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After studying the ACADEMIC HIGHLIGHTS, you will be able to:

- Recognize signs of and describe treatment options for Alzheimer's disease in the primary care setting

This pretest is designed to facilitate your study of the material.

1. **Future and emerging treatments for Alzheimer's disease include different types of compounds used alone or in combination with the cholinesterase inhibitors.**
   a. True
   b. False

Pretest answer and Posttest on page 276.

Disclosure of Off-Label Usage
The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this ACADEMIC HIGHLIGHTS that is outside U.S. Food and Drug Administration–approved labeling.

Answers to Vol. 4, No. 4 Posttest 2002
1. c 2. d 3. b 4. c 5. b 6. d 7. a

ACADEMIC HIGHLIGHTS

Emerging Therapeutic Strategies for Treating Alzheimer's Disease in Primary Care

This ACADEMIC HIGHLIGHTS section of The Primary Care Companion to The Journal of Clinical Psychiatry *presents a report from "Global Challenges in Alzheimer's Disease: Emerging Therapeutic Strategies," a satellite symposium of the Eleventh Annual International Congress of the International Psychogeriatric Association held August 20, 2003, in Chicago, Ill. The symposium and this ACADEMIC HIGHLIGHTS were sponsored by an unrestricted educational grant from Forest Laboratories, Inc.*

*The chair was **George T. Grossberg**, M.D., Department of Psychiatry, Department of Internal Medicine, St. Louis University Health Science Center and Wohl Clinic, St. Louis, Mo. The other faculty members were **Jody Corey-Bloom**, M.D., Ph.D., Department of Neurosciences, University of California, San Diego and Veteran's Affairs Medical Center, La Jolla, Calif.; **Gary W. Small**, M.D., Department of Psychiatry and Biobehavioral Sciences, Neuropsychiatric Institute, University of California, Los Angeles; and **Pierre N. Tariot**, M.D., Departments of Psychiatry, Medicine, and Neurology and the Center for Aging and Developmental Biology, University of Rochester Medical Center and Monroe Community Hospital, Rochester, N.Y.*

Continuing Medical Education Faculty Disclosure

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement.

*The information received is as follows: **Dr. Grossberg** has received grant and research support from Abbott, Forest, Pfizer, Novartis, Janssen, Organon, Eli Lilly, and Eunoe and is a consultant for AstraZeneca, Bristol-Myers Squibb, Forest, Janssen, and Novartis; **Dr. Corey-Bloom** has received grants or research support from Boehringer-Ingelheim, Elan, Forest, Fujisawa, Janssen, Merz, Novartis, Pfizer, Sigma Tau, and Takeda and is on the speakers bureau for Forest, Janssen, Novartis, and Pfizer; **Dr. Small** is a consultant for and has received honoraria from AstraZeneca, Eli Lilly, Forest, Janssen, Novartis, Organon, Pfizer/Eisai, PETNET, and Amersham Health; and **Dr. Tariot** is a consultant for and has received grants and research support from AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, Forest, Pfizer, Janssen, and Schwabe; is a consultant for Novartis; and has received honoraria from AstraZeneca, Eisai, Forest, Pfizer, and Janssen.*

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Overview of Emerging Treatments for Alzheimer's Disease

George T. Grossberg, M.D., began by stating that all physicians need to be aware of the global health care burden posed by Alzheimer's disease. In addition, physicians need to be aware of the different presentations of the disease and the different management strategies available for these patients, regardless of stage of illness.

The current science relative to the pathogenesis of Alzheimer's disease is fueling the development of a variety of novel treatment approaches, pharmacologic and otherwise. Combination treatment strategies, according to Dr. Grossberg, are also becoming more popular as understanding of the disease grows.

Dr. Grossberg went on to review the history of available pharmacotherapy for Alzheimer's disease. Many physicians, especially in Europe, have used various compounds—for example, nootropics such as ergoloid mesylates—for which there are few supporting studies. A number of trials with cholinergic agonist compounds such as arecoline-targeted nerve growth factors and membrane stabilization. These approaches have largely proved to be unrewarding as well.

Current standard treatment of Alzheimer's disease now consists of cholinesterase inhibitors, reported Dr. Grossberg, but many other promising approaches, such as statins and anti-inflammatory agents, are currently being researched. In addition, the scope of treatment has expanded to include not only patients with diagnosed Alzheimer's disease but also those at risk for the disease.

According to Dr. Grossberg, future and emerging treatments include different kinds of compounds, such as *N*-methyl-D-aspartate (NMDA) receptor antagonists, used alone or in combination with the cholinesterase inhibitors. One of these NMDA receptor antagonists, memantine, was recently approved by the U.S. Food and Drug Administration for the treatment of moderate-to-severe Alzheimer's disease. Some researchers are focusing on multitransmitter compounds, with the recognition that Alzheimer's disease is not merely a deficiency of acetylcholine and that many neurotransmitter alterations may be responsible for some of the symptoms of the disease. Anti-amyloid drugs such as secretase inhibitors and vaccine approaches are being examined as well. Dr. Grossberg also reported that his group is studying a surgical approach to Alzheimer's disease, namely, the implantation of a circulatory, shunt pump–type apparatus, in individuals with early Alzheimer's disease to stave off progression and improve functionality. Dr. Grossberg concluded optimistically, noting that many of the treatments currently being investigated hold great promise as treatments for Alzheimer's disease.

Perspectives in Management of Dementia From Early Onset to Severe Disease

Gary W. Small, M.D., opened with a reminder that making the diagnosis of dementia is challenging, especially for primary care physicians, who care for almost two thirds of patients with Alzheimer's disease initially.[1] Unfortunately, a study[1] found that many of these practitioners were not aware that Alzheimer's disease is the most common form of late-life dementia. Callahan and associates[2] confirmed this lack of knowledge, reporting that the diagnosis of dementia was missed in 75% of cases of moderate-to-severe cognitive impairment.

Dr. Small explained the importance of making the diagnosis of Alzheimer's disease as early as possible. Failing to do so, he said, can result in serious consequences such as higher rates of hospitalization and emergency department visits and more medication errors, to name a few. However, he acknowledged that many barriers to early diagnosis exist. For example, comorbid conditions like depression, lack of reporting symptoms by the patient and caregiver, and denial by the patient and his or her family can all prevent a practitioner from recognizing early-stage Alzheimer's. In addition, at times patients maintain their social skills in the early stages of the disease, which can mask the other early symptoms.

Several studies[3–6] have shown the benefits of early diagnosis and treatment, according to Dr. Small. Early, accurate diagnosis and treatment maintained patients at a higher level of functioning, leading to fewer doctor and hospital visits compared with patients who were not treated early.[3] Reduced caregiver burden[3,4] and delay in nursing home placement[5] can also result from early treatment of Alzheimer's disease, as can reduced use of other psychotropic drugs.[6]

Methods of Early Diagnosis

A number of different technologies are available to diagnose patients as early as possible. One that is promising is positron emission tomography (PET) with which the clinician is able to see not just the structure of the brain, which is what would be seen in a typical magnetic resonance imaging (MRI) or computed tomography (CT) scan, but also how the brain cells are functioning. With this type of PET, the patient or study volunteer is injected with a radioactively labeled glucose analog. Glucose is the brain's main food source in a nonstarvation state, so by using the glucose analog, the clinician can see, utilizing the PET scan, how well the brain cells are using glucose.

Several patterns of neurodegeneration are seen in Alzheimer's disease. Early in the course of the disease, the parietal and temporal regions show deficits. As the disease progresses, deficits become apparent in the frontal region as well. Interestingly, the PET scan of the brain of a patient with late-stage Alzheimer's disease looks very much like that of a child's brain.

Dr. Small reported on his collaboration with Silverman and coworkers,[7] which attempted to determine how sensitive and specific the glucose-labeled PET scan is. The study included 284 patients with dementia and/or cognitive complaints, 138 of whom died and underwent an autopsy. Diagnostic accuracy of the PET was high, with a sensitivity of 93% to 95% and a specificity of 73% to 78%—in other words, better than the accuracy of a standard clinical examination. Dr. Small illustrated this difference in diagnostic accuracy with a case from his own clinic. A 65-year-old woman had been diagnosed with depression and attention-deficit/hyperactivity disorder. During a 2½ year period, she received multiple MRIs and neuropsychiatric evaluations, with inconclusive results. Then, PET results showed the parietal temporal deficit common to Alzheimer's disease. Her mood and cognitive symptoms improved within a month of beginning a cholinesterase inhibitor.

Diagnostic Categories of Memory Loss

The mildest condition of memory loss, explained Dr. Small, is age-associated memory impairment. For instance, as people get older, they experience the tip-of-the-tongue phenomenon more often, in which they are unable to remember details when asked, such as the name of an actor in a recently viewed movie. People experiencing this phenomenon will often remember the detail later, when they are not trying to remember. This type of occurrence is common as people age, and although some people with this condition develop Alzheimer's disease, having age-associated memory impairment is not a high-risk state.[8]

In contrast, a more severe form of presymptomatic memory loss is mild cognitive impairment (MCI). People experiencing MCI may have a problem with delayed recall, for example, but are still functionally independent. However, MCI is associated with a higher risk for Alzheimer's disease than age-associated memory impairment.[9]

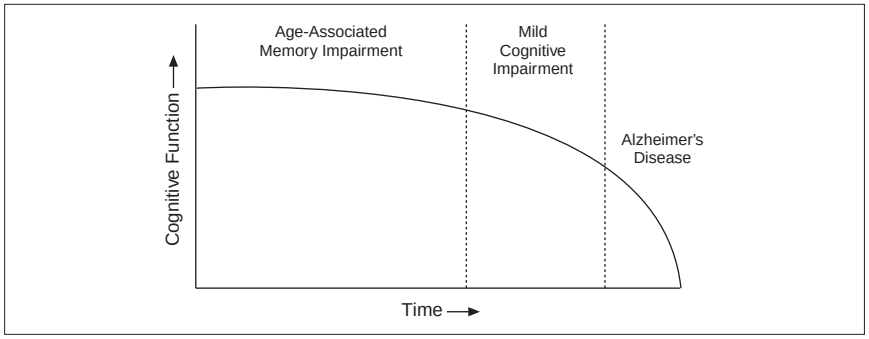
Dr. Small postulated a continuum of brain aging, taking into account these categorical variables—age-associated memory impairment, MCI, and Alzheimer's disease (Figure 1). The divisions between these categories are fuzzy and therefore represented by dotted lines in Figure 1, because movement from one category to another is usually a gradual transition.

Behavioral problems often complicate cognitive deficits, according to Dr. Small. In milder cases, depression and anxiety cloud the differential diagnosis. Later on, many patients experience problems with agitation and psychosis that make the diagnosis and treatment of the underlying Alzheimer's disease difficult.

Innovations Affecting Study Design

Genetic risk factors and imaging technology. Dr. Small explained that he heads up an ongoing research project designed to develop tools that identify candidates for treatment during presymptomatic states in order to protect the brain before there is damage. He and his colleagues have used

Figure 1. Hypothetical Course of Cognitive Impairment in an Aging Brain



PET in conjunction with the identification of genetic risk measures, especially apolipoprotein E4 (APOE-4). They have found that an individual may have a normal memory performance score, but if he or she has APOE-4, an Alzheimer's-like pattern may appear in the brain.[10] One 2-year longitudinal study[11] followed 10 participants who were cognitively normal but who were carriers of APOE-4. According to PET results, these participants had declines in the cerebral metabolic rate for glucose in regions commonly affected by Alzheimer's disease.

With PET results and genetic information, Dr. Small related that he and his colleagues have been able to design studies to test drugs and other treatments in people with very mild memory complaints, using the PET scan as a surrogate marker to see if the treatments work, i.e., whether they slow down brain aging in the Alzheimer's-like pattern. In fact, for a 2-year study using these surrogate markers, researchers need only 60 subjects per treatment arm, if all subjects have the genetic risk. If including patients who already have Alzheimer's disease, regardless of genetic risk status, and if PET imaging is used, a study would need only 36 patients per treatment arm in a 1-year study.

Dr. Small explained that study of Alzheimer's disease in general is moving toward presymptomatic treatment trials. For mild cognitive impairment, studies are now underway examining a variety of pharmacologic treatments, including cholinesterase inhibitors, anti-inflammatory agents, vitamins, and hormones.

Visualization of plaques and tangles. Dr. Small also described developing technologies with which the physical evidence of Alzheimer's disease, the plaques and tangles, can be seen in a living patient. In these studies, the patient is injected with a small radioactively labeled molecule that is attracted to the plaques and tangles in the brain. PET scans in Alzheimer's patients reveal increased staining in the temporal regions. This kind of technology, according to Dr. Small, will be helpful in testing new treatment approaches such as vaccines and anti-amyloid or antitangle treatments.

Overall, using information from multiple sources, whether they be PET scan results, genetic risk profiles, or neuropsychological profiles, will improve early diagnosis and treatment.

Risks and Protective Factors: Clues to Interventions

Until the high-tech approaches he discussed are widely available, Dr. Small explained, clinicians must rely on practical strategies to detect and treat Alzheimer's disease, even in the early stages. For example, one must consider not only clinical research results but also epidemiologic data and laboratory results to first determine the presence or absence of a variety of risk factors (Table 1). In addition, a number of possible protective factors might guide clinicians in managing patients with Alzheimer's disease (Table 2). Dr. Small also reminded his audience that besides the advances in pharmacologic treatment, a number of nonpharmacologic strategies may aid the management of Alzheimer's disease (Table 3).

Table 1. Risk Factors for Alzheimer's Disease

Definite risks
Advanced age
Presence of apolipoprotein E4
Family history
Other genes
Possible risks
Head trauma
Lower educational level
Vascular disease
High homocysteine level
Estrogen

Table 2. Possible Protective Factors in Alzheimer's Disease

Anti-inflammatory drugs
Cholesterol-lowering drugs
Antioxidants
Wine (drunk in moderation)
Low-fat diet
Aerobic conditioning
Mental activity

Table 3. Nonpharmacologic Management Strategies

Educate caregivers
Maintain social and family activities as much as possible
Identify underlying precipitants of troublesome behavior
Optimize sensory input
Arrange regular exercise
Employ familiar surroundings
Keep daily activities routine
Use clocks and calendars to maximize orientation

Progression of Brain Aging in Dementia and Presymptomatic States

According to Dr. Small, looking at activities of daily living and Mini-Mental State Examination (MMSE) scores reveals much about changes in the course of dementia.[12] Early on, patients have trouble keeping appointments and using the telephone. As the disease progresses, basic activities of daily living become impaired—walking, eating, and so forth. Galasko and colleagues[12] found that loss of function was highly correlated with decreasing MMSE scores. For example, of patients who scored ≥ 20 on the MMSE at baseline, more than 80% performed the activity "makes a snack or meal," whereas fewer than 20% who scored 0

to 4 on the MMSE performed the same activity.

Keeping the course of the disease and risk factors in mind, Dr. Small proposed several reasons for performing a cognitive assessment of elderly patients. For example, a patient aged 80 years or older who begins to display any cognitive impairment should be assessed. An older person who has recently moved to a new living environment would be a good candidate for cognitive assessment, as is a patient with a history of delirium, depression, diabetes, or Parkinson's disease who has experienced recent and unexplained functional losses. Finally, any concerns about cognitive or functional decline expressed by elderly patients, their families, and any other people who see them regularly should be taken seriously and should prompt a cognitive assessment.

Advances in Pharmacologic Treatment of Alzheimer's Disease

Dr. Small reflected on recent efforts to identify disease-modifying interventions. Several cholinesterase inhibitor medications are approved for use in the United States, as is memantine, an NMDA-receptor antagonist, and current research is attempting to determine whether these agents can change the course of the disease.

An example of this approach might be studies of the possibly neuroprotective qualities of memantine. One study[13] found that memantine provides neuroprotection against β-amyloid–induced damage in rat hippocampi. The outcome measures showed a reduction in number of injured or dying neurons. Although intriguing, this kind of information has not yet proved the existence of neuroprotective effects of memantine in the human brain; further studies designed to assess this possibility are needed.

Conclusion

Dr. Small reiterated that brain aging continues throughout life. It begins relatively early with a presymptomatic state. The strategy of early detection and prevention may be useful in decelerating brain aging and delaying the onset of Alzheimer's disease. Dr. Small was optimistic about this approach and predicted that the next 5 to 10 years will see major breakthroughs in this area. For now, however, the available symptomatic treatments are efficacious, and they help a tremendous number of patients. Dr. Small concluded by emphasizing the importance of identifying patients in need of cognitive assessment, diagnosing patients early, and treating patients early so they can get the best benefit from the various management approaches currently available.

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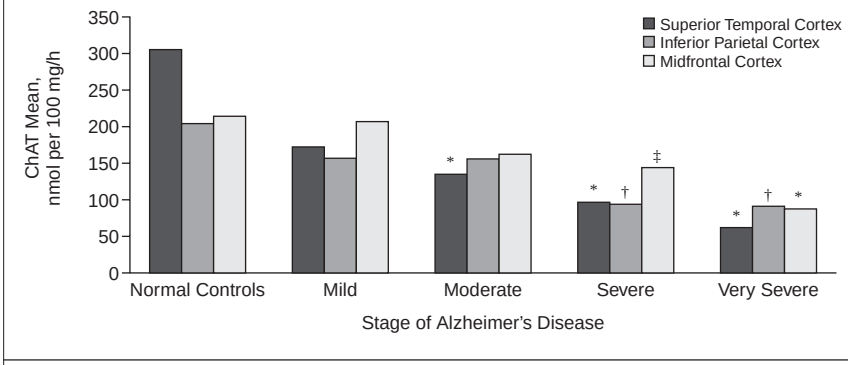
Challenging the Cholinergic Hypothesis: Evolution of Uncompetitive NMDA Antagonists as Treatments for Alzheimer's Disease

Jody Corey-Bloom, M.D., Ph.D., began by stating that research efforts with regard to the treatment of Alzheimer's disease have essentially focused on cholinergic therapy, but that a shift is occurring in the field and that other mechanisms are under investigation. She reminded physicians that different mechanisms in the etiology of the disease are not mutually exclusive and that combination therapies may be on the horizon.

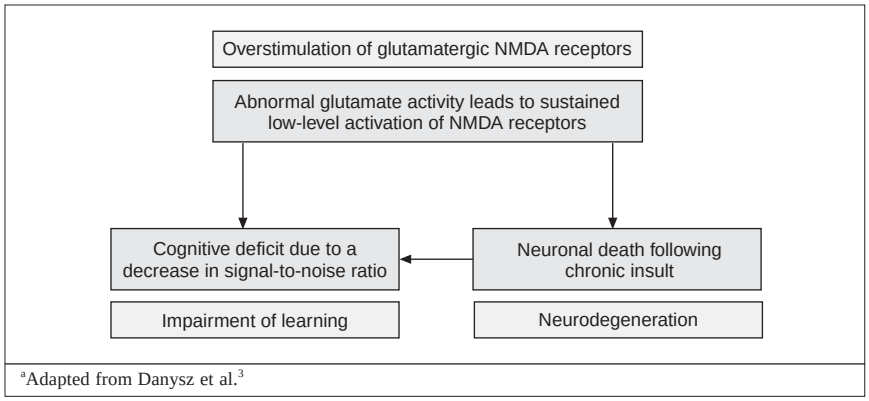
Dr. Corey-Bloom then addressed the question, Why has the cholinergic system received so much attention? One reason is that the cholinergic system has diffuse projections throughout the brain. It originates deep within the brain and projects not only to the hippocampus but also to multiple areas of the neocortex, areas known to be associated with memory and learning. At the level of the cholinergic synapse, in the presynaptic membrane, acetyl coenzyme A combines with choline with the help of the enzyme choline acetyltransferase to form molecules of acetylcholine (ACh). These molecules of ACh are then bundled into synaptic vesicles, released from the presynaptic membrane to diffuse across the cleft, and then bind postsynaptically at cholinergic receptors. Untreated, these molecules of ACh are quickly hydro-

Figure 2. Decline of Cholinergic Activity as Measured by Choline Acetyltransferase (ChAT) Levels in Alzheimer's Disease[a]



[a]Data from Tiraboschi et al.[1]
*p < .001 vs. normal controls; †p < .01 vs. normal controls; ‡p < .05 vs. normal controls.

Figure 3. Glutamate Hypothesis of Alzheimer's Disease[a]



[a]Adapted from Danysz et al.[3]

lyzed and taken back up into the presynaptic terminal. In the presence of a cholinesterase inhibitor, however, this rapid hydrolysis does not occur, and molecules of ACh remain active longer at the postsynaptic receptor.

Major changes occur in the cholinergic systems of patients with Alzheimer's disease, including a decline in choline acetyltransferase activity, loss of cholinergic neurons, and loss of muscarinic receptors. It follows that enhancement of cholinergic function via pharmacotherapy may stabilize or improve cognitive function in patients with Alzheimer's disease.

Unfortunately, these changes in the cholinergic system may occur later in the course of Alzheimer's disease than previously thought. For example, cholinergic activity as measured by choline acetyltransferase levels does not decline until the severe or very severe stages of the disease (Figure 2).[1] Therefore, pharmacotherapy with a cholinergic mechanism of action may effectively preserve cholinergic function only when it is too late, after significant damage has already been done to the patient's brain.

New Focus on the Glutamatergic System in Alzheimer's Disease

According to Dr. Corey-Bloom, many researchers have begun to focus on other neurotransmitter systems, particularly the glutamatergic system, with regard to potential treatments for patients with Alzheimer's disease. Glutamatergic neurons are ubiquitous in the central nervous system (CNS) and are involved in virtually all CNS functions, including plasticity, learning, and memory, and they are the primary excitatory neurons of the CNS. In addition, glutamatergic neurons are predominantly projection neurons, which provide information from one area of the brain to another. For example, the large pyramidal neurons located primarily in layers 3 and 5 of the neocortex have large dendritic arborizations replete with predominantly glutamate receptors. Dr. Corey-Bloom explained that it is, in fact, this very area of the brain, the neocortex, where severe reductions in gray matter—up to 30%—are seen as Alzheimer's disease progresses.[2]

What one sees is a circuit in which information from the neocortex converges on the medial temporal lobe, travels to the hippocampal formation, and then is funneled into the Schaeffer collateral pathway, which is important in the process of long-term potentiation (LTP). LTP refers to increased sensitivity of postsynaptic receptors to volleys of incoming information and is thought to be an elemental feature of learning and memory.

Dr. Corey-Bloom then addressed how glutamate exerts its effects through 3 kinds of receptors: AMPA receptors, metabotropic receptors, and finally, and most importantly, NMDA receptors. NMDA receptors are particularly dense in not only the hippocampus but also the cerebral cortex. It is believed that the phenomenon of long-term potentiation, the best candidate mechanism for memory, occurs through efforts of the NMDA receptor.

Unfortunately, the NMDA receptors and glutamate transmission can be a double-edged sword, in that overstimulation of NMDA receptors can eventually kill neurons in a process called excitotoxicity. Taking this process into account, the glutamate hypothesis of Alzheimer's disease (Figure 3)[3] states that abnormal glutamate activity leads to sustained low-level activation of NMDA receptors. This overstimulation leads to a decreased signal-to-noise ratio as well as cognitive deficits and impairment of learning. With chronic overstimulation, neuronal death and neuronal degeneration can ultimately occur.

Table 4. Efficacy Results From a Memantine Monotherapy Trial[a]

	Baseline Scores		LOCF Change From Baseline (mean ± SD)			Observed Cases Change From Baseline (mean ± SD)		
Measure	Memantine	Placebo	Memantine	Placebo	p Value	Memantine	Placebo	p Value
CIBIC-Plus[b]	NA	NA	4.5 ± 1.12	4.8 ± 1.09	.06	4.4 ± 1.12	4.7 ± 1.13	.03
ADCS-ADL	26.8	27.4	–3.1 ± 6.79	–5.2 ± 6.33	.02	–2.5 ± 6.27	–5.9 ± 6.78	.003
SIB	65.9	68.3	–4.0 ± 11.34	–10.1 ± 13.50	< .001	–4.5 ± 11.48	–10.2 ± 12.66	.002

[a]Data from Reisberg et al.[8]
[b]The CIBIC-Plus is a change scale; baseline scores were set at 4.0 ("no change"). The values for CIBIC-Plus are actual mean ratings; higher values indicate worsening.
Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (modified for severe dementia), CIBIC-Plus = Clinician's Interview-Based Impressions of Change Plus Caregiver Input, LOCF = last observation carried forward, SIB = Severe Impairment Battery.

Additional support for the glutamate hypothesis comes from many disparate areas of clinical and basic science research. Patients with Alzheimer's disease experience reductions in the glutamate transporter for glial cells in the frontal cortex.[4] There are also significant reductions in NMDA receptor subunits in the hippocampus and entorhinal areas of Alzheimer's-diseased brains.[5] β-Amyloid, the principal component of the neuritic plaque, can augment NMDA receptor–mediated transmission and can also enhance release of glutamate to toxic levels. Excitotoxicity increases the production of the amyloid precursor protein, which is processed abnormally in the brains of individuals with Alzheimer's disease.[6,7]

NMDA Antagonists in the Treatment of Alzheimer's Disease: Memantine

What is needed, according to Dr. Corey-Bloom, is a compound that not only preserves the physiologic activation of NMDA receptors required for long-term potentiation and for learning and memory, but also blocks the effects of abnormal glutamate activity that can lead to cognitive dysfunction and eventual neuronal death. Memantine, an uncompetitive NMDA receptor antagonist, may meet those needs. It has fast on/off kinetics, and it has low-to-moderate affinity for the NMDA receptor. It can protect the postsynaptic cells from chronic stimulation by low levels of glutamate, but with neuronal activity, it can release that blockade and normalize transmission.

Dr. Corey-Bloom then addressed how memantine's mechanism of action translates into patient care and the treatment of Alzheimer's disease. The results of a memantine monotherapy study were recently published.[8] This trial was a randomized, double-blind, placebo-controlled phase 3 trial that included 32 sites in the United States and 252 outpatients with probable Alzheimer's disease according to DSM-IV and National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. These patients had moderate-to-severe Alzheimer's disease, with a MMSE score of 3 to 14, a Global Deterioration Scale (GDS) score of 5 or 6, and a Functional Assessment Staging (FAST) score of at least 6a.

Patients were treated with memantine, 20 mg/day (10 mg b.i.d.), for 28 weeks, including an initial 4-week titration. The primary efficacy measures were the Clinician's Interview-Based Impressions of Change Plus Caregiver Input (CIBIC-Plus) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory, modified for severe dementia (ADCS-ADL). Secondary efficacy measures included the Severe Impairment Battery (SIB), a cognitive measure; the Neuropsychiatric Inventory (NPI), an assessment of behavior; the Resource Utilization in Dementia measure; the MMSE; the GDS; and the FAST. The memantine-treated group and the placebo-treated group were well-matched in terms of baseline characteristics.

Over the course of the 28-week trial, placebo-treated patients deteriorated more than did the memantine-treated patients (Table 4). Consistent results were seen on the 2 primary efficacy measures as well as on secondary measures such as the SIB.

In general, the rate of adverse events was similar in the 2 groups. Some were actually more common in the placebo group than the memantine group, such as agitation (32% in the placebo group vs. 18% in the memantine group) and urinary tract infections (13% in the placebo group vs. 6% in the memantine group). No differences were seen with regard to insomnia or diarrhea.

Conclusion

Dr. Corey-Bloom emphasized that in Alzheimer's disease, cholinergic activity may not be diminished to any significant degree until late in the course of the disease. Therefore, researchers should explore options besides cholinergic medications for the treatment of Alzheimer's disease, with combination therapy as a goal.

One of these options may be agents with glutamatergic actions. Glutamatergic neurons are the primary excitatory neurons of the CNS and are involved in functions like learning and memory. One NMDA receptor antagonist, memantine, blocks the effects of abnormal glutamatergic stimulation that has been postulated to lead to neuronal cell death in various neurodegenerative diseases. It also preserves the physiologic activation of NMDA receptors required for learning and memory. Treatment with memantine has been associated with significantly less decline versus placebo on global, functional, and cognitive measures in patients with Alzheimer's disease.

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Combination Therapy for Alzheimer's Disease

Pierre N. Tariot, M.D., began by pointing out that even for patients in later stages of Alzheimer's disease, treatments are needed that will improve or maintain cognition, function, and quality of life. He argued that a combination of agents, for example, a cholinesterase inhibitor such as donepezil with an NMDA receptor antagonist such as memantine, may provide additive or even synergistic symptomatic benefit to patients. Before such a treatment strategy could be widely implemented, however, it had to be studied to determine whether memantine would be safe and efficacious in combination with a commonly used cholinesterase inhibitor.

Memantine Plus Donepezil in Moderate-to-Severe Alzheimer's Disease

Dr. Tariot explained the pharmacokinetics and possible drug-drug interactions of memantine (Tables 5 and 6).

Prior to the initiation of a study of memantine and donepezil in patients with Alzheimer's disease, an open-label, multiple-dose pilot study[3] in 24 healthy individuals was conducted. The results showed that memantine absorption and bioavailability were unaffected by coadministration of donepezil. No pharmacokinetic interaction was noted when these 2 drugs were administered together, nor were any significant adverse events noted.

Dr. Tariot then reviewed the results of a recent multisite, double-blind, placebo-controlled study.[4] In that study, 404 outpatients with probable moderate-to-severe Alzheimer's disease (NINCDS-ADRDA criteria) at 37 U.S. sites were included; 403 were treated. Other inclusion criteria included MMSE score of 5 to 14, MRI or CT results consistent with diagnosis of Alzheimer's disease, and daily donepezil therapy for the previous 6 months and a stable dose for the previous 3 months. By using a single comparator agent, the authors hoped that fewer confounding variables would be introduced. Patients also had to be medically stable and free of other significant neurologic or psychiatric illness, as is common in these types of trials.

Patients were randomly assigned to receive 20 mg/day of memantine (10 mg b.i.d.; N = 202) or placebo (N = 201) for 24 weeks, including an initial 4-week titration, in addition to ongoing donepezil treatment. The primary outcome measures were the SIB, a performance-based assessment of cognition, and the 19-item ADCS-ADL for severe dementia, a functional assessment. The chief secondary efficacy outcomes were the CIBIC-Plus for global assessment, the NPI for behavioral assessment, and the care dependence subscale of the Behavior Rating Scale for Geriatric Patients (BGP) for functional assessment.

Of the randomized patients, 85% of memantine-treated patients completed the study, and 75% of placebo-treated patients completed the study, a significant difference ($p = .011$). The 2 groups were well matched demographically and in severity of Alzheimer's disease. Mean age was 75 years, about two thirds were women, and roughly 90% were white.

Dr. Tariot reported that changes from baseline to endpoint on both primary outcome measures were statistically significantly in favor of memantine plus donepezil. SIB scores gradually declined in the placebo/donepezil group, while a modest improvement was seen in the memantine/donepezil group ($p < .001$). The ADCS-ADL results showed less decline in daily function in the memantine/donepezil-treated group compared with the placebo/donepezil group ($p = .028$). All of the outcome

Table 5. Memantine Pharmacokinetics[a]

Variable	Value
Bioavailability	100%
Time to maximum plasma drug concentration	4 to 7 h
Protein binding	About 45%
Half-life	60 to 80 h
Steady-state plasma concentration	70 to 150 ng/mL
Time to steady state	Within 21 d
Cerebrospinal fluid/serum ratio	0.52
Excreted in urine	Majority unchanged
Hepatic metabolism	Minimal
Inhibition of cytochrome P450 isoenzymes	Minimal
Significant food interaction	None

[a]Adapted from Jain[1] and data on file, Forest Laboratories, Inc.

Table 6. Potential Memantine Drug-Drug Interactions[a]

Pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes are not expected
Memantine does not affect reversible inhibition of aceytlcholinesterase by donepezil, galantamine, or tacrine
Interactions with drugs that are highly bound to plasma proteins (eg, warfarin or digoxin) are unlikely
Memantine has not been studied in patients with renal failure

[a]Adapted from Jain,[1] Wenk et al.,[2] and data on file, Forest Laboratories, Inc.

assessments, primary and secondary, showed a treatment effect in favor of memantine plus donepezil over placebo plus donepezil.

No clinically important changes were observed between the treatment groups in the incidence of patient mortality, severe adverse events, electrocardiogram abnormalities, vital signs (pulse, systolic blood pressure, diastolic blood pressure), potentially clinically significant hematologic or biochemical abnormalities, or urinalysis parameters or in physical examination. A few more patients in the memantine/donepezil group experienced confusion than patients in the placebo/donepezil group, although these events were almost all rated as mild and did not result in disproportionate dropouts, whereas confusion was more severe and resulted in a greater percentage of dropouts in the placebo/donepezil group than in the memantine/donepezil group.

Conclusion

Dr. Tariot noted that this was the first double-blind, placebo-controlled study[4] to examine the safety and efficacy of combining the NMDA receptor antagonist memantine with the cholinesterase inhibitor donepezil in patients with moderate-to-severe Alzheimer's disease. Patients experienced beneficial effects in cognitive, functional, global, and behavioral measures when memantine was given to patients on a stable regimen of donepezil. In addition, the combination was well tolerated. Although more research into other combination therapies is needed, these results are indeed promising.

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***Drug names**: digoxin (Lanoxin and others), donepezil (Aricept), galantamine (Reminyl), memantine (Namenda), tacrine (Cognex), warfarin (Coumadin and others).*

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1. Failing to make a diagnosis of Alzheimer's disease as early as possible can result in all of the following *except*:
   a. Higher rates of hospitalization
   b. Higher rates of emergency department use
   c. More medication errors
   d. Less cognitive impairment

2. A promising technology that may be able to diagnose patients with early stages of Alzheimer's disease is:
   a. Positron emission tomography
   b. Magnetic resonance imaging
   c. Computed tomography
   d. None of the above; it is impossible to diagnose Alzheimer's disease in the early stages

3. Glutamatergic neurons are ubiquitous in the central nervous system and are involved in all of the following functions *except*:
   a. Plasticity
   b. Learning
   c. Preventing information from getting from one part of the brain to another
   d. Memory

4. A compound that _____ is needed in the treatment of Alzheimer's disease.
   a. Affects only the cholinergic system
   b. Only preserves the physiologic activation of *N*-methyl-D-aspartate (NMDA) receptors
   c. Only blocks the effects of abnormal glutamate levels
   d. Preserves the physiologic activation of NMDA receptors and blocks the effects of abnormal glutamate levels

5. Combination therapy with an existing cholinesterase inhibitor plus a new NMDA receptor antagonist may provide additive or even synergistic symptomatic benefit to patients with Alzheimer's disease.
   a. True
   b. False

Answer to Pretest: 1. a

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