On November 13, 2003, a symposium was presented on “Optimizing Care Management Plans Across the Spectrum of Alzheimer’s Disease” at the 34th Annual Meeting of the American Society of Consultant Pharmacists. The speakers discussed potential treatment strategies for Alzheimer’s disease, optimal clinical outcomes for disease management, and care management plans that will maximize treatment outcomes in Alzheimer’s disease.

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants should be able to:

- Discuss the impact of declining cognition, function, and behavior of patients with Alzheimer’s disease on managed care pharmacoeconomics.
- Utilize disease stage-appropriate evaluation methods to assess disease progression in patients with Alzheimer’s disease.
- Critically analyze the clinical effectiveness of current and new drug therapies for patients across the spectrum of Alzheimer’s disease severity.
- Identify the pharmacology of potential and emerging therapeutic options in Alzheimer’s disease management.

Manju T. Beier, PharmD, FASCP (Chairperson)
Elaine R. Peskind, MD
Mark Sey, RPh, CGP, FASCP
Sponsorship and Accreditation Information

Optimizing Care Management Plans Across the Spectrum of Alzheimer’s Disease

Target Audience
This activity is intended for long-term care consultant pharmacists, physicians and nurses who treat elderly patients with Alzheimer’s disease.

Educational Objectives
Upon completion of this activity, participants should be able to:

• Discuss the impact of declining cognition, function, and behavior of patients with Alzheimer’s disease on managed care pharmacoeconomics.
• Utilize disease stage–appropriate evaluation methods to assess disease progression in patients with Alzheimer’s disease.
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• Identify the pharmacology of potential and emerging therapeutic options in Alzheimer’s disease management.

Program Completion Time
Based upon trials, the estimated time to complete this activity is 1 hour.

Educational Grant
This activity is made possible by an unrestricted educational grant from Forest Laboratories, Inc.

Sponsorship
This activity is sponsored by Medical Education Resources, Inc., a nonprofit medical education company.

Pharmacy Accreditation
This program, Program #203-999-04-065-H01, is accredited for 1 hour of continuing education. The American Society of Consultant Pharmacists (ASCP) is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

Physician Accreditation
Medical Education (ACCME) to sponsor continuing medical education for physicians.
MER designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician’s Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Nursing Accreditation
This CE activity is approved for 1.25 contact hours. MER is an approved provider of continuing education by the Colorado Nurses Association, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation.

Provider approved by the California Board of Registered Nursing, Provider CEP #12299 for 1.25 contact hours.

Each participant should claim only those credits that he/she actually spent in the activity.

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Dr. Manju T. Beier indicated that she has received grants or research support from Janssen Pharmaceutica. She has received honoraria from Pfizer and has been a consultant for Janssen and Forest Laboratories, Inc.

Dr. Elaine R. Peskind indicated that she is a consultant for Forest Laboratories, Janssen Pharmaceutica, Novartis Pharmaceuticals, Pfizer, and Bristol-Myers Squibb. She has received grants or research support from Forest, has been on the speaker’s bureau for Johnson & Johnson Long-Term Care Group, and has received honoraria from Pfizer, and has been on the speaker’s bureau for Janssen Pharmaceutica.

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To receive credit, participants must complete the CME Examination and Evaluation that appear at the end of this program and fax or mail as follows:

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A minimum score of 70% on the CME Examination is required for credit. A statement of credit will be mailed within 4 weeks of receipt of the completed answer sheet.

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March 2004
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March 2005
An Era of Potential Treatment Strategies for Alzheimer’s Disease

Manju Beier, PharmD, FASCP, Clinical Associate Professor, University of Michigan School of Pharmacy, Ann Arbor, MI, and Senior Partner, Geriatric Consultant Resources, LLC, Ann Arbor, reviewed the various strategies currently available for the treatment of Alzheimer’s disease (AD), including the pharmacology and pharmacokinetics of memantine. Dr. Beier explained that there are a number of neuropathologies associated with AD, including neurofibrillary tangles, beta-amyloid plaques, neuroinflammation, and oxidative damage, which exist as potential therapeutic targets for treatment strategy development.

According to data from Hebert and associates,1 there are currently an estimated 4.5 million Americans over the age of 65 affected by Alzheimer’s disease in the United States, and after age 65 the prevalence of AD doubles every 5 years. By the year 2050, the prevalence of AD is expected to more than triple. The growing economic and social burden this disease will present is going to be profound, with the greatest portion of the costs being long-term care and hospitalization, while the largest portion of the social burden will be endured by caregivers.2

Alzheimer’s disease progresses from mild to moderate to severe dementia. It is the primary disease for nursing home placement in the United States, and the associated behavioral problems are the number one trigger. Data from Feldman and Gracon3 show patients live an average of 8 years after diagnosis of AD, although it should be noted that AD is present for a long time prior to diagnosis. Of the nearly 4.4 million people affected by AD, only 60% (2.7 million) are diagnosed, less than 40% (1.7 million) are treated, and about 25% (1.2 million) of people that have the disease are treated with cholinesterase inhibitors.4 These treatment data for AD reveal a vast void in terms of pharmacotherapy, early diagnosis, management, and treatment that needs to be filled.

There is a variety of well-known disease scales that can be used to assess the progression of patients with Alzheimer’s disease based on cognitive, functional, global, neurobehavioral, staging, and pharmacoeconomic scores. One tool that is relatively unknown, even to some clinicians and researchers, is the Severe Impairment Battery (SIB) developed by Saxton and associates.5 It is a simple scale used in studies of moderate-to-severe dementia and takes about 20 minutes to administer. The SIB assesses cognitive functioning in the severely impaired using simple one-step commands with gestural clues. For example, one would hold up a cup or a spoon and ask the patient to state what the object is. The SIB has a scale of 0 to 100, with 0 as the greatest decline, and gives credit for nonverbal or partially correct responses. There are nine domains with six scorable subscales, including attention, orientation, language, memory, visuoperception, and construction. It also briefly assesses social skills, praxis, and response to name.

Pathological pathways for Alzheimer’s disease are based on known risk factors such as age, which is a well-known and independent risk factor.6 There are also certain chromosomal abnormalities with 14, 19, 21, and others, which are currently under vigorous study. Apolipoprotein E4 plays a role, and head injury is also considered a risk factor, as well as Down syndrome (trisomy 21).

There are three consistent neuropathologic hallmarks of AD noted by the German physician Louis Alzheimer more than 100 years ago. Dr. Alzheimer defined amyloid-rich senile plaques and neurofibrillary tangles that resulted in neuronal degeneration after examining the brains of his patients in whom he suspected senile dementia. These neuronal changes eventually lead to clinical symptoms but begin years before the onset of symptoms. Therefore, a definitive diagnosis of Alzheimer’s disease by examination of plaques and tangles can only occur upon patient death via autopsy.

Beta-amyloid plaques and their neurodegenerative toxicity are an extracellular abnormality that form as a result of amyloid precursor proteins (APP) depositing $\text{AB}_{1-42}$ fragments that aggregate.7 Neurofibrillary tangles, which consist of paired helical filaments (PHF), are an intracellular abnormality found in regions of the brain involved in learning, memory, and language.8,9,10

Much research is being conducted on plaques and tangles to determine whether they are the start of the process or the end product of a process. The beta-amyloid hypothesis believes that plaques lead to neuronal cell death and synaptic loss with neurotransmitter effects such as cholinergic deficits coming into play. It is the cholinergic deficits on which pharmacotherapy with acetylcholinesterase inhibitors (AChEIs) is based as these agents inhibit the enzyme acetylcholinesterase that breaks down acetylcholine. Intracellular neurofibrillary tangles are being researched in terms of tau protein.

Potential strategies to minimize beta-amyloid deposits include reducing the production of $\text{AB}_{1-42}$ by inhibiting the enzymes beta- and gamma-secretases that process APP, or preventing $\text{AB}_{1-42}$ assembly by altering secondary structure via N-terminus modification.11-12 A third approach is...
enhancing clearance of AB_{1-42} by vaccination with synthetic AB_{1-42} peptide to stimulate inflammation-mediated removal of endogenous AB_{1-42}, for which trials were underway but halted as six patients incurred central nervous system inflammation. There are also new strategies being examined from a vaccination standpoint to enhance beta-amyloid clearance.\textsuperscript{11-12}

There is experimental evidence of neuroinflammation in patients with probable AD, and a large amount of epidemiologic evidence suggests that chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of Alzheimer’s disease. A study conducted in Rotterdam, Netherlands retrospectively looked at patients’ consumption of NSAIDs for 6-8 years and found that after 2 years of constant consumption there was an 80% decrease in the risk of dementia.\textsuperscript{13} Although good animal, in vitro, and epidemiologic data exist, effective randomized, prospective, double-blind, placebo-controlled, clinical trials are needed before NSAIDs can be advocated for the treatment or prevention of AD.\textsuperscript{13-16}

Aisen and colleagues\textsuperscript{17} conducted a multicenter, randomized, placebo-controlled trial with rofecoxib and naproxen in 351 patients with mild-to-moderate AD. They were given either rofecoxib 25 mg per day, naproxen 25 mg per day, or placebo for 1 year. Primary outcomes showed that neither drug arm slowed the rate of cognitive decline in patients with Alzheimer’s disease, and neither drug was superior to placebo. Secondary outcomes showed no evidence of a treatment effect on any outcomes. Therefore, treatment with either of these agents in patients who already have Alzheimer’s disease cannot be advocated.

The Alzheimer’s Disease Anti-inflammation Prevention Trial (ADAPT)\textsuperscript{18,19} is designed to look at prevention in patients with a high risk of developing Alzheimer’s disease. This randomized, double-blind, placebo-controlled, parallel assignment efficacy study will compare naproxen, celecoxib, and placebo during a 7-year period with an expected enrollment of 2625 patients over 70 years of age.

Because postmortem studies of the brains of patients with AD reveal markers of oxidative damage, such as increased lipid peroxidation and increased protein and DNA oxidation, researchers wanted to determine if antioxidants like vitamin E might be protective. Six years ago, Sano and associates\textsuperscript{20} conducted a randomized, double-blind, placebo-controlled trial with vitamin E in 341 patients with moderate AD (mean Mini-Mental State Examination score, 11.3-13.5). Patients received vitamin E 2000 IU per day, selegiline 10 mg per day, or both for 2 years. Results showed that treatment with selegiline or vitamin E slowed the progression of AD with respect to primary endpoints—death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (defined as a Clinical Dementia Rating of 3). Although there were some limitations, vitamin E was numerically superior to selegiline 5 mg twice a day. Although the long-term ramifications of taking vitamin E for 5 or 10 years are not known, the American Academy of Neurology (AAN) guidelines advocate vitamin E as a pharmacotherapeutic option.

The Chinese herb Ginkgo biloba has had mixed results from U.S. clinical trials as a treatment for AD.\textsuperscript{21} Meta-analyses indicate modest improvements in cognitive ability for mild-to-moderate Alzheimer’s disease. However, since these substances are not standardized, there is no way to determine what dose strength a patient is receiving. Ginkgo biloba is also associated with a risk of hemorrhaging and prolonged bleeding time, especially for people taking aspirin or NSAIDs, or who have a previous history of associated problems of this type.\textsuperscript{21}

An ongoing prevention study is being conducted with Ginkgo biloba in high-risk men and women age 75 and older without dementia.\textsuperscript{22} It is a randomized, placebo-controlled, U.S. multicenter trial to determine the efficacy of Ginkgo biloba in decreasing the incidence of AD, and slowing cognitive decline and functional disability. Patients receive ginkgo 240 mg per day or placebo and will be followed up for 6 years. Outcome measures include development of AD or vascular dementia, and total mortality.

Estrogen has neurotrophic, antioxidative, and anti-inflammatory effects, but its role in AD is unknown. Small-scale trials and epidemiologic studies suggest potential benefit from estrogen therapy for Alzheimer’s disease in postmenopausal women. Evidence from recent controlled studies does not support the use of estrogen replacement therapy for the treatment of AD.\textsuperscript{23,24} At the present time, estrogen therapy is not recommended or approved for the prevention or treatment of AD.

The Women’s Health Initiative Memory Study (WHIMS),\textsuperscript{25} a placebo-controlled, randomized trial with hormone replacement therapy (HRT; a combination of conjugated equine estrogen and medroxyprogesterone) in postmenopausal women over the age of 65 contradicted the positive previous epidemiologic data regarding estrogen. The WHIMS trial found that the HRT group versus the placebo group had twice the risk of dementia, and HRT did not prevent mild cognitive impairment. Researchers concluded that the risks associated with HRT (breast cancer, stroke, etc) outweighed the benefits.\textsuperscript{25}
Another ongoing study, the PREventing Postmenopausal memory loss and Alzheimer’s with Replacement Estrogens (PREPARE) study, is being conducted in postmenopausal women over the age of 65 with a family history of Alzheimer’s disease. It is a 3-year double-blind, placebo-controlled clinical trial for which patients are still being recruited. Cholesterol may regulate the production of beta-amyloid because statins have been observed to decrease beta-amyloid in neuronal cultures. The mechanism by which statins may be protective is unclear. Strong epidemiologic data from the last 5 years in the U.K. and U.S. databases show that statin treatment is associated with a lower risk of dementia. However, recently, two randomized controlled trials were published, one a simvastatin study and one a study on pravastatin called the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). These two studies did not look at dementia risk as the primary outcome, but nonetheless were large studies with large numbers of participants using statins for a significant period of time, 1-3 years. No decrease in the risk of dementia was seen in these randomized trials.

The ongoing Cholesterol Lowering Agent to Slow Progression (CLASP) of Alzheimer’s disease study uses simvastatin in a multicenter, randomized, double-blind, placebo-controlled trial to slow the progression of AD in about 400 patients with mild-to-moderate dementia. Assessment will be based on the Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) scale, mental status, functional ability, behavioral disturbances, quality of life, and economic indicators.

The most prominent neurotransmitter abnormalities in AD are cholinergic, involving reduced activity of choline acetyltransferase (synthesis of acetylcholine), a reduction in the number of cholinergic neurons in late-stage AD, particularly in the basal forebrain, and a selective loss of nictinic receptor subtypes in the hippocampus and cortex. The three primary drugs used in patients with mild-to-moderate AD to treat cholinergic abnormalities are donepezil, rivastigmine, and galantamine.

Greenamyre and associates reported on a glutamatergic hypothesis, which suggests that abnormal glutamate stimulation can cause neuronal toxicity or cell death and may lead to cognitive deficits that impair learning. Glutamate is a very important transmitter in the brain with 70% of the synapses using glutamate. It is an excitatory neurotransmitter and maintaining normal levels of glutamate is very important. The rationale for the N-methyl-D-aspartate (NMDA) receptor antagonists is that normalization of glutamatergic neurotransmission may maintain or improve cognition and prevent neurotoxicity. Danysz and colleagues found that abnormal glutamatergic activity leads to sustained low-level activation of NMDA receptors, which leads to cognitive deficit and neuronal damage/loss following chronic insult.

Abnormal glutamatergic activity and persistent activation of NMDA receptors may contribute to the impaired cognition and memory in AD, and need to be reduced. NMDA receptors modulate glutamatergic activity in brain cells, and memantine, through its activity on NMDA receptors, modulates the activity of glutamate in brain cells. Memantine improves performance in learning-impaired animals. It does not alter acetylcholinesterase activity in the presence or absence of AChE inhibitors.

Memantine’s mechanism of action is a voltage-dependent, low-moderate affinity, uncompetitive NMDA receptor antagonist with fast-blocking/unblocking kinetics. The low-moderate affinity is important because other NMDA receptor antagonists, such as ketamine and amantadine, are high-affinity compounds with neuropsychiatric side effects. The fast on/off kinetics are also important because this means that memantine sits on the receptor just long enough to prevent pathologic activation of the glutamate receptors and then quickly goes away when physiologic activation of the glutamate receptors is needed. Memantine blocks the effects of abnormal glutamate activity that may lead to neuronal cell death and cognitive dysfunction. The fast on/off kinetics and low-moderate affinity are the key to memantine because it blocks the effects of excessive glutamate while preserving physiologic activation of NMDA receptors required for learning and memory.

The pharmacokinetics of memantine show the compound to be 100% bioavailable with peak plasma concentrations observed 3-7 hours after oral intake. This agent is not affected by age, gender, or food, and demonstrates very low protein-binding of 45%, which means there is little if any impact on drug-displacement interactions. Memantine is rapidly distributed across the blood-brain barrier, which is important because it is a central nervous system drug. It has a long half-life of 60-80 hours and experiences little hepatic metabolism (ie, there are no or minimal effects on P-450 isoenzymes). Memantine is eliminated mostly in urine as a parent drug and its metabolites are inactive. There are no observed interactions with other compounds eliminated renally, such as hydrochlorothiazide and triamterene. No interactions were found with AChE inhibitors and can therefore be used in combination. Dose reduction should be considered in patients with mod-
erate renal impairment; however, the effect of severe renal impairment has not been evaluated, and use of memantine in this situation is not recommended.39

This compound was introduced two decades ago and has since been studied in AD, vascular dementia, AIDS dementia, neuropathic pain, Parkinson’s disease, spasticity, and other conditions. The memantine development program for AD began in the mid-1990s and was approved in the European Union in May 2002. In the U.S., memantine was approved by the Food and Drug Administration (FDA) on October 17, 2003, to be marketed for the treatment of moderate-to-severe dementia of the Alzheimer’s type.40

Treatment guidelines from the AAN recommend cholinesterase inhibitors in patients with mild-to-moderate Alzheimer’s disease, where symptomatic benefit is seen in 20-30% of patients, and 70-80% stabilize.41 Vitamin E can be taken as 1000 IU twice a day. Selegiline is second-line therapy because vitamin E was numerically superior in the Sano et al trial,20 and selegiline does have side effects.41 Nonsteroidal anti-inflammatory drugs, cyclooxygenase (COX)-2 inhibitors, and estrogen do not have sufficient supportive data and are not advocated by the AAN at this time for the treatment of already-established dementia.41 Patients with unspecified dementia may benefit from Gingko biloba, but evidence-based efficacy data are insufficient.41

In summary, cholinergic agents are considered first-line treatment in patients with mild-to-moderate AD because they have been in use the longest. These drugs initially improve and transiently maintain cognitive abilities. Cognitive abilities worsen over time, indicating that treatment does not stop but may delay the progression of Alzheimer’s disease. Recently-approved memantine is now recommended for the treatment of moderate-to-severe dementia of the Alzheimer’s type as monotherapy or in combination with AChE inhibitors.

References

Optimizing Clinical Outcomes in Alzheimer’s Disease Management

Elaine R. Peskind, MD, Professor, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA; Associate Director, University of Washington Alzheimer’s Disease Research Center; and Associate Director, Mental Illness Research, Education, and Clinical Center, VA Puget Sound Health Care System, Seattle, discussed the efficacy and safety results of a placebo-controlled trial of memantine, a novel NMDA receptor antagonist, and the open-label extension trial in patients with moderate-to-severe AD. Given the differing mechanisms of action of memantine and cholinesterase inhibitors (ChEIs), combination therapy with memantine and donepezil may offer additional treatment benefits to patients with AD. Data from a clinical trial examining the use of a ChEI in combination with memantine will be discussed. Memantine’s clinical efficacy and safety data from these studies will be reviewed in detail and critically evaluated.

Preclinical and clinical data support the glutamatergic hypothesis of AD, which links abnormal neuronal NMDA activation with excitotoxic cell death. Antagonism of the NMDA receptor, where glutamate is most active, offers protection from cell death and preserves both cognitive and learning processes. In nursing home patients, memantine-treated patients demonstrated improved global change and reduced caregiver dependency compared to placebo-treated patients.1 Reisberg and colleagues2 conducted a 28-week double-blind, placebo-controlled phase III study in 252 outpatients with moderate-to-severe Alzheimer’s disease (mean Mini-Mental State Examination [MMSE] score, 7.9 ± 3.64; range, 3-14). Memantine treatment was given in a standard 4-week titration increased weekly in 5-mg increments from 5 mg to 20 mg daily, with the final dose being 20 mg a day dispensed as 10 mg twice a day. Principal efficacy measures were the Severe Impairment Battery (SIB), the Clinical Interview-Based Impression of Change with caregiver information (CIBIC-Plus), and the Alzheimer’s Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale, which measures 19 domains of function ranging from basic activities of daily living (eg, toileting, bathing) to more instrumental activities of daily living (eg, conversing on the telephone and traveling outside the home). Global assessment was recorded using the CIBIC-Plus, which is an examination of the patient done by the clinician with input from the caregiver.

Half of the patients were randomized to memantine and half to the placebo arm. The completion rates were 77% for the memantine group and 67% for the placebo group. The 10% greater completion rate in the memantine group may reflect improvement compared to the placebo group, as well as the more benign side-effect profile of memantine.2

Cognitive assessment data from the SIB scale showed that memantine significantly reduces cognitive decline in patients relative to placebo-treated patients.2 Using the ADCS-ADL-19 scale for functional assessment of daily living, memantine was found to significantly reduce functional deterioration in patients compared to placebo.2 Results from the CIBIC-Plus also showed that memantine significantly reduced global deterioration in patients compared to the placebo study arm.2 Caregiver burden was demonstrated to be substantially less by 51.5 hours per month, or more than 1.5 hours less per day in the memantine group compared to the placebo group.3 Adverse event and safety data for the memantine group showed less agitation and fewer urinary tract infections—which may be related to each other—compared to the placebo group.2

Ninety-five patients from the memantine arm and 80 patients from the placebo group continued on to the 24-week open-label, long-term extension study where all patients were retitrated on the same titration schedule.4 Principal efficacy measures included the SIB, ADCS-ADL-19, and CIBIC-Plus. Sixty-nine percent of the group originally treated with memantine and 89% of the group originally treated with placebo completed the study. Results showed that patients originally in the placebo group who were then started on memantine were observed to catch up to the group that was treated with memantine continuously. Memantine data are different from the ChEI data in that patients who are initially on placebo and then treated with ChEIs in open-label extension never quite catch up to the patients who received active treatment for the whole period. Similar data are seen with the ADL-19 scale and CIBIC-Plus—patients who were initially on placebo, then started on memantine, catch up to patients who are treated with memantine continuously.

Tariot and colleagues5 conducted a 24-week multicenter, randomized, double-blind, placebo-controlled trial in 403 subjects with moderate-to-severe Alzheimer’s disease...
(MMSE range, 5-14) on combination therapy with the ChEI donepezil. All subjects received donepezil for at least 6 months, with at least 3 months on a stable dose. All patients taking donepezil were then randomized to receive either adjunctive memantine 20 mg per day or placebo. Principal efficacy measures were the SIB, ADCS-ADL-19, and CIBIC-Plus. Half of the patients were randomized to memantine plus donepezil, and half to placebo plus donepezil. Completion rates were 85% in the combination donepezil-plus-memantine group and 75% in the donepezil-alone group. SIB results showed patients in the combination therapy group improved over their baseline during the 6-month period, compared to initial stabilization followed by modest decline in the donepezil-alone group. Similar data were seen on the activities of daily living scale. Both groups declined modestly, but the decline in the donepezil group was greater than in the combination group. The CIBIC-Plus scale showed more improvement in the memantine-plus-donepezil group compared to the donepezil-alone group. Forty-four percent of the donepezil-alone group was unchanged or improved, compared to 55% of the combination memantine-donepezil group.

The side-effect profile shows less agitation in the combination group compared to donepezil alone. There were some cases of increased confusion in the combination group, but symptoms were transient. There were fewer gastrointestinal (GI) side effects in the combination group, suggesting that adding memantine to donepezil actually improves GI tolerance.

Winblad and colleagues¹ conducted a 12-week phase III randomized, placebo-controlled trial in 167 nursing home patients with moderate-to-severe dementia (MMSE < 10) with both Alzheimer’s and vascular dementia, and likely the combination of Alzheimer’s/vascular dementia. Patients received a 2-week titration to a total of memantine 10 mg per day. Principal efficacy measures were the Behavioral rating for Geriatric Patients care dependence (BGP-Care) subscale, the Clinical Global Impression of Change (CGIC), and the Dementia Test Battery (D-Test). Half of the patients were randomized to memantine and half to placebo, with completion rates of 95% in both the memantine and placebo groups. Caregiver burden measures show that both groups improved, with a modest placebo effect. This probably reflects more careful medical monitoring and routine urinalysis. More changes were observed in the CGIC assessment, with a greater number of patients in the memantine group showing improvement or no change compared to the placebo group. D-Scale scores, which represent behavior and function, showed that memantine performed better compared to placebo on all the measures, with significant differences in ability to stand up, move, wash, take a shower, dress, use the toilet, and with orientation and space, group activities, hobbies and interests.

In summary, the Reisberg et al study² showed that memantine monotherapy was clinically effective for cognitive, functional, and global domains, as well as reducing caregiver burden by about 1.5 hours a day, in outpatients with moderate-to-severe Alzheimer’s disease. The open-label extension of this study demonstrated significant treatment effects for patients who were initially treated with placebo, and then went on to open-label active memantine, with excellent tolerability at 52 weeks. The dual-therapy study showed that combination memantine and donepezil demonstrated superior efficacy to treatment with donepezil alone. Severely impaired nursing home patients showed improvement on both functional and global measures, as well as reduced care dependence.

References
4. Ferris B, Schmitt F, Doody R, et al. Long-term treatment with the NMDA receptor antagonist memantine: Results of a 24-week, open-label extension study in moderate to severe AD. Presented at: 16th Annual Meeting of the American Association for Geriatric Psychiatry; March 1-4, 2003; Honolulu, HI.

Care Management Plans to Maximize Alzheimer’s Disease Treatment Outcomes

Mark Sey, RPh, CGP, FASCP, Founder and Principal, Mark Sey and Associates, Woodbridge, CA, discussed several frequently used state-appropriate assessment scales and care plans to better educate pharmacists in understanding how patient progression is monitored, and how treatment effects are measured and interpreted. Active involvement of the consultant pharmacist in Alzheimer’s disease is emphasized.

The primary dilemma in optimizing Alzheimer’s disease care is the lack of screening for cognitive impairments among seniors, which frequently results in inadequate assessment, diagnosis, and treatment. In fact, the vast majority of patients with Alzheimer’s dis-
ease admitted into long-term care facilities have never received any treatment specific to AD such as acetylcholinesterase inhibitors. This screening and treatment is essential because the functional and behavioral changes common to Alzheimer’s disease result in institutionalization, which comprises the vast majority of the economic burden placed on the health care system. In addition, there is a failure to recognize dementia as a chronic brain disorder that impairs cognition and affects behavior and function. Proper screening of seniors may lessen the average of 2 years between the identification of early AD symptoms and mild memory impairment before those impairments are brought to the attention of a primary care physician. Frequent screening and early identification of potential AD symptoms may result in early initiation of drug therapy when it is most beneficial.

Assessing cognition among community-based seniors is commonly achieved by performing the MMSE, which is necessary in many instances to receive reimbursement for medications including ChEIs prescribed for individuals with mild-to-moderate AD. Another assessment tool, the Functional Activity Questionnaire (FAQ), is a simple questionnaire given to caregivers regarding the functional status of the residents, and is frequently utilized to determine care needs within assisted living environments. Frequently, FAQ results are used as a structure for payment within the assisted living population.

Despite its value, administration of the MMSE is infrequently performed within the nursing facility population. Best practices would suggest the performance of the MMSE upon admission to the facility and periodically thereafter. If patients are on a “memory medication,” such as a ChEI, they should be reassessed every 6 months. All other residents are assessed on an annual basis. The FAQ is generally not performed in the nursing home population because the Minimum Data Set (MDS) can be used to identify functional impairment. Behavioral charting in nursing facility populations is important to support documentation within the MDS, as well as to support ChEI use or the use of psychotherapeutic medications.

An alternative to the MMSE is the Cognitive Performance Scale (CPS) consisting of five domains: level of consciousness, short-term memory/recall, cognitive skills for daily decision making, making self understood, and ADL self-performance in eating. This screening tool utilizes data from multiple domains within the MDS (noted above) into an algorithm approach, which places an individual in one of seven cognitive categories that correlate to MMSE scores. The CPS can be used in place of the MMSE.

The second dilemma in optimizing AD care is our failure to recognize and completely treat all facets of AD—cognitive decline, functional decline, and behavioral manifestations. Patients with AD in nursing facilities are significantly undertreated, as only 6–7% of these patients receive AD-specific therapy. There are several cholinesterase inhibitors on the market—tacrine, donepezil, rivastigmine, galantamine—and all are indicated for the treatment of mild-to-moderate dementia of Alzheimer’s disease. Short-term clinical trials of ChEIs demonstrate benefits in treating the behavioral, cognitive, and functional impairments. Additionally, there is limited yet growing evidence of benefit in the treatment of moderate-to-severe Alzheimer’s disease. Limited head-to-head studies of ChEIs show very similar cognitive benefits in patients with mild-to-moderate AD.6,7 Short-term clinical studies also show that ChEIs improve or maintain behavioral symptoms near baseline, including aberrant motor behavior, agitation/aggression, anxiety, apathy, delusions, depression/dysphoria, disinhibition, elation/euphoria, hallucinations, and irritability. Long-term clinical trials on the efficacy of ChEIs demonstrated that cognition was maintained at or near baseline, caregiver burden was reduced, and there was an improved reduction in health care costs.

The monotherapy trials with memantine using multiple measurement scales demonstrated that memantine is associated with less decline in cognition, function, and global scores when compared to placebo.11 Treatment with memantine resulted in reductions in caregiver burden, institutionalization rate, and total costs compared with the placebo arm.12

For nursing facility residents, data show that approximately 50% of residents have a diagnosis of Alzheimer’s disease, yet only 6–7% of these patients receive ChEIs or Alzheimer’s-specific therapy. This represents a significant opportunity for consultant pharmacists to recognize and potentially help with the initiation of ChEI therapy or other AD treatment, where appropriate. This is also true for the assisted living population, which is recognized as having a significant AD population, yet data reveal that only 7% receive AD-specific therapy.

The impact of delayed treatment is the third dilemma in optimal AD care. It often takes as long as 2 years between symptom initiation or identification and bringing those symptoms to the attention of the primary care physician. These types of delays result in significantly lessened benefits of treatment with available medications. The consultant pharmacist’s role in facilitating early treatment revolves around education of the
patients, caregivers, and families regarding the importance of participating in early recognition programs. A variety of early recognition programs are available for both assisted living and nursing facilities. This brings the pharmacist more in line with the care objectives of the community, the nursing facility, or the assisted living facility, and with the objectives of the clients. Facilitating early treatment requires early symptom recognition strategies that can help establish the pharmacist as an important member of the health care team.

Dilemma number four in AD care is the early discontinuation of ChEI therapy. It is important to prevent premature discontinuation of appropriate therapy because interruptions in treatment may mean that full benefits are not received and may not be fully recoverable upon reinitiation of medications. Some valid reasons for discontinuation of ChEI therapy include a need for general anesthesia, intolerable adverse effects, comorbid disease state worsened, accelerating decline, lack of compliance, continued decline at pretreatment rate after a 3- to 6-month trial, and drug-free period suggesting medication is no longer effective. One other valid reason for discontinuation of ChEI therapy might be the complete functional dependence upon caregivers. However, a minimum 6-month trial should be stressed and is needed to determine the benefit of the medication.

Therapy is frequently discontinued because of the initial expectations of patients and families, which can be difficult to overcome. When expectations are unclear or treatment goals are inappropriate, patients and their families may think the drug provides no benefit or the patient is not responding to it. Admission to a nursing facility is one of the most common reasons for premature discontinuation of a cholinesterase inhibitor, and identifying those individuals who were treated before admission is important so that therapy can be reinitiated while the patient is in the nursing home or before they are sent back home to their previous living arrangements.

The consultant pharmacist’s role in early discontinuation is to establish realistic treatment goals because it is critical to have a clear understanding of efficacy with these medications. This is a difficult concept for many patients and their families to understand, and often difficult for educated caregivers as well. The pharmacist can become involved in dosing strategies, titration schedules, and with scheduling of the medications. There is opportunity to assist in monitoring the efficacy and potential adverse events, and for the pharmacist to monitor patients once medication has reached its maximum tolerable dose, which may be within 1 or 2 months, or on a frequent basis as often as every 6 months. The pharmacist can provide clarity with the use of combination therapies. It is important to note that under multiple performance measures, cognition, function, global, and behavioral outcomes, the combination of both memantine and donepezil performed significantly better than donepezil and placebo alone. Again, during a 6-month period of time, patients treated with memantine and donepezil show a sustained improvement in cognitive function. The combination of memantine and donepezil therapy was well tolerated with fewer side effects than the donepezil-placebo treated group alone.

Ongoing education comprises a fifth dilemma because of the key role of health care provider willingness to step beyond natural boundaries and participate in Alzheimer’s disease groups and other educational opportunities. The importance of the pharmacist in facilitating early treatment, assisting in establishing realistic treatment goals, monitoring for efficacy and potential adverse events, and communicating with the patient, family, and caregiver cannot be stressed enough. With new therapies now available to our patients with AD, knowledge of these new therapies and the role of combination therapies is also important.

References
CME Examination & Evaluation
Optimizing Care Management Plans Across the Spectrum of Alzheimer’s Disease

To receive credit, participants must complete the following CME Examination and Evaluation and fax or mail as follows:

Pharmacists
(fax or mail to the ASCP) ASCP
Continuing Education, 1321 Duke Street, Alexandria, VA 22314; Fax: 703-739-1500

Physicians and Nurses
(fax or mail to MER) Medical Education Resources: 1300 West Canal Court, Littleton, CO 80120; Fax: 303-798-5731

A minimum score of 70% on the Continuing Medical Education Examination is required for credit. A statement of credit will be mailed within 4 weeks of receipt of the completed answer sheet. Program expiration is March 2005.

1. The number one trigger for placing patients with Alzheimer’s disease in a nursing home is:
   A. Cognitive impairment
   B. Functional decline
   C. Behavioral problems
   D. ADL difficulties

2. The Severe Impairment Battery (SIB) assesses cognitive functioning using:
   A. Computer analysis
   B. Simple one-step commands and gestural clues
   C. Caregiver input
   D. None of the above

3. The identifying hallmark characteristic of Alzheimer’s disease is:
   A. Amyloid plaque
   B. Neurofibrillary tangles
   C. Neuronal degeneration
   D. All of the above

4. Memantine can safely be used in combination with cholinesterase inhibitors.
   A. True
   B. False

5. Phase III study results demonstrated that caregiver burden was not reduced when patients with moderate-to-severe AD were treated with memantine.
   A. True
   B. False

6. Consultant pharmacists can play the following important role in AD treatment:
   A. Facilitate early treatment
   B. Establish realistic treatment goals
   C. Monitor efficacy and adverse events throughout therapy
   D. Strategize medication dosing and titration
   E. All of the above

7. Early discontinuation of treatment should be avoided because:
   A. Treatment benefits are not fully recoverable when reinitiated
   B. It inhibits combination therapy effects
   C. Admission to a nursing facility will be required
   D. None of the above

8. AAN guidelines advocate the following compound as a treatment for slowing AD:
   A. Vitamin E
   B. Estrogen
   C. Naproxen
   D. None of the above

9. One therapeutic approach to treating the hallmark plaques and tangles of AD includes:
   A. Reduce amyloid production
   B. Prevent amyloid assembly
   C. Improve amyloid removal
   D. All of the above

10. Epidemiologic data supporting estrogen as a treatment for AD was contradicted in which controlled, clinical study?
    A. PREPARE
    B. CLASP
    C. ADAPT
    D. WHIMS

CME EVALUATION
Using a scale from 1 to 5, with 5 = excellent, 4 = very good, 3 = adequate, 2 = fair, 1 = poor, please circle the number corresponding to your rating of the following:

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5. Fair balance and objectivity of the material.
6. Completion time.

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