine, Professor McKeith utilized a computerized test battery to measure reaction times. The results demonstrated that the response speed of placebo-treated patients decreased over the length of the trial, compared with those receiving rivastigmine who demonstrated significant improvements. This increase in speed of response was quickly lost on cessation of treatment.

In summarizing, Professor McKeith was of the opinion that the dual ChE inhibitor rivastigmine has the potential to improve cognition and the psychiatric symptoms of DLB. Professor McKeith suggested that BuChE may play a role in both symptom development and treatment response. ❑

Differential Pharmacology of Cholinesterase Inhibitors

Professor Changiz Geula reviewed the pharmacokinetic and pharmacologic profiles of 4 different ChE inhibitors that are used in the treatment of AD and outlined the rationale behind their use. Although studies have indicated that several neurotransmitter systems are affected,[26] it is the cholinergic system that degenerates most profoundly.[27] Cholinergic deterioration begins early in the course of the disease, with the loss of cortical cholinergic axons, the degeneration of basal forebrain cholinergic neurons from which these axons emanate, and substantial changes in number and function of cholinergic receptors. In patients with AD, the symptomatic efficacy of ChE inhibitors results largely from the ability of these agents to increase the availability of synaptic ACh, thus enhancing cholinergic neurotransmission.

The first ChE inhibitor to reach the market for symptomatic treatment of AD was tacrine (1993), followed by donepezil (1997), rivastigmine (1998), and most recently, galantamine (2000). Each agent is a member of a different chemical class, with substantially different molecular structures. Professor Geula highlighted their differential pharmacology, focusing especially on novel mechanisms of action—that is, mechanisms other than the classical reversible inhibition of AChE. While each of the 4 ChE inhibitors inhibit AChE in the brain, tacrine (tetrahydroaminoacridine), an acridine compound, also markedly inhibits ChEs in the peripheral nervous system. Tacrine binds to both AChE and its sister enzyme BuChE in a noncompetitive, reversible manner. The drug is 55% bound to plasma protein and has an elimination half-life of approximately 2–4 hours, which consequently requires dosing 4 times daily. Metabolism of tacrine occurs in the liver, via the cytochrome P450 (CYP450) system, thereby increasing the potential for drug-drug interactions. An unacceptable toxicity profile, particularly hepatotoxicity, has meant that tacrine is no longer in widespread use.

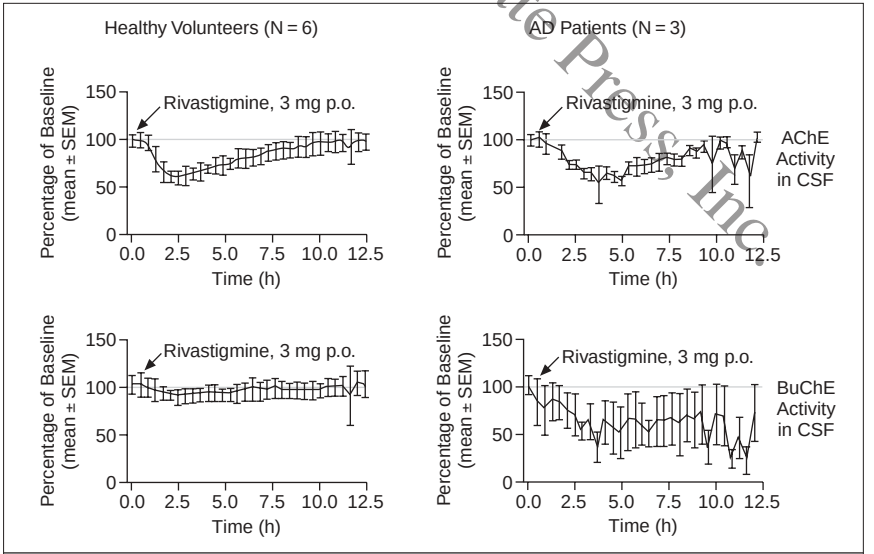
Donepezil is a piperidine compound with a plasma half-life of 70 hours due to being highly (96%) bound to plasma proteins.[28] Donepezil is a selective reversible inhibitor of AChE alone and is eliminated from the body via the CYP450 system.[29]

Galantamine, the most recently licensed ChE inhibitor, is a phenanthrene alkaloid. This agent possesses a serum half-life of approximately 6 hours and binds reversibly to AChE. Enzyme kinetics data for galantamine indicate that, compared with other available ChE inhibitors, it is the least potent in inhibiting AChE.[30,31] This agent is also metabolized via the CYP450 system and eliminated via both hepatic and renal pathways.[32] Galantamine is postulated to act not only through the classical inhibition of AChE, but additionally by allosteric modulation of the nicotinic acetylcholine receptor (nAChR).[33] In acute electrophysiologic experiments in cell lines, galantamine increases the release of ACh presynaptically and may result in potentiation of electrical activity postsynaptically. These effects have been demonstrated only in vitro at nanomolar concentrations. According to Professor Geula, galantamine's effectiveness in humans is achieved at much higher concentrations, which principally result from the inhibition of AChE. Thus, in terms of clinical benefit, the significance of the modulation of nAChRs by galantamine and other ChE inhibitors has yet to be determined.

Professor Geula then turned his attention to the dual ChE inhibitor rivastigmine. Rivastigmine is a carbamate compound with a half-life of approximately 1 hour in plasma and a long enzyme-dissociation time (approximately 8 hours) in the brain. This allows rivastigmine to provide sustained inhibition of AChE and BuChE, even as plasma levels of the agent fall. Rivastigmine is eliminated via the renal system and does not interact with the hepatic CYP450 system.[34] Low protein binding, a short half-life in plasma, and metabolism independent of CYP450 enzymes means rivastigmine is unlikely to interact with other medications. Indeed, in a prospective analysis of rivastigmine and concomitant medication usage in clinical trials, no clinically significant adverse events were identified with 22 different classes of frequently prescribed concomitant medications.[35]

Unique among the widely prescribed ChE inhibitors, rivastigmine is a potent inhibitor of both AChE and BuChE (Figure 6). Professor Geula noted that this is particularly important because as AD progresses, levels of AChE in

Figure 6. Rivastigmine: Dual Inhibition of AChE and BuChE in CSF[a]



[a]Reprinted with permission from Kennedy et al.[36] and data on file, Novartis Pharma AG, 1998.

the brain are significantly reduced compared with levels in normal individuals, while the levels of BuChE increase. Professor Geula explained that as AD develops BuChE is likely to assume a greater role in the regulation of brain ACh levels. "Therefore, the inhibition of BuChE is important in terms of cholinergic enhancement," said Professor Geula. However, BuChE may also have roles beyond this association with the cholinergic system. For example, BuChE is thought to be associated with plaque maturation, transforming diffuse amyloid deposits into the mature compact neurotoxic form that characterizes AD.[37] The activity of BuChE has been found to correlate positively with the density of amyloid plaque deposition,[11] indicating that the increase in BuChE is likely to be related to the pathogenesis of AD.

There are several molecular isoforms of ChEs, including the G1 and G4 globular forms. In healthy individuals, G4 is the predominant form of both BuChE and AChE located in the CNS. In patients with AD, it appears that there is a reduction in the G4 form of AChE whereas the G1 forms of AChE and BuChE are preserved or increased, particularly in hippocampus and neocortex.[7,11] This results in an imbalance in the ratio of G1:G4 ChEs. "Therefore, pharmacologic agents with the ability to specifically inhibit G1 forms would prove highly desirable for the treatment of AD," said Professor Geula. Thus far, only rivastigmine has been demonstrated to effectively and preferentially inhibit the G1 over the G4 form in the CNS.

Professor Geula concluded that, as a class of compounds, ChE inhibitors act to ameliorate the cholinergic deficit. However, the different ChE inhibitors each have unique pharmacokinetic and pharmacologic properties. Rivastigmine has a novel mode of action that inhibits BuChE as well as AChE. Evidence from clinical studies indicates that BuChE participates not only in cholinergic neurotransmission, but also in amyloidogenesis. "The inhibition of BuChE is sure to provide additional clinical benefits in patients with AD," concluded Professor Geula. ❑

Problem Behaviors in Alzheimer's Disease: Biological Mechanisms and Management Over the Course of Disease Severity

Dr. Pierre Tariot discussed the common finding of psychopathology in Alzheimer's patients. Behavioral and neuropsychiatric disturbances are often the earliest manifestations of AD, and symptoms range from anxiety and irritability in the early stages to aggressiveness and hallucinations as the disease progresses. The changing nature of psychopathology and behavioral deterioration over time are most likely related to underlying neuropathologic and neurotransmitter changes occurring with disease progression. Neurofibrillary tangles in frontal cortical areas appear as behavioral abnormalities emerge. An autopsy study by Farber and colleagues[38] found an apparent relationship between the presence of neurofibrillary tangles in the orbitofrontal cortex and the emergence of agitation, a common behavioral symptom characterizing AD. More recently, greater neurofibrillary tangle burden in the anterior cingulate cortex has been associated with increasing apathy,[39] further strengthening the view that behavioral abnormalities may be mediated by underlying neuropathologic changes.[39]

Dr. Tariot went on to discuss cholinergic projections affecting regulation of emotion, temperament, and cognition. The observed widespread destruction of cholinergic neurons and proliferation of glial cells in AD may lead to the well-established changes in the levels of the ACh-degrading enzymes AChE and BuChE as the disease progresses. Although activity of AChE falls, BuChE levels are augmented by 40% to 90%. These findings indicate the potential importance of ChE inhibitors in symptom management. This argument is strengthened by the observation that disruption of the extensive cholinergic projections throughout the limbic system may lead to behavioral deficits that become increasingly more severe as the cholinergic deficit increases. These findings highlight the concept that neurotransmitter changes may mediate psychopathologic as well as cognitive impairments.

In summarizing, Dr. Tariot stressed the value of ChE inhibitors in the treatment of AD and the attendant psychopathologic symptoms. Finally, he identified the strategy of his own group, whereby ChE inhibitors are always the first-line choice for antidementia therapy. In his practice, desired outcomes include effective symptom management and the possibility of withdrawal from concomitant psychotropic medication use. ❑

Rivastigmine Treatment of Behavioral Disturbances in Mild-to-Moderate AD

Professor Philippe Robert described how up to 80% of AD patients are affected by behavioral and psychological symptoms of dementia (BPSD), which represent the primary cause of nursing home admission. Furthermore, the results of a recent study show a correlation between BPSD and impairments in the ability to perform activities of daily living (ADL) (P. Robert, M.D., oral communication, 2001).

Before the development of ChE inhibitors, behavioral disturbances were typically treated with anxiolytics, neuroleptics, or antipsychotics. In agreement with a previous report from Jeffrey Cummings,[40] Professor Robert described ChE inhibitors as "a new class of psychotropic compounds." The differing pharmacologic profiles of the currently available ChE inhibitors have the potential to provide variable efficacy along the continuum of disease severity. Moreover, the increasingly important role played by BuChE as AD progresses may high-

light the therapeutic value of rivastigmine, which is unique in its ability to inhibit both AChE and BuChE and may therefore provide additional clinical benefits over agents inhibiting AChE alone.

With a focus on rivastigmine, Professor Robert went on to discuss the pivotal U.S. and European studies investigating the effects of rivastigmine on patients with mild to moderately severe AD.[13] The 3 studies used a prospective, randomized, double-blind, placebo-controlled parallel-group design of 26 weeks' duration. The primary outcome of the trials was a significant improvement in cognition at 26 weeks in those patients receiving 6–12 mg/day of rivastigmine, as assessed by the ADAS-Cog. However, the study also provided data indicative of the beneficial effects of rivastigmine on behavioral disturbances, as evaluated by improvements in the behavioral component of the Clinician Interview-Based Impression of Change (CIBIC-Plus). While the CIBIC-Plus is predominantly a measure of the cognitive and daily functioning abilities of dementia patients, the behavioral component indicated that the AD patients included in these trials received benefit from rivastigmine relative to placebo in behavioral as well as cognitive domains.

The suggestion that rivastigmine is beneficial in the treatment of the behavioral symptoms of AD was evaluated and reinforced by the findings of a U.S. open-label nursing home study assessing the drug for efficacy in 173 AD patients with more severe AD (mean MMSE score of 9.6) who exhibited more pronounced behavioral disturbances. As determined by the 12-item NPI-NH, significant reductions in NPI baseline scores were obtained for the symptoms of disinhibition ($p < .001$ vs. baseline), delusions, hallucinations, irritability, anxiety, aberrant motor behavior, inappropriate nighttime behavior, and appetite ($p < .05$ vs. baseline) following 52 weeks of treatment. Overall, 50% of patients with behavioral symptoms at baseline exhibited a reduction in their NPI score of 30%.[40] Such results suggest that dual ChE inhibition can be effective in patients with more severe behavioral disturbances, facilitating increase of ACh levels along the continuum of disease severity.

A further observation to emerge from this 52-week study concerned those patients also taking concurrent antipsychotic medications (N = 55). Anand and colleagues[41] found that following 52 weeks of treatment with rivastigmine, 31% of these patients terminated concomitant antipsychotic medication use, with 13% reducing dose. Furthermore, patients being treated with other psychotropic medications such as anxiolytics and antidepressants also decreased or terminated use following 52 weeks of rivastigmine therapy. These results clearly indicate that rivastigmine provides clinical benefits to AD sufferers with regard to behavioral disturbances, as shown not only by the improvement of behavioral symptoms but also by the reduction or cessation of concomitant psychotropic medication use.

In the final section of his presentation, Professor Robert discussed combination therapy. A recent randomized, open-label, parallel-group study of 20 weeks' duration in dementia patients experiencing behavioral disturbances assessed the safety and tolerability of coadministration of rivastigmine and the antipsychotic risperidone.[42] After 20 weeks, patients receiving both medications showed significant reductions in NPI scores ($p < .001$), while those receiving only risperidone or rivastigmine showed a less marked improvement. The reported lack of clinically relevant adverse interactions arising from coadministration of rivastigmine and risperidone suggests that such combination therapy may provide a tolerable, effective treatment strategy for dementia patients with behavioral disturbances. The lack of drug-drug interactions with rivastigmine was highlighted further in a study by Grossberg and colleagues,[35] which investigated pharmacodynamic drug-drug interactions between rivastigmine and 22 classes of concomitant medications commonly prescribed in the elderly. The study revealed no significant increases in adverse events in patients taking rivastigmine, compared with placebo, in combination with the other medications. It has been suggested that this lack of drug-drug interactions may be attributed to the metabolism of rivastigmine by its target enzymes rather than by the hepatic CYP450 system.[35] The lack of clinically relevant drug interactions suggests that rivastigmine may be given safely to elderly patients, a population that is frequently comorbid and comedicated.

In conclusion, Professor Robert reemphasized the increasing evidence suggesting that rivastigmine is effective in improving the behavioral disturbances in AD, either alone or in combination with other psychotropic agents. ■

Future Directions for Treating Dementia: Building on Our Experience in AD

The final presentation of the IPA symposium was given by the meeting chair, Professor Alistair Burns, who expressed the opinion that ChE inhibitors currently represent the most effective treatment for AD. He observed that the possible association of AChE and BuChE with protease activity and toxicity of Aβ may provide a target for disease modification through intervention with ChE inhibitor therapy. Furthermore, a possible increasing involvement of BuChE in the development of Aβ toxicity as AD progresses indicates that dual inhibition of BuChE and AChE may positively influence disease progression to a greater extent than AChE inhibition alone. He went on to speak about the lack of adequate long-term studies comparing the ChE inhibitors, briefly discussing the recently launched EXCEED (Exelon comparison of efficacy versus donepezil) trial. This international multicen-

ter trial will enroll 1000 AD patients and compare the efficacy, safety, and tolerability of rivastigmine and donepezil over 2 years.

Professor Burns also discussed the utility of switching between ChE inhibitors with different pharmacologic profiles; although few such studies are currently available, switching drugs is common medical practice and may extend the benefits provided by this class of drugs. Following this, a few moments were spent discussing risk factors for dementia, which fall into 2 categories: those factors that can be changed (e.g., diet, alcohol consumption, smoking) and those that cannot (e.g., genotype, sex, age). He explained how identification and understanding of these factors may, in the future, enable the development of individually targeted therapies.

To conclude, Professor Burns spoke of the excellent results so far achieved with rivastigmine for the treatment of the symptoms of dementia. The promising results obtained to date, in the study of vascular dementia, dementia of Parkinson's disease, and DLB may translate into similar benefits when used to treat other disorders such as frontal lobe dementia, schizophrenia, and delirium. ❑

Conclusion

Since their introduction in 1993, ChE inhibitors have made a significant impact on the treatment of AD. By targeting the underlying pathophysiology of the disease, i.e., the "cholinergic deficit," these agents have shown efficacy across multiple symptom domains including effective management of troublesome behavioral disturbances commonly observed in AD and related dementias.

While all ChE inhibitors share the common class effect of AChE inhibition, they differ substantially in pharmacologic profiles, including their potency for inhibiting AChE. Rivastigmine is a dual inhibitor of both AChE and BuChE, with unique preferential selectivity for the G1 molecular form of AChE. This agent has demonstrated significant and clinically relevant benefits in ADL, behavior, and cognition and the potential to modify the progression of the disease.

Emerging evidence suggests that, like AD, other forms of dementia may be responsive to ChE treatment, perhaps explained by a common cholinergic deficit. Studies with rivastigmine in DLB and preliminary findings from treatment of dementia of Parkinson's disease have provided encouraging data suggestive of a future role for ChE inhibitors in these conditions.

The importance of early therapeutic intervention is widely accepted and has been confirmed by the findings of recent studies. Indeed, it seems that in patients whose treatment is delayed, some therapeutic benefit is irretrievably lost. It is therefore essential that patients with AD are identified at the earliest stage of disease progression and treated appropriately. Advances in imaging techniques (e.g., PET scans), which can be used to identify early functional changes in the brain, may have a pivotal role to play in supporting early diagnosis and initiating ChE therapy as soon as possible. With early therapeutic intervention, it seems likely that the natural progression of AD may be slowed, thus substantially improving the lives of patients and caregivers alike.

It is clear that the differences in pharmacokinetic and pharmacologic profiles among the approved agents for AD therapy are likely to have implications for clinical outcomes. There are, however, no large, well-controlled, randomized, long-term clinical trials directly comparing the efficacy of any of the available ChE inhibitors. The EXCEED trial was launched in July 2001 in patients with moderate to moderately severe AD. This 2-year study represents the first closely controlled, long-term study directly comparing the 2 most commonly prescribed ChE inhibitors rivastigmine and donepezil. Patients are equally randomized to the 2 compounds and patients and physicians are blinded to the treatment administered. Slow, flexible dosing regimens are being employed to minimize issues of tolerability. The study has sufficient power to offer meaningful comparison of acute symptomatic efficacy and is of adequate duration to evaluate long-term efficacy and the rates of disease progression across the 2 treatment groups. Safety assessments are being performed throughout. Sensitive and reliable assessment instruments will be employed to assess efficacy across the key symptomatic domains of ADL, behavior, and cognition. Patterns of concomitant drug use will also be monitored in a population likely to be comorbid and comedicated. Preliminary data from this study are eagerly awaited and will appear in 2003; full results will be available in 2004. ❑

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