Memantine Treatment in Patients With Moderate to Severe Alzheimer Disease Already Receiving Donepezil

A Randomized Controlled Trial

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Context Memantine is a low- to moderate-affinity, uncompetitive *N*-methyl-D-aspartate receptor antagonist. Controlled trials have demonstrated the safety and efficacy of memantine monotherapy for patients with moderate to severe Alzheimer disease (AD) but no controlled trials of memantine in patients receiving a cholinesterase inhibitor have been performed.

Objective To compare the efficacy and safety of memantine vs placebo in patients with moderate to severe AD already receiving stable treatment with donepezil.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled clinical trial of 404 patients with moderate to severe AD and Mini-Mental State Examination scores of 5 to 14, who received stable doses of donepezil, conducted at 37 US sites between June 11, 2001, and June 3, 2002. A total of 322 patients (80%) completed the trial.

Interventions Participants were randomized to receive memantine (starting dose 5 mg/d, increased to 20 mg/d, n=203) or placebo (n=201) for 24 weeks.

Main Outcome Measures Change from baseline on the Severe Impairment Battery (SIB), a measure of cognition, and on a modified 19-item AD Cooperative Study–Activities of Daily Living Inventory ($ADCS\text{-}ADL_{19}$). Secondary outcomes included a Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), the Neuropsychiatric Inventory, and the Behavioral Rating Scale for Geriatric Patients (BGP Care Dependency Subscale).

Results The change in total mean (SE) scores favored memantine vs placebo treatment for SIB (possible score range, 0-100), 0.9 (0.67) vs –2.5 (0.69), respectively ($P<.001$); $ADCS\text{-}ADL_{19}$ (possible score range, 0-54), –2.0 (0.50) vs –3.4 (0.51), respectively ($P=.03$); and the CIBIC-Plus (possible score range, 1-7), 4.41 (0.074) vs 4.66 (0.075), respectively ($P=.03$). All other secondary measures showed significant benefits of memantine treatment. Treatment discontinuations because of adverse events for memantine vs placebo were 15 (7.4%) vs 25 (12.4%), respectively.

Conclusions In patients with moderate to severe AD receiving stable doses of donepezil, memantine resulted in significantly better outcomes than placebo on measures of cognition, activities of daily living, global outcome, and behavior and was well tolerated. These results, together with previous studies, suggest that memantine represents a new approach for the treatment of patients with moderate to severe AD.

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ALZHEIMER DISEASE (AD) IS A neurodegenerative disorder characterized by cognitive decline, impaired performance of activities of daily living, and behavioral and psychiatric signs and symptoms. Pathological features of AD include intraneuronal neurofibrillary tangles containing abnormally phosphorylated tau protein, extracellular amyloid plaques containing the peptide β amyloid, neuronal cell death, and anatomic as well as functional impairment of neurotransmitter systems.[1,2] Alzheimer disease affects approximately 4.5 million people in the United States.[3] Treatments approved by the Food and Drug Administration were previously limited to monotherapy with cholinesterase inhibitors in patients with mild to moderate AD.[2] In October 2003, the Food and Drug Administration approved memantine for the treatment of moderate to severe AD; memantine is now available in more than 40 countries worldwide.

Memantine, a low- to moderate-affinity, uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, represents the first member of a new class of medications showing clinical benefit and good tolerability in AD. Although other NMDA receptor modulators (eg, milacemide and D-cycloserine) have failed in development as

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potential AD therapeutic agents,[4,5] memantine has exhibited efficacy and safety in a recent placebo-controlled trial in outpatients with moderate to severe AD and in an earlier study in nursing home patients with dementia.[6,7] An open-label study suggested that the combination of memantine and various cholinesterase inhibitors was well tolerated.[8] We hypothesized that administration of memantine to patients with moderate to severe AD receiving stable donepezil therapy would result in clinical benefit and would be safe and well tolerated.

METHODS

Participants

The trial was conducted from June 11, 2001, through June 3, 2002. Participants were recruited from 37 US sites; 404 patients who had a diagnosis of probable AD, according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association criteria, were enrolled. Inclusion criteria were as follows: Mini-Mental State Examination (MMSE) score of 5 to 14 at both screening and baseline; minimum age of 50 years; a recent magnetic resonance imaging or computed tomographic scan (within 12 months) consistent with a diagnosis of probable AD; ongoing cholinesterase inhibitor therapy with donepezil for more than 6 months before entrance into the trial and at a stable dose (5-10 mg/d) for at least 3 months; a knowledgeable and reliable caregiver to accompany the patient to research visits and oversee the administration of the investigational agent during the trial; residence in the community; ambulatory or ambulatory-aided (ie, walker or cane) ability; and stable medical condition. Patients were permitted to continue receiving stable doses of concomitant medications, including antidepressants, antihypertensives, anti-inflammatory drugs, atypical antipsychotics, antiparkinsonian drugs, anticoagulants, laxatives, diuretics, and sedatives/hypnotics.

Patients were excluded for clinically significant B_{12} or folate deficiency; active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease; other psychiatric or central nervous system disorders; computed tomographic or magnetic resonance imaging evidence of clinically significant central nervous system disorders other than probable AD; dementia complicated by other organic disease; or a modified Hachinski Ischemia Score[9] of more than 4 at screening. Written informed consent was obtained from the caregiver and either the patient (if possible) or a legally acceptable representative (if different from the caregiver) before the initiation of any study-specific procedures. The study was reviewed and approved by the institutional review board at each site.

Interventions

This study was a prospective randomized, placebo-controlled, parallel-group, fixed-dose trial in which participants were assigned to double-blind treatment for 24 weeks, with a 1- to 2-week single-blind placebo lead-in period before randomization solely to assess compliance. Patients were randomly allocated to 1 of the 2 treatment groups in permuted blocks of 4 in accordance with the randomization list generated and retained by the Department of Biostatistics at Forest Laboratories. At the baseline visit, each investigator sequentially assigned a randomization number to each patient. No individual patient randomization code was revealed during the trial.

Patients assigned to double-blind memantine treatment were titrated in 5-mg weekly increments from a starting dose of 5 mg/d to 20 mg/d (administered as two 5-mg tablets twice daily) at the beginning of week 4. Masked study medication was supplied to each study site for dispensation in blister packs at each visit. Drug and placebo tablets were visually identical and all patients received 4 tablets of study medication daily (in combinations of memantine [5 mg] and matching placebo tablets). All patients were to maintain stable donepezil therapy at entry dose as prescribed by the patient's physician for the duration of the study; adherence to this protocol was monitored by routine assessment of concomitant medication use. Any change in the dosing regimen or discontinuation of donepezil was recorded, and patients were discontinued from the study if the inclusion criterion of concomitant donepezil therapy was no longer met. From week 3 to the end of week 8 of double-blind treatment, transient dosage adjustments for memantine treatment were permitted for patients experiencing dose-limiting adverse events. All patients receiving memantine were required to receive the target dose of 20 mg/d by the end of week 8. Patients not tolerating the target dose by week 8 were disenrolled. Adherence with study medication was assessed by returned tablets and more than 95% of both treatment groups had more than 75% compliance (95% for the placebo-treatment group and 96.5% for the memantine-treatment group). Most patients who completed the double-blind phase entered the currently ongoing open-label extension.

Outcome Measures

Cognitive, functional, and global outcome measures were obtained at baseline and at the end of weeks 4, 8, 12, 18, and 24, unless otherwise specified. Patients who discontinued prematurely were evaluated during the final visit. The primary efficacy parameters were the change from baseline on the Severe Impairment Battery (SIB) and on a modified 19-item AD Cooperative Study–Activities of Daily Living Inventory ($ADCS\text{-}ADL_{19}$) at week 24.

The SIB is a 40-item test developed for the evaluation of cognitive dysfunction in patients with more severe AD. Six primary subscales assess memory, orientation, language, attention, visuospatial ability, and construction. In addition, the scale assesses praxis, social interaction, and orienting to name.[10,11] Validity, reliability, and sensitivity to longitudinal change have been established.[10,11] The SIB scores range from 0 to 100, with higher scores reflecting

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higher levels of cognitive ability. The SIB was assessed at baseline and all subsequent visits.

The ADCS-ADL$_{19}$ was the second primary efficacy instrument.[12] This 19-item subset of the original 42-item inventory focuses on items appropriate for the assessment of later stages of dementia (ie, the level of independence in performing everyday tasks including eating, walking, grooming, telephone use, hobbies, complex tasks, and communications). The sensitivity and reliability of this modification have been established.[13] The ADCS-ADL$_{19}$ was administered as an interview to the patient's caregiver and focused on the performance of each activity of daily living during the previous 4 weeks. Possible scores range from 0 to 54. Higher scores reflect higher levels of functioning. The ADCS-ADL$_{19}$ was assessed at baseline and all subsequent visits.

The secondary outcomes included a Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus),[14] the Neuropsychiatric Inventory (NPI), and the Behavioral Rating Scale for Geriatric Patients (BGP). The CIBIC-Plus was administered according to the format of the Alzheimer Disease Cooperative Study–Clinician's Global Impression of Change. The CIBIC-Plus is used to assess the effect of medication on overall clinical status in patients with dementia, incorporating caregiver observations as well as patient interviews. Change is rated on a scale from 1 (marked improvement) to 7 (marked worsening). A global assessment of severity of illness was made at baseline; the CIBIC-Plus was assessed at all postbaseline visits.

The NPI was designed to assess the frequency and severity of behavioral symptoms in patients with dementia, based on an interview of the caregiver.[15] The 12-item version of the instrument was used with a total score ranging from 0 to 144. Higher scores reflect greater symptoms. The NPI was assessed at baseline, at the end of week 12, and at the final visit.

The BGP consists of 35 items (scored 0, 1, or 2 by the rater) assessing observable aspects of cognition, function, and behavior.[16] A higher score reflects worse function. The BGP care dependency subscale reflects cognitive and functional characteristics associated with increased need for care. The BGP was administered at baseline and the final visit.

The Functional Assessment Staging (FAST) was administered as an index of staging and not as a secondary outcome.[17] The FAST evaluates a patient's ability to perform daily and necessary life activities and is divided into 7 major stages, from normality (FAST stage 1) to severe dementia (FAST stage 7). Stages 6 and 7 are further divided into 11 substages (6a to 6e and 7a to 7f), each of which is based on specific functional deficits. The FAST was administered at baseline and the final visit.

Concomitant medications and vital signs were recorded at every visit; adverse events were recorded at baseline and all subsequent visits; and laboratory tests, electrocardiograms, and physical examinations were performed at the screening and final visits.

Sample Size

Assuming a hypothetical effect size of 0.35, a sample size of at least 170 patients in each treatment group provided a 90% power at a 2-sided α level of .05, based on a 2-sample t test for change from baseline to week 24 in both SIB and ADCS-ADL$_{19}$ scores.

Statistical Analyses

Three populations were considered in the statistical analyses. The randomized population consisted of all patients randomized into the study (n=404); the safety population consisted of all randomized patients who received at least 1 dose of double-blind study medication (n=403); the modified intent-to-treat population specified by the protocol consisted of patients in the safety population who completed at least 1 postbaseline SIB or ADCS-ADL$_{19}$ assessment (n=395). The statistical analysis plan for this study stipulated that only postbaseline data could be carried forward. Particularly for the CIBIC-Plus, it is not possible to carry forward baseline data because by definition this is a change score and is not applicable to baseline. All efficacy analyses were based on the modified intent-to-treat population. Primary efficacy analyses were conducted by using the last observation carried forward (LOCF) approach for missing data imputation. Supportive analyses were performed by using the observed case approach. Change from baseline was compared between memantine and placebo groups using a 2-way analysis of covariance, with treatment group and center as main effects and baseline total score as the covariate. The study was to be declared positive if memantine was statistically significantly better than placebo ($P<.05$) on both the SIB and ADCS-ADL$_{19}$. For categorical measures, the Cochran-Mantel-Haenszel statistic using modified Ridit scores (Van Elteren test) controlling for study center was used to compare distributions between memantine and placebo groups. No interim analyses were performed. SAS version 6.12 (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Participants

The trial profile is summarized in FIGURE 1. Of the 404 patients who entered the study, 201 were randomized to placebo and 203 were randomized to memantine (1 in the memantine group withdrew consent before receiving treatment). No patients were excluded during the placebo lead-in period for lack of compliance. Significantly more participants in the memantine group (n=172, 85.1%) completed the study than in the placebo group (n=150, 74.6%, $P=.01$). No patients discontinued because of changes in administration of donepezil.

The demographic and clinical characteristics of the 2 groups at baseline are summarized in TABLE 1. Patients in the memantine group were slightly heavier ($P=.003$) than those in the pla-

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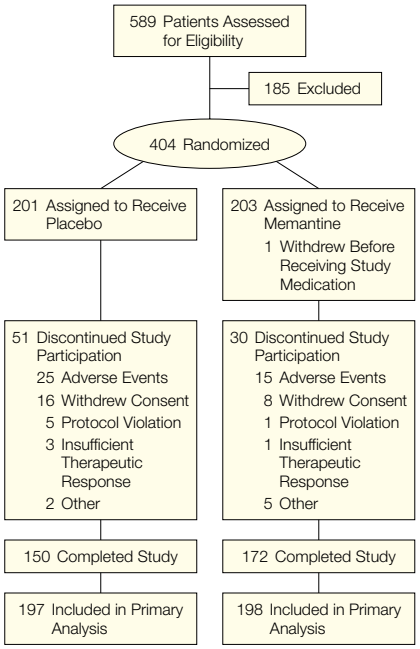
Figure 1. Study Flow



cebo group; retrospectively adding this variable to the analysis of covariance did not affect the primary outcomes. No clinically relevant group differences were observed for the duration of donepezil use before baseline or for any other characteristic at baseline. Most patients (87%) had a FAST rating between 4 and 6c. The most frequent medical conditions were not recorded, but the following body systems were noted to be affected at screening for placebo and memantine groups, respectively: eyes-ears-nose-throat (43% and 43%), neurological (34% and 38%), appearance/skin (40% and 33%), musculoskeletal (29% and 29%), cardiovascular (20% and 23%), abdomen (12% and 17%), head/neck (6% and 9%), other (10% and 9%), and pulmonary (3% and 5%). The most frequent medication classes (>20%) used during treatment with placebo and memantine, respectively, were vitamins (74% and 77%), analgesics (48% and 48%), antidepressants (36% and 36%), mineral supplements (22% and 27%), lipid-reducing agents (23% and 25%), anxiolytics/neuroleptics (26% and 22%), and anti-inflammatory agents (21% and 24%). There were no statistically significant differences between groups in the number or type of medical disorders experienced previously or at the time of enrollment, or in the number or type of concomitant medications used during the study.

Efficacy

Statistically significant benefits of treatment with memantine vs treatment with placebo were observed on all primary and secondary outcome measures as presented. TABLE 2 summarizes primary and secondary efficacy outcomes at week 24 and at end point, using both the observed case and LOCF analytical approaches.

Primary Outcomes

Analyses using the LOCF approach showed a statistically significant benefit of memantine treatment vs treatment with placebo on the SIB ($P<.001$) and the ADCS-ADL$_{19}$ ($P=.03$), as did analyses using the observed case approach ($P<.001$ for SIB; $P=.02$ for ADCS-ADL$_{19}$). Post hoc analyses including all randomized patients also showed statistically significant benefits consistent with analyses using the modified intent-to-treat population (for SIB, $P<.001$ and for ADCS-ADL$_{19}$, $P=.03$).

FIGURE 2 depicts the mean change from baseline by visit and at end point on the SIB by using observed case and LOCF, showing statistically significant differences between the memantine and placebo groups at all visits beginning at week 8; the mean SIB values for the patients receiving memantine remained above baseline throughout the trial. Figure 2 also depicts the mean change in total ADCS-ADL$_{19}$ from baseline by visit and at end point by using observed case and LOCF, respectively, showing a statistically significant difference ($P<.05$) from placebo beginning at week 4.

Secondary Outcomes

A CIBIC-Plus score was used as a measure of overall clinical response to therapy. The mean CIBIC-Plus score was statistically significantly better for the memantine group vs the placebo group using both observed case and LOCF (Table 2). Furthermore, 55% of the memantine group was rated as improved or unchanged vs 45% of the placebo group at end point. FIGURE 3 provides the distribution of CIBIC-Plus ratings at end point using LOCF analysis.

The total NPI score was significantly lower for the memantine group compared with the placebo group at week 24 ($P=.01$ with observed case analysis and $P=.002$ with LOCF), representing fewer behavioral disturbances and psychiatric symptoms for patients in the memantine group. The BGP care dependency subscale was also statistically significantly improved for the memantine group compared with the placebo group ($P=.001$ using observed case and $P=.001$ using LOCF; Table 2).

Safety and Tolerability

Overall treatment-emergent adverse events are summarized in TABLE 3. More participants (n=25, 12.4%) in the placebo-treated group discontinued prematurely because of adverse events than in the memantine group (n=15, 7.4%; Figure 1). The adverse event most often associated with discontinuation was confusion, resulting in discontinuation in 1.5% of patients in the placebo group and 2% in the memantine group.

Adverse events occurred in 72% of the placebo and 78% of the memantine groups. Most adverse events were rated as mild or moderate in severity and were judged to be not related to study drug for participants in both treatment groups. The only adverse events that occurred in at least 5% of the memantine group and with an incidence of at least twice that of the placebo group were confusion (7.9% vs 2.0%, respectively; $P=.01$) and headache (6.4% vs 2.5%, respectively; $P=.09$). By similar criteria, lower incidences of diarrhea (4.5% vs 8.5%) and fecal incontinence (2.0% vs 5.0%) were observed in the memantine group compared with the placebo group, respectively. Other gastrointes-

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tinal effects of interest for patients receiving cholinesterase inhibitors included nausea, which was reported by 3.5% of the placebo group and 0.5% of the memantine group, and constipation, which was reported by 1.5% of the placebo group and 3.0% of the memantine group.

Of the patients who experienced confusion, 4 (25%) of 16 patients receiving memantine discontinued treatment because of this adverse event, whereas 3 (75%) of 4 patients receiving placebo did so. In most of the patients receiving memantine, confusion was rated as mild, occurred at a median of 32 days, and remitted within 2 weeks. In patients receiving placebo, confusion was more likely to be rated as severe, occurred at a median of 55 days, and did not remit. No patients discontinued because of headache, which usually lasted 1 day.

No clinically significant differences were detected between treatment groups in the mean change from baseline to end point or in the incidence of potentially clinically significant values for laboratory tests, vital sign measurements, or electrocardiogram parameters.

COMMENT

To our knowledge, this is the first published, prospective, double-blind, placebo-controlled study examining the benefits of an NMDA receptor antagonist in patients with AD receiving a stable dose of donepezil. Efficacy of memantine was significantly better than placebo for treatment of moderate to severe AD in community-dwelling patients. Specifically, measures of cognitive function, activities of daily living,

Table 1. Baseline Demographic and Clinical Characteristics*

Characteristics	Placebo (n = 201)	Memantine (n = 202)
Men	67 (33)	74 (37)
Women	134 (67)	128 (63)
Age, mean (SD), y	75.5 (8.73)	75.5 (8.45)
Weight, mean (SD), kg	66.4 (14.12)	70.7 (14.31)†
White race	186 (92.5)	182 (90.1)
MMSE score, mean (SD)	10.2 (2.98)	9.9 (3.13)
Duration of donepezil treatment, mean (SD), wk	129 (70.3)	126 (64.9)
Donepezil dose, mean (SD), mg	9.49 (1.88)	9.25 (1.79)
Any concurrent medical condition	149 (74.1)	149 (73.8)
Any concomitant medication during treatment	197 (98.0)	197 (97.5)
Tocopherol	120 (59.7)	131 (64.9)
Multivitamins	78 (38.8)	80 (39.6)
Acetylsalicylic acid	76 (37.8)	73 (36.1)
Ascorbic acid	35 (17.4)	43 (21.3)
Paracetamol	25 (12.4)	32 (15.8)
Ginkgo biloba	24 (11.9)	31 (15.3)
Calcium	21 (10.4)	25 (12.4)

Abbreviation: MMSE, Mini-Mental State Examination.
*Data are No. (%) unless otherwise specified. One randomized patient discontinued the study prior to receiving any treatment and was not included in the analyses.
†P = .003.

Table 2. Efficacy Outcomes at Week 24 (Observed Case) and at End Point (LOCF)*

	Least Squares Mean Score (SE)							
			Change From Baseline					
	Baseline		End Point LOCF†			Week 24 Observed Case		
Outcome Measure	Placebo	Memantine	Placebo	Memantine	*P* Value	Placebo	Memantine	*P* Value
SIB	80.0 (1.13)	78.0 (1.11)	–2.5 (0.69)	0.9 (0.67)	<.001	–2.4 (0.74)	1.0 (0.70)	<.001
No. of patients	197	198	196	198		153	171	
ADCS-ADL$_{19}$	35.8 (0.74)	35.5 (0.73)	–3.4 (0.51)	–2.0 (0.50)	.03	–3.3 (0.55)	–1.7 (0.51)	.02
No. of patients	197	198	197	198		152	172	
CIBIC-Plus‡	NA	NA	4.66 (0.075)	4.41 (0.074)	.03	4.64 (0.087)	4.38 (0.081)	.03
No. of patients	197	198	196	198		152	172	
NPI	13.4 (1.08)	13.4 (1.07)	3.7 (0.99)	–0.1 (0.98)	.002	2.9 (1.06)	–0.5 (0.99)	.01
No. of patients	197	198	189	193		152	171	
BGP Care Dependency Subscale	9.8 (0.46)	9.5 (0.45)	2.3 (0.38)	0.8 (0.37)	.001	2.2 (0.40)	0.6 (0.37)	.001
No. of patients	196§	198	179	185		151	172	

Abbreviations: ADCS-ADL$_{19}$, 19-item Alzheimer Disease Cooperative Study–Activities of Daily Living Inventory; BGP, Behavioral Rating Scale for Geriatric Patients; CIBIC-Plus, Clinician's Interview-Based Impression of Change Plus Caregiver Input; LOCF, last observation carried forward; NA, not applicable; NPI, Neuropsychiatric Inventory; SIB, Severe Impairment Battery.
*SIB range of possible scores, 0 to 100; higher score indicates better function. ADCS-ADL$_{19}$ range of possible scores, 0 to 54; higher score indicates better function. CIBIC-Plus was defined as a change score, therefore baseline values are not applicable; range of possible scores, 1 (marked improvement) to 7 (marked worsening). NPI range of possible scores, 0 to 144; higher scores indicate worse symptoms. BGP range of possible scores, 0 to 70; higher scores indicate worse function.
†For the end point LOCF approach, only postbaseline assessments were carried forward.
‡Arithmetic mean.
§One patient had an incomplete BGP baseline assessment and was not included.

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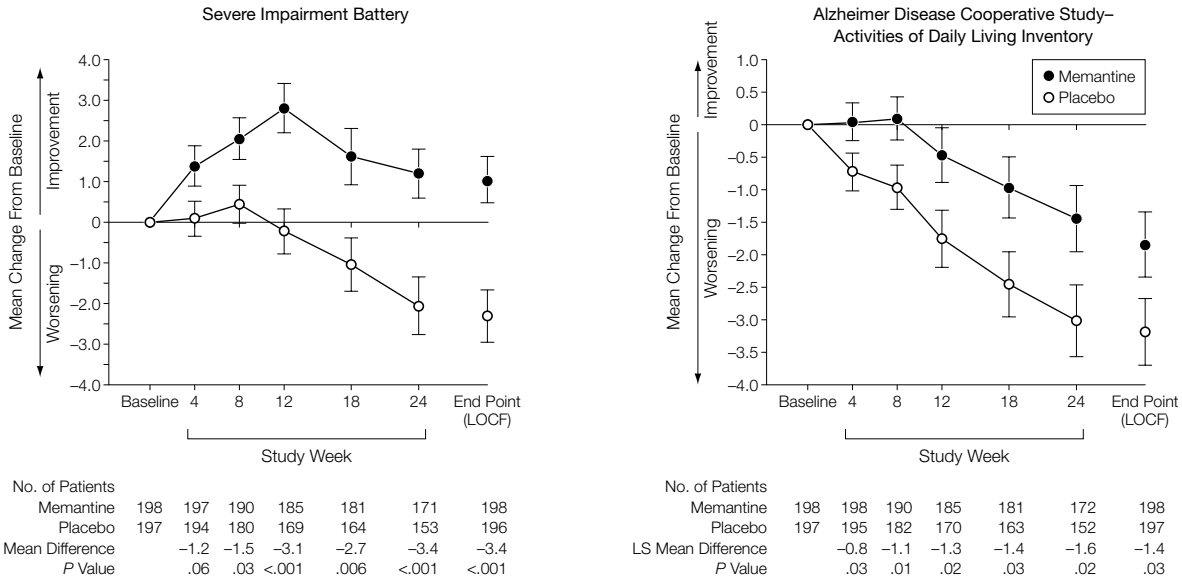
Figure 2. SIB and ADCS-ADL$_{19}$ by Visit (Observed Case) and at End Point (LOCF)

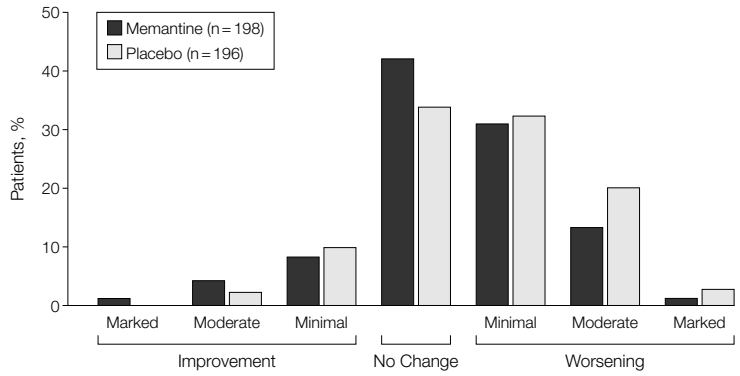


No. of Patients							
Memantine	198	197	190	185	181	171	198
Placebo	197	194	180	169	164	153	196
LS Mean Difference		−1.2	−1.5	−3.1	−2.7	−3.4	−3.4
P Value		.06	.03	<.001	.006	<.001	<.001

No. of Patients							
Memantine	198	198	190	185	181	172	198
Placebo	197	195	182	170	163	152	197
LS Mean Difference		−0.8	−1.1	−1.3	−1.4	−1.6	−1.4
P Value		.03	.01	.02	.03	.02	.03

SIB indicates Severe Impairment Battery; ADCS-ADL$_{19}$, 19-item Alzheimer Disease Cooperative Study–Activities of Daily Living Inventory; LOCF, last observation carried forward. For the Severe Impairment Battery, the mean (SD) score at baseline was 79.8 (14.18) for the placebo group and 77.8 (15.46) for the memantine group. For the Alzheimer Disease Cooperative Study–Activities of Daily Living Inventory, the mean (SD) score at baseline was 36.2 (9.32) for the placebo group and 35.9 (9.75) for the memantine group. Only patients with at least 1 postbaseline assessment were included in the LOCF analysis. The end point is the last nonmissing postbaseline assessment carried forward to end of study. Error bars indicate SEM.

Figure 3. Distribution of CIBIC-Plus Ratings at End Point (LOCF)



CIBIC-Plus indicates Clinician's Interview-Based Impression of Change Plus Caregiver Input; LOCF, last observation carried forward. *P* = .03 for the comparison between the distribution of values for the memantine and placebo groups, determined by the Cochran Mantel-Haenszel statistic using modified Ridit scores (Van Elteren test) controlling for study center.

behavior, and clinical global status were significantly improved with memantine compared with placebo. Treatment with memantine during the 6-month trial in patients with MMSE scores of 5 to 14 resulted in the maintenance of cognitive function (0.9 increase in SIB score compared with baseline), whereas treatment with placebo was associated with cognitive decline (2.5 decrease in SIB score compared with baseline). In comparison, the AD Cooperative Study group reported that for untreated patients with AD with MMSE scores of 5 to 9, the mean deterioration rate on the SIB was roughly 3.19 per month and for untreated patients with AD with MMSE scores of 10 to 15, the rate of change was 2.08 per month.[10] Treatment with memantine was associated with less decline on the CIBIC-Plus.

These efficacy findings confirm and extend results from previous placebo-controlled trials of memantine in dementia. A 12-week multicenter European trial[6] of memantine 10 mg/d was conducted in 166 nursing home residents with severe dementia, including both Alzheimer type and vascular dementias, diagnosed by *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria[18] (mean baseline MMSE of 6.3). Significant benefit of memantine vs placebo was observed on the Clinician's Global Impression of Change and the BGP care dependency subscale, and there were no clinically relevant differences in adverse events between memantine (21%) and placebo (22%) groups. A more recent 28-week multicenter US trial of memantine 20 mg/d monotherapy was conducted in 252 patients with moderate to severe probable AD by the National Institute of Neurological and Communicative Disorders and Stroke–

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Alzheimer Disease and Related Disorders Association criteria and who were not permitted to receive a cholinesterase inhibitor.[7] Significant benefit of memantine treatment was observed on the ADCS-ADL$_{19}$, an assessment of function, and on the SIB, an assessment of cognition using both observed case and LOCF approaches, and on the CIBIC-Plus in the observed case but not the LOCF analysis. Adverse events were similar between the memantine (84%) and placebo (87%) groups.

Patients in the memantine monotherapy outpatient study[7] were more cognitively impaired (mean baseline MMSE of 7.9), more functionally impaired (mean baseline ADCS-ADL$_{19}$ score of approximately 27), and experienced more psychopathology (mean baseline NPI of approximately 20; rates of agitation as an adverse event in 32% and 18% of patients treated with placebo and memantine, respectively) than patients included in this trial. In addition, the magnitude of the memantine-placebo differences in outcomes common to both studies, as well as the magnitude of decline in most measures over time, was greater in the memantine monotherapy study than observed in this trial. This finding may be related to the higher severity of dementia in patients enrolled in the memantine monotherapy trial or because the present trial required donepezil therapy and permitted use of most psychotropics, factors which may have contributed to slower rates of decline in both the memantine and placebo groups. However, this type of inference is speculative given the absence of patients who were not treated with donepezil. Similar to the finding in the present trial, discontinuation rates because of adverse events in the monotherapy study were lower in patients receiving memantine than in those receiving placebo (10% vs 17%, respectively).[7] These trials support the efficacy of memantine for patients with moderate to severe AD.

Memantine administered at a dosage of 20 mg/d to patients receiving stable doses of donepezil was safe and well tolerated. Significantly more patients receiving placebo discontinued the trial than patients receiving memantine and the rate of discontinuation because of adverse events was lower in the memantine-treated group than in the placebo-treated group. The incidence of individual adverse events was generally similar in the 2 groups. Confusion, although occurring at a low frequency, was more common in patients receiving memantine than in those patients receiving placebo. However, it did not lead to a greater proportion of discontinuations and was mild in intensity and duration. The gastrointestinal adverse effects associated with cholinergic compounds were more commonly reported by patients receiving placebo, which was suggestive of a possible amelioration of these adverse events by the addition of memantine treatment to patients receiving a stable regimen of donepezil therapy. There were no clinically significant memantine-related mean changes in laboratory test results, vital signs, or electrocardiogram parameters.

There are limitations to the generalizability of our results. The trial did not address different doses or titration rates, the use of other cholinesterase inhibitors besides donepezil, or the impact of commencing memantine therapy before donepezil. Although there is no a priori reason to expect different results with other cholinesterase inhibitors, studies of memantine in combination with other cholinesterase inhibitors are being conducted to address this issue. Furthermore, results from an open-label European trial indicated that tolerability was not affected when donepezil or other cholinesterase inhibitors were administered to patients already receiving memantine or vice versa.[8] Preclinical studies show that memantine does not affect the inhibition of acetylcholinesterase by donepezil, nor does it bind to muscarinic receptors.[19-21] Furthermore, in healthy volunteers, no pharmacokinetic or pharmacodynamic interactions were observed between memantine and donepezil.[22] Although memantine has demonstrated positive cognitive effects in patients with mild to moderate vascular dementia, the efficacy of memantine administered alone or along with any cholinesterase inhibitor in other forms of dementia was not systematically evaluated in this trial.[23,24]

Table 3. Adverse Events Reported in at Least 5% of Patients in Either Treatment Group*

	Adverse Event, No. (%)	
	Placebo (n = 201)	Memantine (n = 202)
Agitation	24 (11.9)	19 (9.4)
Confusion	4 (2.0)	16 (7.9)
Fall	14 (7.0)	15 (7.4)
Influenza-like symptoms	13 (6.5)	15 (7.4)
Dizziness	16 (8.0)	14 (6.9)
Headache	5 (2.5)	13 (6.4)
Urinary tract infection	10 (5.0)	12 (5.9)
Urinary incontinence	6 (3.0)	11 (5.4)
Accidental injury	16 (8.0)	10 (5.0)
Upper respiratory tract infection	13 (6.5)	10 (5.0)
Peripheral edema	8 (4.0)	10 (5.0)
Diarrhea	17 (8.5)	9 (4.5)
Fecal incontinence	10 (5.0)	4 (2.0)

*Patients may have reported more than 1 adverse event.

The long-term effects of memantine and cholinesterase inhibitor treatment were not addressed in this double-blind trial but are the focus of the open-label extension and other ongoing trials. Considering that patients in this study had been receiving stable long-term donepezil therapy before enrollment, it is possible that participants were more likely to experience good tolerability and efficacy in the trial, perhaps because of having fewer medical problems or experiencing a slower rate of decline than patients without any prior AD treatment. However, the use of concomitant medications was typical for this elderly patient population and was similar between the groups. In addition, the dropout rate was approximately 15% in the memantine group vs approximately 25% in the placebo group, a phenomenon that perhaps led to an underestimation of the effect of memantine.

Drugs that target the glutamatergic system appear to have a therapeutic role in AD.[25,26] Memantine may block pathological activation of NMDA receptors while dissociating from the NMDA re-

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ceptor channel during normal physiological conditions,[20] in theory improving cognition in states of glutamatergic excess. It is plausible that combining donepezil and memantine, which affect separate neurotransmitter systems, may confer independent clinical benefits. However, given the complex interconnection of different neurotransmitter systems, a synergistic mechanism is also plausible. Although the specific mechanisms and interactions between these therapies have not yet been defined, this and other studies demonstrate that memantine alone or together with a cholinesterase inhibitor results in significantly better outcomes than placebo in patients with moderate to severe AD.

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