Emerging Therapeutic Strategies in Alzheimer's Disease

This ACADEMIC HIGHLIGHTS section of 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.*

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Treatment of Alzheimer's Disease

George T. Grossberg, M.D., opened the symposium by reviewing the current state of treatment strategies for Alzheimer's disease and offering examples of future direction of research for both treatment and prevention. The current science relative to the pathogenesis of Alzheimer's disease is fueling the development of a variety of novel treatment approaches, both pharmacologic and otherwise. Cholinergic as well as noncholinergic and combination treatment strategies are becoming more and more popular in the treatment of Alzheimer's disease. European nations continue to administer compounds such as the nosotropics and ergoloid mesylates, which, at least at the present time, have fallen out of favor in the United States. Some trials of agonist-type compounds—for example, bethanechol and approaches that examine nerve growth factors and membrane stabilizers—have been largely unrewarding.

Dr. Grossberg stated that at the present time, cholinesterase inhibitors (i.e., tacrine, donepezil, rivastigmine, and galantamine) are the only therapies approved worldwide for the treatment of mild-to-moderate Alzheimer's disease. The development of several different compounds (e.g., statins, anti-inflammatory compounds, and antioxidant drugs) and new approaches to treatment and prevention are underway. In addition to treating patients with Alzheimer's disease, some of these approaches have the potential to delay or prevent Alzheimer's disease in at-risk individuals.

Effective pharmacologic antagonism of the *N*-methyl-D-aspartate (NMDA) receptor may help to slow the progression of Alzheimer's disease. The NMDA receptor antagonist memantine, recently approved for moderate-to-severe Alzheimer's disease, can be used alone or in combination with the current cholinesterase inhibitors. Recognizing that a cholinergic deficit is not the only indicator of Alzheimer's disease but that neurotransmitter alterations may be implicated could lead to the development of multitransmitter compounds.

Since amyloid is the first component of the disease cascade, drugs that affect amyloid, whether in the form of an anti-amyloid vaccine (currently being reformulated) or a secretase inhibitor, which has the possibility of decreasing the synthesis of β-amyloid, may have a major impact on the course of Alzheimer's disease.

Lastly, Dr. Grossberg noted that several centers in the United States are involved in the first double-blind, placebo-controlled, multicenter study of a surgical approach to Alzheimer's disease, namely, the implantation of what has been called the COGNIShunt System (Eunoe, Inc.; Pleasanton, Calif.). The COGNIShunt is a circulatory, almost shunt-pump type, apparatus that is implanted in the brains of individuals in the early stages of Alzheimer's disease as a way to stave off progression and improve functionality. Indeed, many optimistic treatments are on the horizon for the future.

The Spectrum of Dementia From Early Onset to Severe Disease: Perspectives in Management

Gary W. Small, M.D., started his presentation by pointing out that it is a challenge to make a diagnosis of dementia today. Most patients with dementia are cared for in primary care initially, yet primary care physicians lack knowledge about dementia. A recent study[1] found that 60% of these generalists and other professionals were not aware that Alzheimer's disease is the most common form of late-life dementia. As a possible consequence of that lack of knowledge, Callahan et al.[2] found that moderate dementia was missed in 75% of primary care patients.

The consequences of missing an early diagnosis and the benefits of receiving an early diagnosis are far reaching. According to Dr. Small, missing a diagnosis of dementia leads to higher hospitalization rates, more medication errors, more visits to the emergency room, more motor vehicle accidents, and a higher mortality rate. Diagnosis, however, is often delayed or confounded by comorbid conditions, depression, lack of reporting by the patient and caregiver, and denial among family members. Further, many patients maintain social skills in early Alzheimer's disease, and physicians are unaware of the signs and symptoms of Alzheimer's disease. The health care reimbursement system and financial disincentives also work against trying to diagnose these patients.

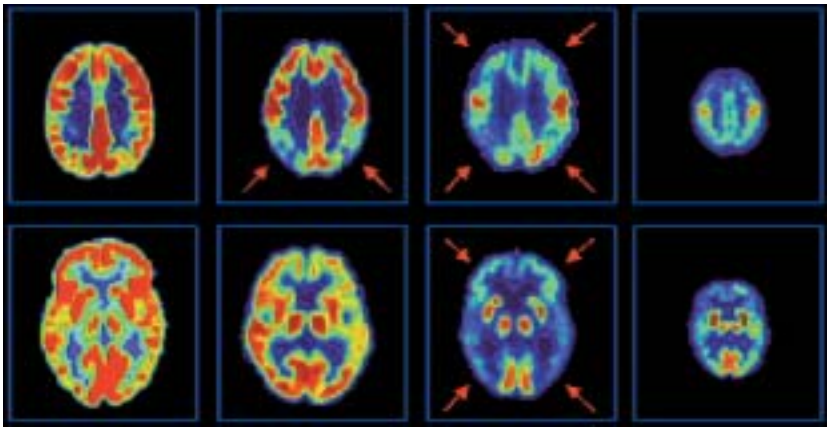
The benefits of early diagnostic accuracy are seen in the improved quality of life of the patient as well as family and caregivers. Accurate diagnostic information and education reduce family and caregiver burden, decrease the likelihood of repeated diagnostic assessments, delay nursing home placement, maintain patients at higher levels of functioning which leads to fewer medical visits and hospitalizations, and reduce the use of other psychotropic drugs.[3–6] Further, according to Dr. Small, early treatment can help preserve and maintain function at a higher level over the course of the disease.

Brain Imaging Tools

Dr. Small explained that research at the University of California Los Angeles (UCLA) Aging and Memory Research Center follows the premise that it is probably easier to protect the brain before damage occurs than to reverse the damage once it is there. To help pinpoint the progression of damage in the brain, researchers at UCLA inject the patient or the volunteer with a radioactively labeled glucose analog and use positron emission tomography (PET) scanning to see how the brain cells are functioning. Since glucose is the brain's main food source in a non-starvation state, a PET scan shows how well those cells are using glucose and how well the neurons are firing. To illustrate, Dr. Small showed a PET scan of cerebral metabolism in a normal brain, an Alzheimer's disease brain, and a child's brain (Figure 1). The red colors represent greater metabolic activity or neuronal activity. Early in the course of the disease, the back part of the brain, the parietal area, and even the temporal region show a deficit. As the disease progresses, there are deficits in the frontal region as well. A late stage Alzheimer's disease case looks very much like an immature brain, similar to that of a child. Dr. Small commented that it is perhaps not surprising, then, that patients in late stage Alzheimer's disease often exhibit the same behaviors as children.

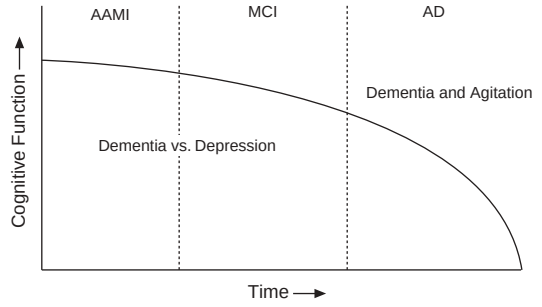
Dr. Small gave examples of the greater accuracy of the PET scan compared with clinical assessments and magnetic resonance imaging (MRI) in the early diagnosis of Alzheimer's disease. Silverman et al.[7] found that early diagnostic assessment using PET scans in 286 patients presenting with symptoms of dementia was both highly sensitive and highly specific. PET scans identified patients with Alzheimer's disease and patients with any neurodegenerative disease with a sensitivity of 94% and specificities of 73% and 78%, respectively. Dr. Small further commented that PET scans appear to be more accurate than the standard clinical examination. Clinical data from an earlier study[8] revealed that of 134 cases of dementia, 95 (71%) had probable Alzheimer's disease and 83% of these were correctly diagnosed

Figure 1. Cerebral Metabolism in Alzheimer's Disease Progression and in Healthy Brains



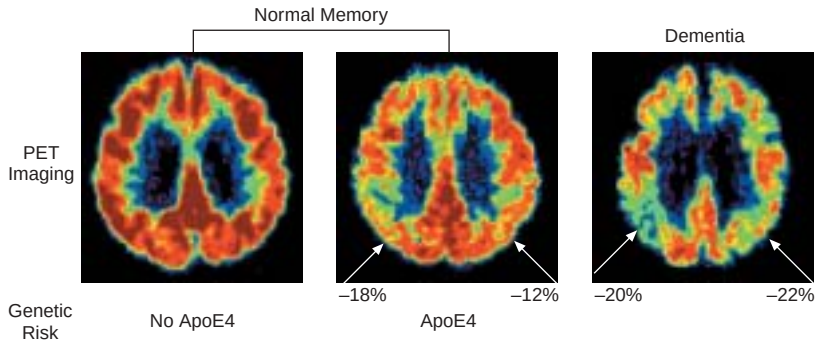
Abbreviation: AD = Alzheimer's disease.

Figure 2. Course of Alzheimer's Disease: Behavior and Cognitive Function Change[a]



[a]Reprinted with permission from Small.[10]
Abbreviations: AAMI = age-associated memory impairment, AD = Alzheimer's disease, MCI = mild cognitive impairment.

Figure 3. PET and Genetic Risk for Alzheimer's Disease: Lower Inferior Parietal Metabolism in Persons Without Dementia Who Have a Single Copy of ApoE4[a]



[a]Reprinted with permission from Small et al.[11] Abbreviations: ApoE4 = apolipoprotein, PET = positron emission tomography.

(compared with 94% using a PET scan[7]). Dr. Small described a case at UCLA (G.W.S., personal observation) of a 65-year-old woman who was diagnosed with depression and attention-deficit disorder. Over the course of 2.5 years, she had neuropsychiatric evaluations and multiple MRI scans. The results of many different assessments were inconclusive. Finally, a fluoro-2-deoxy-D-glucose (FDG)-PET scan was performed that clearly showed a parietal deficit (indicating early Alzheimer's disease). She was started on cholinesterase inhibitor treatment, and her mood and cognitive symptoms improved within about 1 month.

Course of Alzheimer's Disease

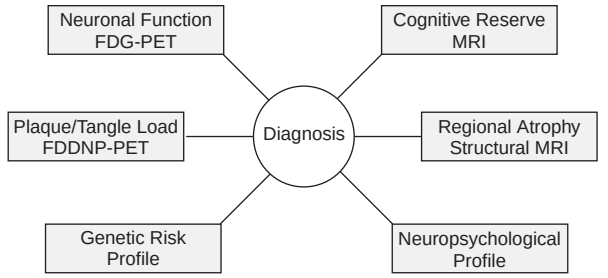
Dr. Small stated that several diagnostic categories are used to identify patients who are in presymptomatic states, prior to an actual diagnosis of Alzheimer's disease. Probably the mildest condition is age-associated memory impairment (AAMI). This is a common phenomenon that involves a mild decline in memory ability compared with average memory ability in young adults. A majority of older adults experience this condition, and it is not a high-risk factor for getting Alzheimer's disease. By contrast, mild cognitive impairment (MCI) is a more severe form of memory loss that involves a problem with delayed recall. The memory deficit that constitutes MCI is very similar to mild Alzheimer's disease, but people are still functionally independent. A recent study[9] showed that individuals with MCI are at risk for Alzheimer's disease at a rate of about 10% per year.

One can hypothesize that a continuum of brain aging begins with AAMI, moves toward MCI, and culminates in Alzheimer's disease (Figure 2). Diagnosing this gradual transition, however, is complicated by behavioral problems, cognitive deficits, and in the mild cases, depression and anxiety. In later stages, problems with agitation and psychosis make Alzheimer's disease more complicated to treat.

Dr. Small reported that efforts to develop tools to diagnose or identify candidates for treatment in these presymptomatic states are underway at UCLA and other centers around the world. The goal is to protect the brain before damage occurs. To help with early diagnosis, Dr. Small explained that some subjects at UCLA who are at genetic risk for Alzheimer's disease are undergoing PET scans before any symptoms appear. If an individual has the apolipoprotein (ApoE4) gene, the major genetic risk for late onset Alzheimer's disease, an Alzheimer's-like pattern is evident in the brain even when memory function is normal (Figure 3).[11] Ten such subjects who had ApoE4 and normal memory performance with some mild memory complaints at baseline were followed for 2 years. PET scans over time showed a rapid decline in metabolism in key memory centers: parietal, temporal, and posterior cingulate regions. After 2 years, all 10 subjects had declined in parietal and temporal regions, areas of the brain that are eventually affected by Alzheimer's disease.

On the basis of this information, Dr. Small and others have designed studies that test drugs and other treatments in individuals with very mild memory complaints. The PET scan is used as a surrogate marker to see if the drugs are effectively slowing down brain aging in an Alzheimer's-like pattern. In fact, by using surrogate markers, researchers at UCLA and the University of Arizona[11–13] have found that only 60 subjects with the ApoE4 gene per treatment arm are needed to detect a drug effect in 2 years using PET (posterior cingulate metabolism). Using PET imaging for patients with Alzheimer's disease regardless of genetic risk status, only 36 patients per treatment arm

Figure 4. Using Information From Multiple Sources to Improve Early Diagnosis and Treatment



Abbreviations: FDDNP = fluoroethyl (methyl) amino-2-naphthyl ethylidene malononitrile, FDG = fluoro-2-deoxy-D-glucose, MRI = magnetic resonance imaging, PET = positron emission tomography.

are needed in a 1-year study. Dr. Small estimates that if all the subjects have ApoE4, a baseline PET scan and a follow-up PET scan will reflect about a 4% to 5% decline in metabolism in parietal and temporal regions in subjects taking placebo. The decline in metabolism should slow in subjects taking an active drug that might be working to slow the brain aging process, which could possibly delay the onset of Alzheimer's disease.

At UCLA, thanks to funding from the National Institutes of Health, several compounds are being studied. For subjects with very mild memory complaints who have a genetic risk and PET scan indications for Alzheimer's disease, celecoxib, an anti-inflammatory drug, and donepezil, a cholinesterase inhibitor drug, are being tested. Further, at the MCI stage, many studies[10,14] are examining the effectiveness of cholinesterase inhibitors, anti-inflammatory drugs, vitamins, and hormones. In these studies, because there is no surrogate marker, many more subjects are needed to demonstrate the effect, making these costly studies to conduct.

In Vivo Studies

Dr. Small reported that although in vitro studies have moved research forward, in vivo studies (i.e., studies of the brains in living patients) may hold the key to early diagnosis and treatment. Recent innovations in technology under development at UCLA are allowing researchers to view the physical evidence of Alzheimer's disease, plaques and tangles, in living patients. A radiolabeled small molecule that is attracted to the plaques and tangles is injected into the cerebrospinal fluid brain of patients. In the plaque and tangle scan, the radiolabeled molecule shows increased staining in the temporal regions. Interestingly, Dr. Small pointed out that the signal correlates very well with memory scores on the Mini-Mental State Examination (MMSE). Very good correlations are seen in subjects who do not have Alzheimer's disease but are beginning to build up plaques and tangles and in patients who have the disease.

Referring to the approaches mentioned by Dr. Grossberg, i.e., anti-amyloid vaccines and anti-tangle treatments, Dr. Small stated that using a new level of technology and information from multiple sources will be very helpful in testing these strategies, predicting brain aging, and improving early diagnosis and treatment (Figure 4). Clinicians can select and combine tests to aid in accurate diagnosis and treatment. An FDG-PET scan can be used to obtain information about neuronal function, for example, but a fluoroethyl (methyl) amino-2-naphthyl ethylidene malononitrile (FDDNP)-PET scan or amyloid plaque tangle imaging can be used to obtain information about plaque and tangle load. In addition, brain imaging techniques are tools to help researchers with proof-of-concept studies. If a treatment appears to be clearing plaques and tangles out of the brain, a plaque and tangle scan can be performed in a few patients to see if there is an effect. This information then can help determine if research should move forward into a large-scale clinical trial.

Risk Factors and Protective Factors

Laboratory and clinical studies as well as epidemiologic data have helped to determine various risk factors for Alzheimer's disease.[10] Definite risks include advanced age, ApoE4 gene, and family history. Possible risks include other genes, head trauma, lower educational level, vascular disease, high homocysteine levels, and lowered estrogen levels following menopause. Possible protective factors that are under investigation include anti-inflammatory drugs, cholesterol-lowering drugs, antioxidants, wine (in moderation), low-fat diet, aerobic conditioning, and mental activity. Key factors in research efforts are, assuming efficacy, determining the treatment course (whether monotherapy or combination therapy) and at what point in the progression of brain aging treatment should begin (whether at advanced dementia or in the presymptomatic states). In the presymptomatic stage, activities of daily living and MMSE scores indicate changes in the course of dementia. Early in the disease course, subjects have trouble keeping appointments and using the telephone. But as the disease progresses, very basic activities of daily living become impaired, such as walking and eating. Again, early intervention may help to delay the onset of Alzheimer's disease.

Intervention

Besides medication, nonpharmacologic approaches are also helpful. Education and support for caregivers as well as practical strategies such as keeping daily activities routine, arranging for regular exercise, and using clocks and calendars to maximize orientation will help to keep patients at the highest level of functioning.[15] PET imaging and new technology approaches to early detection and cognitive assessment are not yet widely available, and keeping a high index of suspicion is important to early diagnosis and treatment. Age, a

recent move to a new living environment, other illnesses such as delirium, depression, diabetes, Parkinson's disease, or some kind of unexplained functional loss, and any concerns on the part of the patient or the family should trigger an assessment.

Cholinesterase-inhibitor medications are approved for mild-to-moderate stage use in the United States. Some cholinesterase-inhibitor drugs, NMDA antagonists (e.g., memantine), or other treatments may have disease-modifying effects, but this has never been demonstrated. Pathologic pathways are being studied to determine when various treatments should be initiated, i.e., during MCI or during clinical dementia (when basic changes are going on in the brain that may include synaptic loss, neuronal death, or plaque and tangle accumulation). One study[16] found that memantine provides neuroprotection against β-amyloid–induced damage in the hippocampus. Memantine, 20 mg/kg/day, was infused over 2 days and then β-amyloid was injected into the hippocampus of the brain in a rat. Outcome measures showed a reduction in number of injured or dying neurons in response to the β-amyloid infusion. Data like these tend to drive clinical science in determining when and at what point in the disease a clinical trial should begin. While this information is intriguing, Dr. Small stated that it does not prove whether there is going to be a disease-modifying effect. Proper study design with enough patients will determine that.

Conclusion

Dr. Small emphasized that brain aging continues throughout life and the Alzheimer's disease process begins relatively early in the presymptomatic state. Some of the data suggest that mental activity protects the brain. Early detection and prevention strategies may be useful in decelerating brain aging and delaying the onset of Alzheimer's disease. Over the next 5 to 10 years, major breakthroughs in this area will have significant impact in delaying the onset of Alzheimer's disease. Current symptomatic treatments are efficacious and are helping many patients. An early diagnosis leads to early treatment, so clinicians must look for cognitive assessment triggers so that patients can get the best benefit from these various treatment approaches.

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Challenging the Cholinergic Hypothesis: Evolution of Uncompetitive NMDA Antagonists as Treatments for Dementia

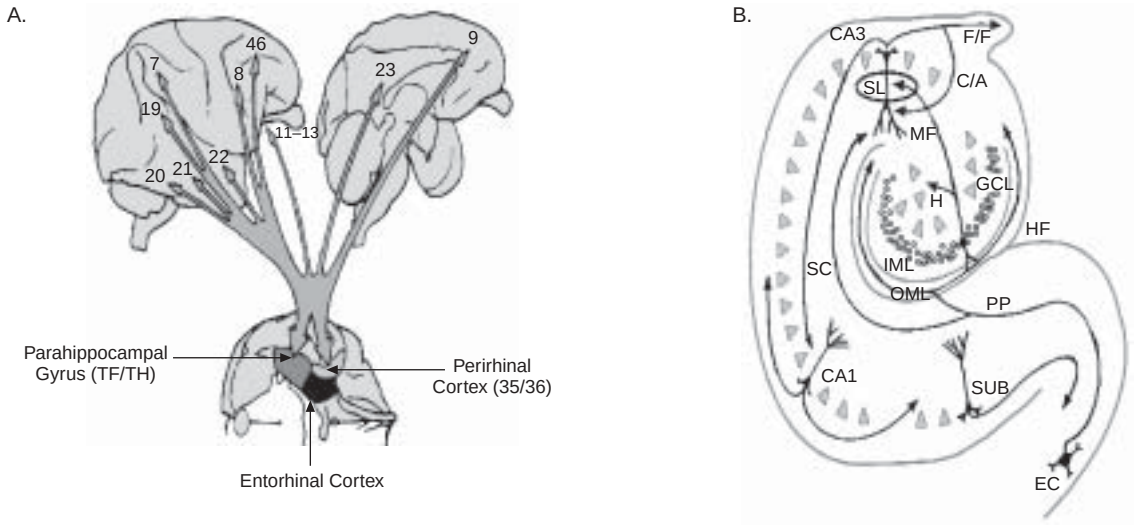
Jody Corey-Bloom, M.D., Ph.D., began by stating that current approved treatment strategies for Alzheimer's disease focus on correcting cholinergic deficits in the brains of patients with the disease. Given the newer understanding of the multiple pathologic mechanisms that culminate in neurodegeneration, however, such a simplistic rationale is no longer appropriate. These mechanisms are not mutually exclusive, and combination therapy is likely in the future.

Cholinergic Hypothesis

The cholinergic system has diffuse projections throughout the brain. It originates deep within the brain, in the nucleus basalis, and projects not only to the hippocampus but also to diffuse areas of the neocortex—areas known to be associated with memory and learning.

Dr. Corey-Bloom went on to explain that at the level of the cholinergic synapse, in the presynaptic membrane, acetyl coenzyme A (CoA) combines with choline with the help of the enzyme choline acetyltransferase (ChAT) to form molecules of acetylcholine (ACh). These are then bundled into synaptic vesicles, released from the presynaptic membrane to diffuse across the cleft, and then bind post-

Figure 5. Critical Role of Glutamatergic Neurons in Learning and Memory[a]



[a]Adapted with permission from Morrison and Hof.[4] Panel A demonstrates the convergence of cortical inputs onto cortical areas of the medial temporal lobe (thick arrows), which receive a widespread array of topographically organized projections from most regions of the neocortex and send more discrete reciprocal projections (thin arrows) to association areas throughout the neocortex (numbered following Brodmann's nomenclature).
Panel B is a schematic of corticocortical connectivity within the hippocampal formation and includes the perforant pathway (PP) projection from layer II of the entorhinal cortex (EC) to the outer molecular layer of the dentate gyrus (OML), the mossy fiber projection (MF) from the dentate granule cells to the stratum lucidum (SL) of the CA3 field, and the Schaffer collaterals (SC) innervating the pyramidal neurons in the CA1 field. Commissural and associational afferents (C/A) from the fimbria/fornix (FF) and the output projection from the subiculum (SUB) to the deep layers of the EC are also shown.
Abbreviations: GCL = granule cell layer of the dentate gyrus, H = hilus, HF = hippocampal fissure, IML = inner molecular layer of the dentate gyrus.

synaptically at cholinergic receptors. Untreated, those molecules of ACh are quickly hydrolyzed into choline and acetate and then taken back up into the presynaptic terminal where they are again used to make additional molecules of acetylcholine. In the presence of a cholinesterase inhibitor, however, this rapid hydrolysis does not occur, and in fact, the molecules of acetylcholine are free to remain bound at the postsynaptic receptor where they stay active longer.

Major changes occur in the cholinergic systems of patients with Alzheimer's disease, including the depletion of acetylcholine, loss of muscarinic receptors, loss of cholinergic neurons, and decline in the synthetic enzyme choline acetyltransferase activity. Dr. Corey-Bloom stated that correcting cholinergic deficits is a logical first approach to enhancing cholinergic function and to perhaps stabilizing or improving not only cognition but also behavior and functioning in patients with Alzheimer's disease. Acetylcholine is an important neurotransmitter in brain regions involved in memory, so loss of it correlates with memory impairment in Alzheimer's disease. One of the problems with focusing on the cholinergic system, however, was recently highlighted in a study by Tiraboschi et al.[1] Their findings showed that loss of ChAT activity is less severe and occurs later in the clinical course of Alzheimer's disease compared with dementia with Lewy bodies, in which the loss of ChAT activity is prominent in the earliest stages of the illness. Reduced ChAT activity begins to appear in the superior temporal area of the brain during the moderate stages of Alzheimer's disease; however, the decline in ChAT activity does not appear in the midfrontal and inferior parietal regions of the brain until the severe and very severe stages of the disease. Dr. Corey-Bloom noted that these types of findings have led researchers to focus on other neurotransmitter systems.

Glutamatergic Neurons

According to Dr. Corey-Bloom, the glutamatergic system has received much attention recently with regard to potential treatment for patients with Alzheimer's disease. Glutamatergic neurons, the primary excitatory neurons of the central nervous system (CNS), are ubiquitous in the CNS and are involved in virtually all its functions. As predominantly projection neurons, they provide information from one brain area to the next.

Most cholinergic inputs to the neocortex terminate on pyramidal neurons whose large dendritic arborizations are replete with predominantly glutamate receptors. Severe reductions in cortical neurons are seen as Alzheimer's disease progresses. In some neuroimaging studies,[2] declines of as much as 30% of cortical gray matter have been described in the superior temporoparietal areas, and pathologic studies[1,3,4] of these same regions show similar degrees of actual neuronal loss. Thus, it is likely that appreciable numbers of glutamatergic neurons and receptors are lost during the course of Alzheimer's disease.

The critical role played by glutamatergic neurons in plasticity, learning, and memory is evidenced by their presence in important structures of the medial temporal lobe, including the parahippocampal gyrus, the perirhinal

cortex, and the entorhinal cortex (Figure 5).[4] The medial temporal lobe acts as a convergence point for input from the neocortex, much of it from association areas within the neocortex, into the medial temporal lobe, and specifically into the entorhinal cortex. Figure 5B shows a coronal section of the medial temporal lobe including the entorhinal cortex, the hippocampus, and also the dentate gyrus. The entorhinal cortex serves as the portal of entry for information from the neocortex to the hippocampus. The perforant pathway is the key interconnection between all of that entorhinal input and the outer molecular layer of the dentate gyrus, a structure critical in the formation of memories and learning.

The pathway from the CA3 region of the hippocampus to CA1 (so-called Schaffer collaterals) has been extensively studied with regard to the phenomenon of long-term potentiation (LTP). LTP refers to long-lasting enhancement of synaptic transmission or increased sensitivity of postsynaptic receptors to volleys of incoming information. LTP is thought to be the elemental feature of learning and memory. Dr. Corey-Bloom emphasized that all fast excitatory projection pathways to, within, and from the hippocampus utilize glutamate as their transmitter.

NMDA Receptors

Next, Dr. Corey-Bloom explained that glutamate exerts its effects primarily through 3 kinds of receptors: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, metabotropic receptors, and—most important with regard to the process of LTP—NMDA receptors. The NMDA receptor is a complex receptor that not only has binding sites for glutamate and NMDA but has an obligatory co-agonist, glycine, which has to also bind at the NMDA receptor for the receptor to become activated.

An important feature of the NMDA receptor is that it is an ion-gated channel that is blocked by magnesium. NMDA receptors are particularly dense in not only the hippocampus but also the cerebral cortex. It is believed that the phenomenon of LTP, the best candidate mechanism for memory, is actually mediated through NMDA receptors. Unfortunately, these receptors may also mediate damage to neurons. Overactivation of NMDA receptors can eventually kill neurons. Known as *excitotoxicity* since the late 1980s, this overactivation is thought to literally excite neurons to death.

Glutamatergic Hypothesis

Dr. Corey-Bloom then described the current "glutamate hypothesis" of Alzheimer's disease: abnormal glutamate activity may lead to sustained low-level activation of NMDA receptors. Overstimulation of NMDA receptors causes a buildup of excessive calcium, with a resultant decrease in signal-to-noise ratio, cognitive deficits, and impairment of learning. Chronic overstimulation results in neuronal death and ultimately neuronal degeneration. Additional support for this hypothesis comes from many disparate areas of clinical and basic science research.[5–8] Patients with Alzheimer's disease have reductions in the glutamate transporter for glial cells—which is important because the transporter helps to mop up excess glutamate in the extracellular fluid—and significant reductions in NMDA-receptor subunits in the hippocampus and entorhinal areas of the brain. Further, β-amyloid, the principal component of the neuritic plaque, enhances glutamate toxicity and augments NMDA-receptor–mediated transmission. Excitotoxicity increases the production of the amyloid precursor protein (the precursor molecule that is processed abnormally in the brains of individuals with Alzheimer's disease).

New Therapy

Dr. Corey-Bloom explained that the ideal compound would not only preserve the good physiologic activation of NMDA receptors required for LTP and for learning and memory, but also block ill effects, such as abnormal glutamate activity that can lead to cognitive dysfunction and eventual neuronal death. Such a compound may be memantine, an uncompetitive NMDA-receptor antagonist that was recently approved by the U.S. Food and Drug Administration (FDA) for use in patients with moderate-to-severe Alzheimer's disease. Memantine has very fast blocking/unblocking kinetics and only a mild-to-moderate affinity for the NMDA receptor.

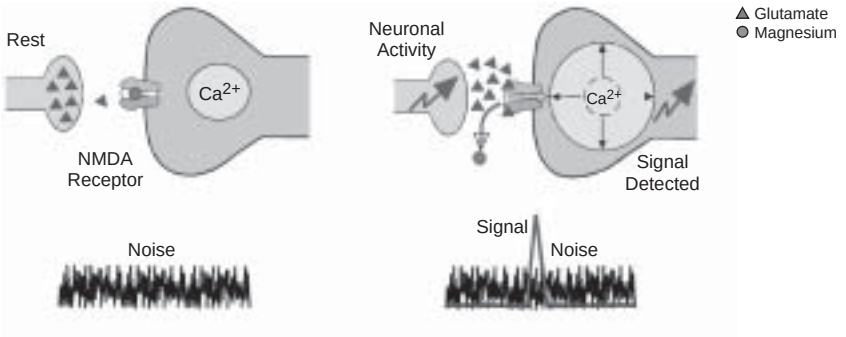
In the resting state of NMDA-receptor transmission, a molecule of magnesium blocks the ion-gated channel (Figure 6). However, with an increased volley of neuronal activity, the blockage is actually released and glutamate ions can bind to the postsynaptic membrane, allowing a good signal-to-noise ratio and detection of that neuronal signal. With degenerative diseases such as Alzheimer's disease, however, the story is quite different (Figure 7). Chronic low levels of glutamate in the extracellular space may be enough to remove the blockade at the level of the NMDA receptor, leaving those channels open. As a result, glutamate can actually cause increases of calcium intracellularly. A lot of noise occurs as a result of those channels being open. Even though there may be a signal with neuronal activation, that signal gets buried in the noise. Ultimately, as the neurodegeneration becomes chronic, the neuron itself becomes damaged.

Compounds like memantine can help because they block the channel (acting as a sort of supermagnesium) and protect the postsynaptic cell from the chronic stimulation by low levels of glutamate. Memantine is not sensitive to those low levels of glutamate. This reduction in transmission leads to a reduction in the noise. Memantine moves out of the ion channel with a high level of neuronal activity. When the blockade is released, good physiologic stimulation of the postsynaptic membrane occurs and a good signal-to-noise ratio follows normalization of the transmission.

Memantine Monotherapy

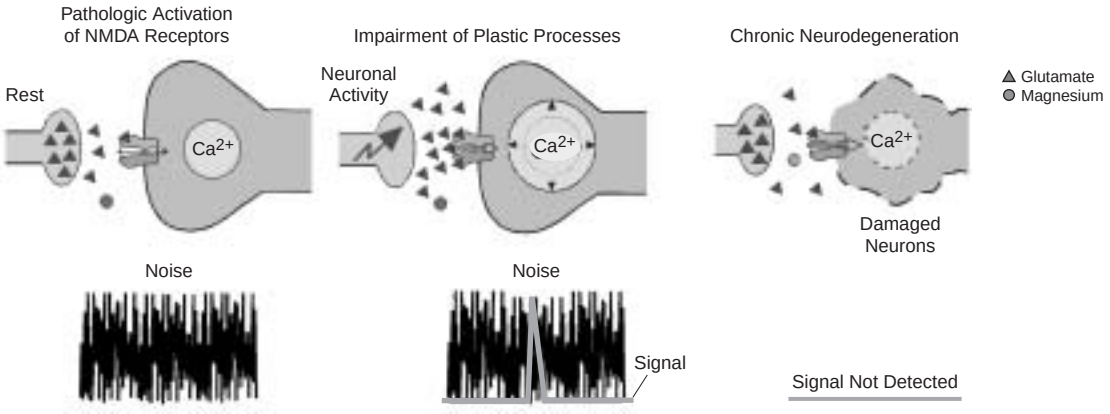
How does blockade of pathologic activation of NMDA receptors translate into patient care and the treatment of Alzheimer's disease? Dr. Corey-Bloom stated that the results of a recent memantine monotherapy study[9] may help to answer these questions. The

Figure 6. Normal NMDA-Receptor Transmission[a]



[a]Adapted with permission from Parsons et al.[8]
Abbreviation: NMDA = *N*-methyl-D-aspartate.

Figure 7. Pathologic Activation of NMDA Receptors[a]



[a]Adapted with permission from Parsons et al.[8]
Abbreviation: NMDA = *N*-methyl-D-aspartate.

study was randomized, double-blind, and placebo-controlled. More than 250 outpatients with moderate-to-severe Alzheimer's disease (baseline MMSE scores of 3–14) participated in the multicenter trial involving 32 sites in the United States.

Other inclusion criteria were (1) DSM-IV and NINCDS diagnosis of probable Alzheimer's disease; (2) computed tomography (CT) or MRI scan consistent with a diagnosis of Alzheimer's disease; (3) Global Deterioration Scale stages 5 or 6, suggesting fairly significant dementia; and (4) a Functional Assessment Staging scale (FAST) score of at least 6a.

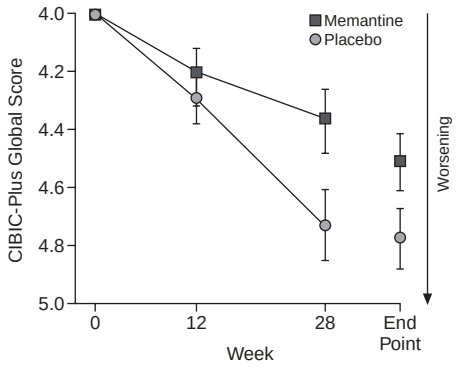
Primary efficacy measures focused on global and functional measures as required by the FDA, the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), and the 19-item Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) inventory modified for severe dementia. Secondary efficacy measures included a cognitive measure, the Severe Impairment Battery (SIB); a behavioral assessment, the Neuropsychiatric Inventory (NPI); and an economic effects measure, Resource Utilization in Dementia (RUD). In addition, the MMSE, the Geriatric Depression Scale (GDS), and the FAST were used.

Baseline characteristics of the groups were well matched: mean age was about 75 years, mean education about 12 years, and mean MMSE scores at baseline were 7 to 8.

Patients were treated with memantine for a total of 28 weeks with an initial 4-week titration up to the final dose of 20 mg/day, taken as 10 mg b.i.d. Over the course of the 28 weeks, progressive deterioration was seen in patients who were given placebo, whereas individuals given memantine deteriorated much more slowly. At endpoint, the differences in primary efficacy variables between patients given memantine and patients given placebo were statistically significant (Figures 8 and 9).

Adverse events reported in ≥ 10% of patients in either treatment group were quite similar, and in some cases,

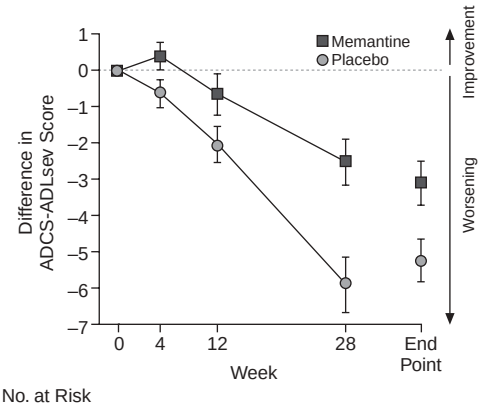
Figure 8. Mean ± SE Change From Baseline on CIBIC-Plus[a]



No. at Risk				
Memantine	126	107	97	118
Placebo	126	105	84	118
p Value	N/A	N/A	.03	.06

[a]Reprinted with permission from Reisberg et al.[9] The mean ± SE scores at each specified time in the observed-cases analysis are shown. The scores at endpoint indicate the mean ± SE with the last observation carried forward in the intent-to-treat population.
Abbreviation: CIBIC-Plus = Clinician's Interview-Based Impression of Change Plus Caregiver Input.

Figure 9. Mean ± SE Change From Baseline on ADCS-ADL[a]



No. at Risk					
Memantine	126	119	107	97	124
Placebo	126	117	106	84	123
p Value	N/A	N/A	N/A	.003	.02

[a]Reprinted with permission from Reisberg et al.[9] The mean ± SE scores at each specified time in the observed-cases analysis are shown. The scores at endpoint indicate the mean ± SE with the last observation carried forward in the intent-to-treat population.
Abbreviation: ADCS-ADLsev = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory, modified for severe dementia.

adverse events were worse in the placebo group. Thirty percent of the placebo group, for example, exhibited agitation compared with only 18% of the memantine group. Other adverse events included urinary incontinence or urinary tract infection, insomnia, and diarrhea. For unknown reasons, a higher prevalence of urinary tract infections occurred in the placebo group than in the memantine group. There were no differences with regard to insomnia or diarrhea between the two groups, which is an important consideration when combining these medications with cholinesterase inhibitors.

Conclusion

Dr. Corey-Bloom summarized her presentation by stating that cholinergic activity is probably not lost to any significant degree until later in the course of Alzheimer's disease, so it makes sense to explore other options. Glutamatergic neurons are actually the primary excitatory neurons of the CNS involved in virtually all functions, but importantly in plasticity, learning, and memory. Lastly, one NMDA receptor antagonist, memantine, blocks the effects of abnormal glutamatergic stimulation that has been postulated to lead to neuronal cell death in many neurodegenerative diseases. Memantine preserves the physiologic activation of NMDA receptors required for learning and memory. A clinical trial of treatment with memantine showed significantly less decline versus placebo on global, functional, and cognitive measures.

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Two Mutually Exclusive Mechanisms and a New Hope for the Future: Combination Therapy for Alzheimer's Disease

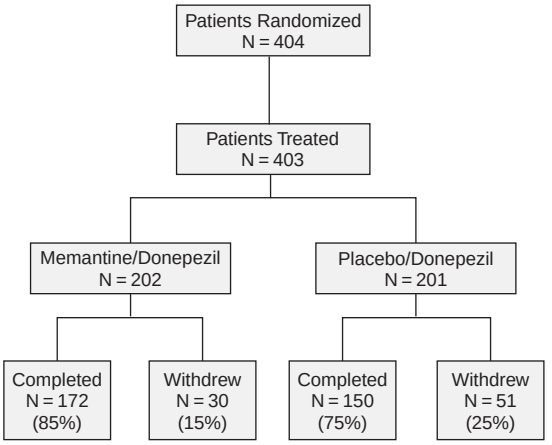
Pierre N. Tariot, M.D., said that even for patients in later stages of Alzheimer's disease, treatments are needed that will improve or maintain cognition, daily functioning, and quality of life. A combination of existing approved therapy (cholinesterase inhibition) with NMDA receptor antagonism may provide additive or even synergistic symptomatic benefit to patients. The question of whether memantine would be safe and efficacious in combination with a commonly used cholinesterase inhibitor

Table 1. Memantine Pharmacokinetics[a]

Variables	Value
Bioavailability	100%
Time to maximum (peak) 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 plasma concentration	Within 21 d
Cerebrospinal fluid/serum ratio	0.52
Linear and dose-proportional kinetics at doses of 10 to 40 mg/d	
Majority excreted unchanged in urine	
Hepatic metabolism	Minimal
Inhibition of cytochrome 450 isoenzymes (CYP450)	Minimal
Food interaction	Not significant

[a]Data from Jain[2] and data on file, Forest Laboratories, Inc.

Figure 10. Disposition of Patients Randomly Assigned to Memantine/Donepezil or Placebo/Donepezil in Memantine Combination Study[a]



[a]Data from Tariot et al.[1]

has led to the first randomized, controlled study of the combination of memantine and donepezil in patients with moderate-to-severe Alzheimer's disease. The full report is in press.[1]

Pharmacokinetics

Dr. Tariot stated that pharmacokinetic issues related to combining one medication with another were addressed before the study began. The pharmacokinetics of memantine are shown in Table 1. Pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes were not expected. Memantine does not affect reversible inhibition of AChE by donepezil, galantamine, or tacrine. Since plasma protein binding for memantine is low (45%), interactions with drugs that are highly bound to plasma proteins, such as warfarin or digoxin, are unlikely. There is no evidence thus far regarding use in patients with renal failure.

Prior to the initiation of the 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 not altered with administration of donepezil and there was no pharmacokinetic interaction when these 2 drugs were administered together. Also, no significant adverse events were noted.

Study Design

Dr. Tariot explained that the double-blind, placebo-controlled study[1] included 404 outpatients with moderate-to-severe Alzheimer's disease (MMSE scores ranging from 5 to 14). Donepezil was chosen because it is the most widely used cholinesterase inhibitor. By using a single comparator agent, fewer confounding variables would be introduced. The inclusion/exclusion criteria were fairly standard; patients needed to be medically stable and free of other significant neurologic and psychiatric illnesses. Dr. Tariot emphasized, however, that patients needed to be taking donepezil for at least 6 months and be at a stable dose for at least 3 months to be included. Thirty-seven U.S. sites participated in this 24-week study. Memantine or placebo was administered and patients were titrated to 20 mg/day (10 mg b.i.d.) of memantine over a 4-week period.

The primary efficacy outcome assessments in this trial were the Severe Impairment Battery (SIB) (for cognition) and the 19-item ADCS-ADL inventory modified for severe dementia (for function). The chief secondary efficacy outcomes were the CIBIC-Plus for global assessment, the Neuropsychiatric Inventory (NPI) for behavioral assessment, and the care dependence subscale of the Behavior Rating Scale for Geriatric Patients (BGP) for functional assessment. Primary outcome measures were assessed at each visit, whereas secondary outcomes were measured on a less frequent basis.

Of the 404 patients, 403 were treated; 85% of patients completed the memantine arm, while 75% completed the placebo arm (Figure 10). A significantly greater number of patients taking memantine/donepezil completed the study compared with those taking placebo/donepezil ($p = .011$). Nearly twice as many patients withdrew in the placebo arm compared with the memantine arm, with the 2 chief reasons being adverse events and withdrawal of consent. Dr. Tariot stated that patients with an average MMSE score of around 10 are likely to have complex issues at this stage of illness, and over the course of a 6-month trial, it is likely that some families "gave up" for one reason or another and withdrew consent.

Table 2. Baseline Assessments for Alzheimer's Disease Severity[a]

	Placebo/Donepezil			Memantine/Donepezil		
Outcome Measure	N	Mean	SD	N	Mean	SD
MMSE	201	10.2	2.98	202	9.9	3.13
SIB	197	79.8	14.18	198	77.8	15.46
ADCS-ADL	197	36.2	9.23	198	35.9	9.75
NPI	197	13.8	12.83	198	13.7	14.11
BGP-care	197	9.2	5.99	198	8.9	5.83

[a]Data from Tariot et al.[1]
Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; BGP-care = Behavior Rating Scale for Geriatric Patients, care dependence subscale; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; SIB = Severe Impairment Battery.

Table 3. Comparison of Baseline Characteristics in Treatment Studies of Moderate-to-Severe Alzheimer's Disease

Outcome	Memantine[a]			Donepezil[b]			Memantine/Donepezil[c]		
Measure	N	Mean	SD	N	Mean	SD	N	Mean	SD
MMSE	252	7.9	3.6	290	11.8	…	403	10.1	3.06
SIB	252	67.1	21.6	290	79.3	…	395	78.7	14.85
ADCS-ADL	252	27.0	10.1	…	…	…	395	36.1	9.53
NPI	252	20.5	15.7	290	19.4	…	395	13.7	13.47

[a]Data from Reisberg et al.[4]
[b]Data from Feldman et al.[5]
[c]Data from Tariot et al.[1]
Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, SIB = Severe Impairment Battery.

Table 4. Adverse Events Experienced by ≥ 5% of Patients in Either Treatment Group[a]

Adverse Event	Placebo/Donepezil % (N = 201)	Memantine/Donepezil % (N = 202)
Agitation	12	9
Confusion	2	8
Fall	7	7
Influenza-like symptoms	7	7
Dizziness	8	7
Headache	3	6
Inflicted injury	8	5
Upper respiratory tract infection	7	7
Urinary tract infection	5	6
Urinary incontinence	3	5
Peripheral edema	4	5
Diarrhea	9	5
Fecal incontinence	5	2

[a]Data from Tariot.[1]

Demographics

Dr. Tariot reviewed patient demographics and stated that patients in the 2 groups were well matched at baseline and fairly typical of studies of this nature: mean age was about 75 years, roughly two thirds were women, and roughly 90% were Caucasian. Surprisingly, the average duration of prior donepezil therapy was more than 2 years, which may indicate that there is something special about this cohort. The average dose of donepezil was close to 10 mg/day, consistent with evidence indicating that, in general, using the highest tolerated dose of the cholinesterase inhibitor represents best practice.

Dr. Tariot pointed out how well matched the 2 groups were at baseline on the key outcome measures as well (Table 2). He also presented comparisons of mean values with 2 other major studies of memantine[4] and donepezil[5] to facilitate comparisons of the study populations (Table 3).

Outcomes

Changes from baseline to endpoint on both primary outcome measures were statistically significant in favor of the efficacy of memantine in combination with donepezil.[1] The SIB showed a gradual decline over 6 months in cognitive performance in the placebo/donepezil arm, while a modest improvement and maintenance improvement were observed throughout the 6 months in the memantine/donepezil arm ($p < .001$). The cognitive outcome was mirrored by the functional outcome. Throughout the trial, functional performance in the memantine/donepezil arm was at least quantitatively superior to that in the placebo/donepezil arm and was statistically significant at endpoint ($p = .028$).

The domains affected by the illness include not only cognition, function, and behavior but also neurologic status. NPI data showed a 4-point deterioration over the 6 months in the placebo/donepezil group, with no deterioration seen in the memantine/donepezil group. The BGP-care dependence subscale also showed effects in favor of the memantine/donepezil arm. All of the outcomes showed a treatment effect in favor of memantine/donepezil over placebo/donepezil.

Adverse Events

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. Adverse events seen in ≥ 5% of patients are shown in Table 4. A few more patients in the memantine/donepezil group experienced confusion than patients in the placebo/donepezil group, although this symptom was rated as mild and did not result in disproportionate dropouts. Confusion was more severe and resulted in a greater percentage of dropouts in the placebo/donepezil group than the memantine/donepezil group. Dr. Tariot also

pointed out that it is somewhat interesting that the incidence of both diarrhea and fecal incontinence was lower in the memantine/donepezil group, which might in theory reflect action of memantine at the 5-HT_3 receptor.

Combination therapy with memantine and donepezil was safe and well tolerated.

Conclusion

Dr. Tariot noted that this was the first double-blind, placebo-controlled study to examine the safety and efficacy of combining a well-tolerated NMDA-receptor antagonist, memantine, with a 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. Patients treated with memantine and donepezil for 6 months appeared to show a sustained improvement in cognitive function. The combination was well tolerated, with overall dropout and dropout for adverse events rates favoring the memantine-treated group.

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Drug names: bethanechol (Urecholine), celecoxib (Celebrex), digoxin (Lanoxin and others), donepezil (Aricept), galantamine (Reminyl), memantine (Namenda), rivastigmine (Exelon), tacrine (Cognex), warfarin (Coumadin and others).

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 that is outside U.S. Food and Drug Administration–approved labeling. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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