

Treating Patients With Moderate to Severe Alzheimer's Disease: Implications of Recent Pharmacologic Studies

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Background and Objective: As the prevalence of Alzheimer's disease (AD) continues to rise, physicians will be challenged to manage increasing numbers of patients with moderate to severe AD. Despite the need for active treatment and management, the growing AD population has been overlooked in the primary care setting. Currently, the approved treatments for AD are the cholinesterase inhibitors donepezil, rivastigmine, and galantamine and the *N*-methyl-D-aspartate receptor antagonist memantine. The objective of this article is to review recent pharmacologic studies and discuss implications for treatment of moderate to severe AD.

Data Sources and Study Selection: A PubMed search was performed for publications from 1995 to 2004 using the search terms *moderate* or *severe*, *efficacy*, and *Alzheimer*. The search was limited to randomized, controlled trials published in English. The search was further restricted to prospective studies of pharmacologic agents that included patients with severe dementia (Mini-Mental State Examination score < 10). A total of 96 citations were retrieved. Of these, 5 met the inclusion criteria.

Data Extraction and Synthesis: Randomized, double-blind, placebo-controlled studies in patients with moderate to severe AD have been conducted for donepezil and memantine. Patients treated with donepezil monotherapy showed improved cognition, stabilized function, and improved behavioral symptoms. Patients treated with memantine monotherapy showed less than expected decline in cognition, function, and behavioral symptoms. Patients who received memantine treatment adjunctive to stable, long-term donepezil treatment derived cognitive, functional, and behavioral benefits from add-on therapy.

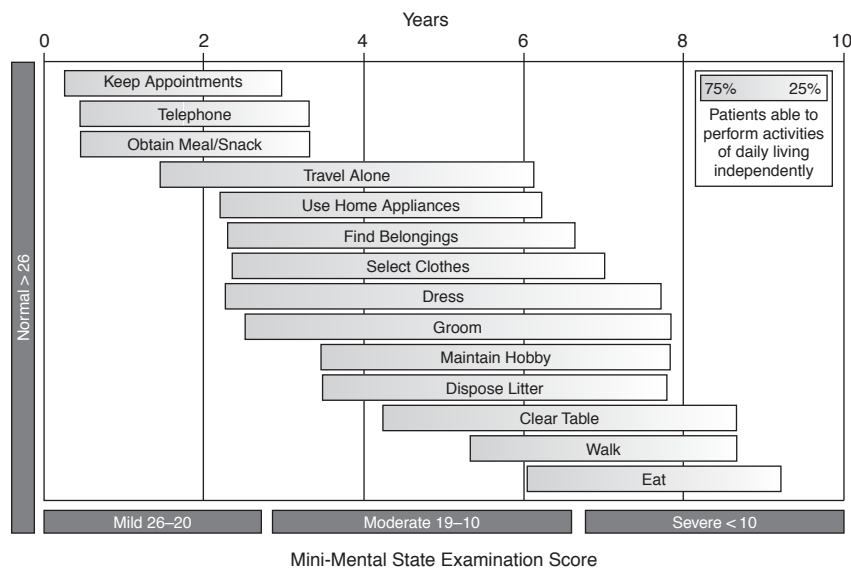
Conclusion: Overall, published studies of donepezil and memantine report treatment benefits.

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Alzheimer's disease (AD) is a neurodegenerative disorder associated with advanced age. Currently, total annual costs of AD exceed \$100 billion,¹ making AD the third most expensive disease in the United States, preceded only by heart disease and cancer.² The prevalence of AD doubles approximately every 5 years after the age of 65,³ approaching 50% in persons over the age of 85.⁴ As the baby boomer generation is reaching retirement age, AD will affect more people than ever before. By the year 2025, an estimated 18% of the U.S. population will be over age 65.⁵ Therefore, the aging of the population will have a profound medical and social impact.

AD is characterized by the gradual onset and progressive worsening of cognitive, functional, and behavioral symptoms (Figure 1).⁶ In the mild stage of the disease (Mini-Mental State Examination [MMSE] score of 20-26), symptoms can be subtle and include short-term memory loss, impaired ability to perform instrumental activities of daily living (IADLs) such as driving or managing finances, and behavioral changes such as depression.⁶ In the moderate stage of AD (MMSE score of 10-19), cognitive decline is more pronounced, affecting language and abstract thought. IADLs are almost completely lost, and behavioral and mood symptoms increase in number and severity.⁶ In the severe stage (MMSE score < 10), patients lose the ability to use complex language and perform basic activities of daily living (ADLs), such as feeding and dressing oneself, with overall decline such that patients become totally dependent.⁶ Agitation, dysphoria, anxiety, apathy, irritability, and aberrant motor function are the most prevalent behavioral symptoms in this stage.⁷

In more advanced AD, symptoms have profound medical and social consequences. Cognitive deficits prevent patients from comprehending written material or television and from engaging in meaningful conversation. Functional deficits prevent these patients from getting

Figure 1. Stages of Alzheimer's Disease Symptoms as Defined by the Mini-Mental State Examination^a

^aAdapted with permission from Galasko.⁶

needed exercise and from participating in social activities. Physical outlets are important for preventing other medical conditions such as pneumonia, pressure sores, and urinary tract infections. Behavioral symptoms in patients with more advanced AD often result from discomfort because these patients are unable to report conditions such as pain, hunger, or cold. Behaviors resulting from discomfort can be complicated by the frustration of functional impairment, mood disorders, and delusions and hallucinations.⁸

As the elderly population grows, more patients with AD will be managed in the primary care setting. Providing optimal care for patients with severe AD represents a major health care challenge. In many cases, primary care physicians will need to provide care for the entire course of the disease. Complications such as decubitus ulcers, aspiration pneumonia, and malnutrition may arise in the severe stage of AD.⁸ Diagnosis and treatment of comorbid illnesses are critical for the success of treatment plans.⁹ Primary care physicians will also need to monitor caregiver burden, which increases significantly with disease progression and often makes nursing home placement necessary.¹⁰ The additional demands of caring for patients with advanced dementia drive up the costs of treatment, which increase approximately 2-fold as the disease progresses from the mild to severe stage.¹¹

The following discussion summarizes the data from recent prospective pharmacologic studies in patients with moderate to severe AD. Of the pharmacologic treatments, cholinesterase inhibitors (ChEIs) are approved for use in patients with mild to moderate AD,¹²⁻²⁰ while memantine is an approved treatment for patients with moderate to

severe AD.²¹ Studies of donepezil also suggest that ChEIs have efficacy in AD beyond the mild to moderate stage.^{19,22}

DATA SOURCES AND STUDY SELECTION

A PubMed search was performed for publications from 1995 to 2004 using the search terms *moderate* or *severe*, *efficacy*, and *Alzheimer*. The search was limited to randomized, controlled trials published in English. A total of 96 references were retrieved. Of these, 5^{19,21-24} met the additional criterion of being prospective pharmacologic studies including patients with severe dementia (MMSE score < 10).

DATA EXTRACTION AND SYNTHESIS

This literature search returned a relatively small number of studies investigating the efficacy of donepezil and memantine for moderate to severe AD. Although rivastigmine and galantamine are approved for the treatment of mild to moderate AD, randomized, double-blind, placebo-controlled studies of their efficacy in more advanced disease have yet to be published.

Primary outcome measures used in some of the studies included the following instruments. Severe Impairment Battery (SIB): SIB estimates cognitive aptitudes and other skills in severely impaired dementia patients. Clinician's Interview-Based Impression of Change-Plus (CIBIC-Plus): CIBIC-Plus is a clinical tool used to evaluate cognition, behavior, and activities of daily living in patients with AD. Disability Assessment for Dementia

Table 1. Summary of Pharmacologic Efficacy in Patients With Moderate to Severe Alzheimer's Disease^a

Variable	Patient Outcome (last observation carried forward data compared with baseline)				
	Donepezil Monotherapy ²²	Memantine Monotherapy ²¹	Memantine Add-On Therapy ²³	Donepezil Monotherapy in the Nursing Home ¹⁹	Memantine Monotherapy in the Nursing Home ²⁴
Symptom domain					
Cognition	Improved ^b (assessed with the SIB)	Declined ^c (assessed with the SIB)	Improved ^c (assessed with the SIB)	Stabilized ^d (assessed with the MMSE)	
Global function	Stabilized ^b (assessed with the CIBIC-Plus)	Declined ^c (assessed with the CIBIC-Plus)	Stabilized ^d (assessed with the CIBIC-Plus)	Stabilized ^d (assessed with the CDR)	Stabilized ^c (assessed with the CGI-Change)
Daily function	Stabilized ^b (assessed with the DAD)	Declined ^d (assessed with the ADCS-ADL)	Declined ^d (assessed with the ADCS-ADL)		
Behavior	Improved ^c (assessed with the NPI)	Declined ^e (assessed with the NPI)	Stabilized ^d (assessed with the NPI)	Stabilized ^e	
Study duration	24 wk	28 wk	24 wk	24 wk	12 wk
Baseline MMSE score	5–17	3–14	5–14	5–26	< 10

^aData from Tariot et al.,^{19,23} Reisberg et al.,²¹ Feldman et al.,²² and Winblad and Poritis.²⁴

^b $p < .0001$ compared with placebo.

^c $p < .001$ compared with placebo.

^d $p < .05$ compared with placebo.

^eNot significant compared with placebo.

Abbreviations: ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, CDR = Clinical Dementia Rating (nursing home version; sum of the boxes), CGI-Change = Clinical Global Impression of Change, CIBIC-Plus = Clinician's Interview-Based Impression of Change-Plus, DAD = Disability Assessment for Dementia, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, SIB = Severe Impairment Battery.

(DAD): DAD is a 10-domain, 40-item instrument that measures basic and instrumental activities of daily living. Physical Self-Maintenance Scale (PSMS): PSMS is a self-assessment questionnaire for dementia patients. Neuropsychiatric Inventory (NPI): NPI is a 10-item assessment of behavioral symptoms such as delusions, hallucinations, and agitation/aggression, with decreasing scores indicating clinical improvement.

PHARMACOLOGIC TREATMENT OPTIONS

ChEIs are approved by the U.S. Food and Drug Administration for the treatment of mild to moderate AD and are recommended as standard therapy.²⁵ The 3 most widely prescribed drug treatments for mild to moderate AD are the second-generation ChEIs donepezil, rivastigmine, and galantamine. Donepezil was approved for the treatment of mild to moderate AD in 1996. Several clinical trials provide evidence for donepezil's efficacy in treating the cognitive, functional, and behavioral symptoms that affect patients in the mild, moderate, and severe stages of AD.^{12,14,16,20,22} Rivastigmine was approved in 2000 and has clinical evidence suggesting treatment benefit in mild to moderate AD.^{13,17,26} Galantamine was approved in 2001 and also has clinical data to show that it benefits patients with mild to moderate AD.^{18,27} Memantine, a noncompetitive *N*-methyl-D-aspartate receptor antagonist, has demonstrated clinical efficacy²¹ and was approved in 2003 for the treatment of moderate to severe AD. Table 1 summarizes the findings from published, prospective studies in patients with moderate to severe AD.

Cholinesterase Inhibitors

Rivastigmine and galantamine. Rivastigmine and galantamine are approved for the treatment of mild to moderate AD. No prospective clinical trials of these agents have reported efficacy in patients with moderate to severe AD. Post hoc analyses of patients with moderate²⁸ and "advanced moderate"^{29,30} dementia have reported clinical efficacy. However, these preliminary findings remain to be confirmed in well-designed placebo-controlled studies enrolling patients with moderate to severe AD.

Donepezil. Donepezil is approved for the treatment of mild to moderate AD and is, to date, the only ChEI that has been studied prospectively in patients with moderate to severe AD. In a 6-month, double-blind, placebo-controlled study of donepezil treatment,²² cognition improved significantly on the MMSE and the SIB. Global function, as measured by the CIBIC-Plus, stabilized in the donepezil group, while in the placebo group, global function declined throughout the study.²² IADLs and ADLs were also used to assess daily function. DAD scores were stable for the donepezil group compared with the placebo group, in which DAD scores declined. Similarly, the modified Instrumental Activities of Daily Living Scale showed a significant improvement in the donepezil group compared with placebo, as did the PSMS. Behavioral symptoms, as measured by the NPI, improved significantly with donepezil treatment.²² Item analysis of these NPI data showed improvement in favor of donepezil for all items, with significant treatment differences for depression/dysphoria, anxiety, and apathy.

The efficacy of donepezil in AD patients residing in nursing homes was studied in a prospective, randomized, double-blind, 24-week clinical trial¹⁹ conducted at 27 sites across the United States. In this study, the majority of donepezil-treated patients (88%) and placebo-treated patients (82%) had moderate to severe AD (MMSE score of 5–20), with the remainder having mild AD (MMSE score of 21–26). Patients were generally older, had more comorbid illnesses and higher concomitant medication usage, and exhibited more severe symptoms than patients enrolled in prior clinical studies of donepezil.^{12,14,20} Nevertheless, global function and cognition were stabilized in these patients after 24 weeks of treatment with donepezil.¹⁹

ChEIs are approved for the treatment of mild to moderate AD. The clinical trial data for donepezil, however, also demonstrate efficacy in patients with moderate to severe AD. Patients in these later stages of AD had improved cognition, stabilized function, and improved behavioral symptoms after treatment with donepezil. The body of clinical evidence for donepezil shows that it provides significant benefits for patients in all stages of AD (mild, moderate, and severe).

Memantine

Memantine is approved for the treatment of moderate to severe AD. A 28-week study²¹ showed that cognition, as measured by the SIB, declined less in memantine-treated patients than in the placebo group. MMSE scores did not show a difference in cognition between memantine and placebo treatment. Measures of function in memantine-treated patients also showed less than expected decline. Global function, as measured by the CIBIC-Plus and Global Deterioration Scale, declined less for the memantine group than the placebo group. Assessment of ADLs by the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL; modified for severe dementia) and Functional Assessment Staging scale showed less decline for the memantine group than the placebo group.²¹ Behavior was measured by the NPI and was not improved over placebo in patients treated with memantine.²¹

A 3-month clinical trial of memantine in nursing home patients with severe dementia²⁴ showed treatment benefit compared with placebo on the global function measure, the Clinical Global Impression of Change scale, and the care dependence subscale of the Behavioral Rating Scale for Geriatric Patients. However, this trial was too short to provide evidence for long-term benefit from memantine treatment in patients with severe dementia.²⁴

Memantine monotherapy provides cognitive and functional benefits for patients with moderate to severe AD, since patients tended to have less than expected decline. Studies of memantine monotherapy have not shown treatment benefit for the behavioral symptoms of AD.

Table 2. Treatment Objectives in Advanced Stages of Alzheimer's Disease^a

Objective
Improve or stabilize cognition
Maintain functional ability
Decrease behavioral disturbances
Decrease caregiver burden
Reduce utilization of health care resources
Prevent medical complications (eg, bed sores, infection)

^aBased on Volicer⁸ and Hill et al.⁹

Memantine Add-On Treatment

In patients with moderate to severe AD who were receiving stable, long-term donepezil therapy (mean of 2.45 years), adjunctive memantine treatment improved cognition, ADLs, global function, behavior, and care dependence.²³ Over the 6-month course of this trial, cognition, as measured by the SIB, was improved from baseline for patients receiving adjunctive treatment, while patients receiving donepezil monotherapy declined slightly. Daily functioning was assessed by the ADCS-ADL and declined less in the group receiving adjunctive treatment than in the group receiving donepezil monotherapy. Global function, as measured by mean CIBIC-Plus scores, was stabilized in both groups, with 55% of the adjunctive treatment group and 45% of the donepezil monotherapy group rated as improved or unchanged. Behavioral symptoms, as assessed by the NPI, were stabilized for the adjunctive treatment group compared with the donepezil monotherapy group, which declined slightly. The Behavioral Rating Scale for Geriatric Patients care dependency subscale showed that patients receiving adjunctive treatment had a more slowly increasing need for care than patients receiving donepezil monotherapy.²³

Patients who received memantine adjunctive to stable, long-term donepezil treatment had improved cognition, function, and behavioral symptoms compared with patients receiving donepezil monotherapy. This 6-month study²³ suggests that adjunctive memantine treatment may offer benefit to patients with advanced AD who have been stabilized on long-term ChEI therapy.

PHARMACOLOGIC MANAGEMENT OF MODERATE TO SEVERE ALZHEIMER'S DISEASE

Treatment Expectations

Table 2 summarizes the clinically and socially meaningful outcomes for patients with more advanced dementia and their families.

Clinical outcomes. ChEIs provide treatment benefits for the cognitive, functional, and behavioral symptoms of mild to moderate AD. However, decline in these symptom domains is an inevitable consequence of the progressive neurodegeneration in AD. Treatment with ChEIs

may lead to clinical stabilization of AD, and this stabilization or slowed decline should be considered treatment success.³¹ Meaningful clinical treatment objectives in the more advanced stages of AD include maintaining daily function, decreasing behavioral symptoms, and reducing or delaying emergence of medical complications.⁸ Long-term symptomatic benefits in cognition, function, and behavioral symptoms may help patients with advanced AD maintain some of their independence.

Memantine add-on therapy improves cognition while stabilizing both global function and behavior.²³ Memantine monotherapy shows decreased decline in cognition, global function, daily function, and behavioral symptoms.²¹ Stabilization of global function was observed for memantine-treated patients with severe dementia.²⁴

Social outcomes. Deterioration in the daily functioning of an AD patient places great burden on caregivers. Caregivers of patients receiving ChEI therapy have been shown to spend less time giving care and to have lower indirect and direct health care costs, the results of lost time at work and the stress of providing care.³²⁻³⁴ In patients with moderate to severe AD, the disease stages requiring the most assistance, caregivers of those receiving donepezil reported spending 52 minutes per day less providing ADL assistance than caregivers of placebo-treated patients.³² In an economic evaluation,³⁵ donepezil treatment in patients with moderate to severe AD resulted in cost savings. Most of the cost savings could be attributed to less need for residential care by patients and less need for caregivers to spend time assisting with ADLs.³⁵ A recent study³⁶ in the United Kingdom found that donepezil improved cognitive and functional outcomes for patients with mild to moderate AD. Although the study was not statistically powered to measure cost outcomes, it reported no significant difference in costs under the U.K. National Health Service for patients receiving either donepezil or placebo treatment. The potential time and cost saved by ChEI treatment provide needed relief for caregivers and reduce the economic burden on health care resources.

Although most families prefer to keep AD patients at home as long as possible,³⁷ increasing cognitive decline, functional impairment, and behavioral symptoms result in nursing home placement. Treatments that delay costly nursing home placement are highly desirable. A prospective follow-up study in patients with mild to moderate AD revealed that dementia-related nursing home placement was delayed by nearly 2 years with donepezil treatment.³⁸ In a retrospective analysis performed by Lopez et al.,³⁹ ChEI treatment was associated with a significant reduction in the risk of nursing home admission. No studies to date have reported the effects of memantine treatment on the risk of nursing home placement. Delaying nursing home placement helps keep patients in the community longer and reduces the social costs of care.

TOLERABILITY OF TREATMENT IN ADVANCED ALZHEIMER'S DISEASE

Studies of donepezil report the cholinomimetic effects common to ChEI therapy, including diarrhea, nausea, vomiting, and weight loss. In patients with moderate to severe AD, these effects occurred more frequently in patients receiving donepezil than in those receiving placebo.²² Generally, adverse events were mild in severity. Likewise, adverse events were similar between treatment groups in nursing home patients, where the majority of adverse events were transient and mild or moderate in severity.¹⁹ All patients in the moderate to severe AD study²² and more than 80% of patients in the nursing home study¹⁹ had at least 1 comorbid condition. In both studies, 95% of patients were receiving concomitant medications.

A study of memantine in patients with moderate to severe AD²¹ reported that the frequency of adverse events was similar between treatment groups. Most adverse events were reported as mild to moderate in severity. Agitation, urinary incontinence, urinary tract infection, insomnia, and diarrhea were the most frequently occurring adverse events.²¹ Likewise, the frequency of adverse events was reported as similar between treatment groups for a study of memantine in care-dependent patients with severe dementia.²⁴

In a study²³ of patients with moderate to severe AD who received memantine adjunctive to stable, long-term donepezil treatment, adverse events were reported to be mild to moderate in severity. Generally, the frequency of adverse events was reported as similar between the group receiving adjunctive treatment and the group receiving donepezil monotherapy. Confusion, headache, and constipation occurred more frequently in the adjunctive treatment group than in the donepezil monotherapy group. Diarrhea, fecal incontinence, and nausea occurred more frequently in the donepezil monotherapy group than in the adjunctive treatment group.

Although direct comparisons of memantine and ChEIs have yet to be made, both memantine and donepezil appear to be well tolerated in patients with moderate to severe AD as well as in patients with dementia who reside in nursing homes.

SUMMARY

Patients with moderate to severe AD have shown consistent clinical benefit from donepezil monotherapy as well as from memantine treatment adjunctive to stable, long-term donepezil therapy. As monotherapy, donepezil improves cognitive and behavioral symptoms while stabilizing function in patients with moderate to severe AD. Memantine monotherapy in patients with moderate to severe AD has shown cognitive and functional benefit.

Behavioral symptoms, however, were not improved with memantine monotherapy.

Adding memantine to ChEI therapy in the advanced stage of AD appears to benefit patients. Patients with moderate to severe AD who received stable, long-term donepezil therapy followed by memantine add-on treatment had improved cognition, function, and behavior. This study²³ suggests that patients who are likely to experience good tolerability and efficacy from donepezil therapy may also respond well to adjunctive memantine treatment.

Finally, a growing need exists in primary care settings for increased emphasis on treatment and management of AD across the disease continuum. More specifically, in moderate to severe AD, recent pharmacologic studies have shown benefit in cognition, function, and behavior. Enhanced understanding and application of these findings will enable beneficial treatment of moderate to severe AD.

Drug names: donepezil (Aricept), galantamine (Reminyl), memantine (Namenda), rivastigmine (Exelon).

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