

ORIGINAL ARTICLE

Memantine in Moderate-to-Severe Alzheimer's Disease

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ABSTRACT

BACKGROUND

Overstimulation of the N-methyl-D-aspartate (NMDA) receptor by glutamate is implicated in neurodegenerative disorders. Accordingly, we investigated memantine, an NMDA antagonist, for the treatment of Alzheimer's disease.

METHODS

Patients with moderate-to-severe Alzheimer's disease were randomly assigned to receive placebo or 20 mg of memantine daily for 28 weeks. The primary efficacy variables were the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev). The secondary efficacy end points included the Severe Impairment Battery and other measures of cognition, function, and behavior. Treatment differences between base line and the end point were assessed. Missing observations were imputed by using the most recent previous observation (the last observation carried forward). The results were also analyzed with only the observed values included, without replacing the missing values (observed-cases analysis).

RESULTS

Two hundred fifty-two patients (67 percent women; mean age, 76 years) from 32 U.S. centers were enrolled. Of these, 181 (72 percent) completed the study and were evaluated at week 28. Seventy-one patients discontinued treatment prematurely (42 taking placebo and 29 taking memantine). Patients receiving memantine had a better outcome than those receiving placebo, according to the results of the CIBIC-Plus ($P=0.06$ with the last observation carried forward, $P=0.03$ for observed cases), the ADCS-ADLsev ($P=0.02$ with the last observation carried forward, $P=0.003$ for observed cases), and the Severe Impairment Battery ($P<0.001$ with the last observation carried forward, $P=0.002$ for observed cases). Memantine was not associated with a significant frequency of adverse events.

CONCLUSIONS

Antiglutamatergic treatment reduced clinical deterioration in moderate-to-severe Alzheimer's disease, a phase associated with distress for patients and burden on caregivers, for which other treatments are not available.

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ALZHEIMER'S DISEASE AFFECTS AT least 15 million persons throughout the world.^{1,2} The number of persons with Alzheimer's disease is increasing substantially as populations age.³ As Alzheimer's disease advances, patients become progressively impaired in both cognitive and functional capacities,^{2,4} and the burden on caregivers increases. Pharmacologic treatments are currently approved for treating mild-to-moderate Alzheimer's disease.⁵ However, there are no treatments for the more advanced stages of Alzheimer's disease.

Glutamate is the principal excitatory neurotransmitter in the brain.^{6,7} Glutamatergic overstimulation may result in neuronal damage, a phenomenon that has been termed excitotoxicity. Such excitotoxicity ultimately leads to neuronal calcium overload and has been implicated in neurodegenerative disorders.⁸ Glutamate stimulates a number of postsynaptic receptors, including the N-methyl-D-aspartate (NMDA) receptor, which has been particularly implicated in memory processes, dementia, and the pathogenesis of Alzheimer's disease.⁹⁻¹¹

Memantine, an uncompetitive NMDA-receptor antagonist, could be of therapeutic value in Alzheimer's disease.¹² A recent study in patients with advanced dementia (Alzheimer's disease and vascular dementia) suggested therapeutic benefits.¹³ Accordingly, we conducted a trial of the efficacy of memantine in outpatients with moderate-to-severe Alzheimer's disease.

METHODS

PATIENTS

Patients at least 50 years old who were residing in the community and had probable Alzheimer's disease according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV)⁴ and of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association¹⁴ were recruited. The eligibility criteria included base-line Mini-Mental State Examination scores of 3 to 14,¹⁵ a stage of 5 or 6 on the Global Deterioration Scale,¹⁶ and a stage of 6a or greater on the Functional Assessment Staging instrument,¹⁷ signifying the presence of dementia-related deficits in the ability to perform one or more basic activities of daily living. The patients had reliable caregivers and had undergone computed tomography (CT) or magnetic resonance imaging (MRI) of the brain within the previous 12 months.

Patients with vascular dementia, dementia or clinically significant neurologic disease due to conditions other than Alzheimer's disease, major depressive disorder, or a score greater than 4 on the modified Hachinski Ischemic Rating Scale¹⁸ were excluded. Patients with clinically significant coexisting medical conditions or laboratory abnormalities were also excluded, as were patients receiving specific concomitant medications (anticonvulsant agents, antiparkinsonian agents, hypnotic agents, anxiolytic agents, neuroleptic agents, cholinomimetic agents, or any other investigational compounds). Patients who had been receiving stable antidepressant treatment for at least two months were eligible, and chloral hydrate could be used as a sedative or hypnotic, but not within 24 hours before an assessment.

STUDY DESIGN

In this 28-week, double-blind, parallel-group study, patients were randomly assigned to receive either memantine (20 mg per day; Merz) or an identical-appearing placebo. Randomization was stratified according to site with the use of RanCode (version 3.1) and in blocks of four, with staff at the individual sites blinded to the randomization process. The assigned treatment was discontinued if continuation represented a medical risk in the opinion of the study physician, or if the patient declined ongoing participation. Subjects who withdrew prematurely were asked to complete end-point measures at the time of early termination and to return at 28 weeks for a "retrieved-dropout visit," which included all end-point assessments. The results of an optional 24-week open-label study extension, in which all patients took memantine, are still being analyzed.

Thirty-two U.S. centers participated. The trial was conducted in compliance with the Declaration of Helsinki and its amendments and was approved by study-center institutional review boards. The eligible patients and responsible caregivers provided written informed consent.

Merz Pharmaceuticals provided study medication and funding and was involved in planning the design and protocol. Data analysis was performed by a contract research organization (Quintiles), along with the authors. The data are stored at Merz Pharmaceuticals.

EFFICACY VARIABLES

The prespecified primary efficacy variables were the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) global

score (New York University version)¹⁹ at 28 weeks and the change from base line to week 28 in the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL)²⁰ modified for more severe dementia (ADCS-ADLsev).²¹ If values from the 28-week observation were not available, the last observed value was used. Assessments were conducted at base line, at mid-study (week 12), and at the end of treatment (week 28) or at early termination, with a 28-week retrieved-dropout visit when possible.

The CIBIC-Plus measures overall global change relative to base line and is scored on a seven-point scale ranging from 1 (markedly improved) to 7 (markedly worse). The domains of cognition (assessed by patient interview), function (caregiver interview), and behavior (separate patient and caregiver interviews) are systematically evaluated. Experienced clinicians, blinded to adverse events and other study assessments, conducted separate interviews with study patients and caregivers to assess overall change on the CIBIC-Plus. To ensure consistency, the same clinician completed all CIBIC-Plus interviews for each study patient and associated caregiver wherever possible.

The ADCS-ADL is a structured questionnaire originally created to assess functional capacity over a broad range of severity of dementia. Each item consists of a series of hierarchical questions designed to determine a patient's ability to perform one of the activities of daily living, ranging from total independence to total inability. A subgroup of 19 individually validated items (the ADCS-ADLsev) was used; a total score of 54 signified optimal performance, and lower scores indicated worse performance. Caregivers assessed a patient's activities during the preceding four-week interval. The differences in total scores were analyzed.

In addition, six other efficacy variables were measured. The Severe Impairment Battery^{22,23} was designed to evaluate cognitive performance in advanced Alzheimer's disease. A 51-item scale, it assesses social interaction, memory, language, visuospatial ability, attention, praxis, and construction. The scores range from 0 (greatest impairment) to 100. The Severe Impairment Battery was part of a predefined responder analysis. The Mini-Mental State Examination¹⁵ is a 30-point scale that measures cognitive function, with higher scores indicating better function. The Global Deterioration Scale¹⁶ is a seven-stage scale that assesses overall cognitive and functional capacity on the basis of ob-

servations of the patient and reports from the caregiver. Higher stages signify greater impairment.

The Functional Assessment Staging scale¹⁷ assesses the magnitude of progressive functional deterioration in patients with dementia by identifying characteristic progressive disabilities. Its seven major stages range from normal (stage 1) to severe dementia (stage 7). Five substages in stage 6, corresponding to the loss of ability to independently dress, bathe, and handle proper mechanics and cleanliness in using the toilet, and to remain continent, respectively, of urine and feces and six substages in stage 7, corresponding to the loss of speech, ambulation, and other motor capacities, are assessed. The Neuropsychiatric Inventory²⁴ assesses neuropsychiatric disturbances with a 12-item scale based on information from the caregiver regarding the patient's behavior and associated distress felt by the caregiver. The scores range from 0 to 144 for the patient-assessment rating and from 0 to 60 for the caregiver-distress rating, with 0 indicating the optimum in each case. The Resource Utilization in Dementia²⁵ instrument was designed to assess the burden on the caregiver and to provide Alzheimer's disease-related health economics data through structured interviews with caregivers. To assess the clinical relevance of treatment effects further, a multifactor responder analysis was predefined.

Measures of safety, assessed at specified intervals, included neurologic and physical examinations, measurement of vital signs, electrocardiography, laboratory tests (hematologic tests, blood chemical values, and urinalysis), and recording of adverse events.

STATISTICAL ANALYSIS

The main efficacy analysis was based on the randomized patients who received at least one assessment after base line. This analysis included both those who completed the study and those who discontinued their assigned treatment prematurely. For the latter, the efficacy observation at week 28 was imputed from the last available observation carried forward.²⁶ Three additional analyses were also performed to adjust for missing values. One analysis was identical to the primary analysis, except that the actual retrieved-dropout values at week 28 were used when available. A second analysis included patients for whom no value after base line was available in addition to the intention-to-treat population and assumed no change in the outcome

measures for these patients. In the third analysis, missing values were replaced for those with no value after base line by the mean observed value for decline in the placebo group. An observed-cases analysis was also performed based on data for all randomized patients who were available for evaluation at week 28.

Efficacy outcomes were analyzed by application of the Wilcoxon–Mann–Whitney test for independent samples to the change from base line. There were no interim analyses. The prespecified group with an individual response was defined as the patients who improved or had no deterioration on the CIBIC-Plus and who improved or had no deterioration on either the ADCS-ADLsev or the Severe Impairment Battery. All patients were included in the safety analysis. All reported P values are two-sided.

RESULTS

STUDY POPULATION

Of 345 patients screened between August 1998 and April 1999 at 32 U.S. centers, 252 were randomly

assigned to study groups. Seventy-one of the patients (42 of the 126 assigned to placebo and 29 of the 126 assigned to memantine) discontinued their assigned treatment before week 28, and the remaining 181 completed the double-blind portion of the study. Five patients were excluded from the analysis of the ADCS-ADLsev results and 16 from the analysis of the CIBIC-Plus results because they had not been assessed after the base-line assessment. The mean (\pm SD) duration of treatment for both groups was 24 \pm 8 weeks. Only 5 of the 71 patients who left the study returned for a retrieved-dropout visit at week 28. Premature discontinuations were due to adverse events in 22 of the patients in the placebo group (17 percent) and 13 of the patients in the memantine group (10 percent). Other major reasons for discontinuation included the patient's refusal of ongoing participation (14 patients receiving placebo [11 percent] and 12 patients receiving memantine [10 percent]), death (4 patients receiving placebo [3 percent] and 1 patient receiving memantine [1 percent]), protocol violation (3 patients receiving placebo [2 percent] and 3 patients receiving memantine [2 percent]), and change of caregiver (2 patients receiving placebo [2 percent] and none receiving memantine). Patients could have multiple reasons for discontinuation.

The base-line characteristics were similar in the two treatment groups (Table 1). Of the randomized patients, 67 percent were female, and the mean age was 76 years. The mean base-line score on the Mini-Mental State Examination for the study population was 7.9.

EFFICACY

The base-line scores and the results based on analyses with the last observation carried forward and analyses of observed cases for the efficacy variables are shown in Table 2. The CIBIC-Plus ratings at the end point (mean difference between the groups, 0.3; P=0.06) and week 28 (mean difference, 0.3; P=0.03) supported the effectiveness of memantine (Fig. 1A).

The total ADCS-ADLsev scores at base line were similar in the two groups (27.4 in the placebo group and 26.8 in the memantine group) (Table 2). At the end point and at week 28 (Fig. 1B), there was significantly less deterioration in the memantine group than in the placebo group (in the analysis with the last observation carried forward, the mean difference was 2.1 [P=0.02]; in the observed-cases analysis, the mean difference was 3.4 [P=0.003]).

Table 1. Base-Line Characteristics of the Intention-to-Treat Population.*

Characteristic	Memantine (N=126)		Placebo (N=126)		Total (N=252)
	Completed Study (N=97)	Did Not Complete Study (N=29)	Completed Study (N=84)	Did Not Complete Study (N=42)	
Sex — no. (%)					
Female	70 (72.2)	21 (72.4)	55 (65.5)	24 (57.1)	170 (67.5)
Male	27 (27.8)	8 (27.6)	29 (34.5)	18 (42.9)	82 (32.5)
Age — yr	75.5 \pm 8.16	77.3 \pm 9.17	75.8 \pm 7.28	77.5 \pm 8.61	76.1 \pm 8.07
Education — yr	12.3 \pm 3.06	13.0 \pm 3.14	12.9 \pm 3.14	11.7 \pm 2.91	12.5 \pm 3.09
Race — no. (%)					
White	85 (87.6)	27 (93.1)	75 (89.3)	40 (95.2)	227 (90.1)
Black	4 (4.1)	1 (3.4)	4 (4.8)	2 (4.8)	11 (4.4)
Other	8 (8.2)	1 (3.4)	5 (6.0)	0	14 (5.6)
MMSE score	7.8 \pm 3.76	7.6 \pm 3.67	8.1 \pm 3.60	7.9 \pm 3.54	7.9 \pm 3.64
GDS stage — no. (%)					
5	46 (47.4)	13 (44.8)	41 (48.8)	12 (28.6)	112 (44.4)
6	51 (52.6)	16 (55.2)	43 (51.2)	30 (71.4)	140 (55.6)

* The intention-to-treat population included all randomized patients. Plus–minus values are means \pm SD. MMSE denotes Mini-Mental State Examination, and GDS Global Deterioration Scale.

The Severe Impairment Battery showed significant differences favoring memantine ($P < 0.001$ with the last observation carried forward, $P = 0.002$ for observed cases) (Fig. 2A). On the basis of the predetermined definition of a response in the study protocol, 29 percent of the patients receiving memantine and 10 percent of those receiving placebo had a response ($P < 0.001$).

Memantine-treated patients showed significantly less deterioration in their functional Alzheimer's disease stage, as measured by the Functional Assessment Staging score ($P = 0.02$ with the last observation carried forward, $P = 0.007$ for observed

cases) (Fig. 2B). In the analysis of the intention-to-treat population with the last observation carried forward and at week 28 no significant differences were observed between treatment groups in the Mini-Mental State Examination score, Global Deterioration Scale stage, or Neuropsychiatric Inventory score.

Additional analyses were performed with different strategies used for missing values, as described above. The results were unchanged in each of these analyses.

A subgroup analysis examined whether efficacy was seen in both patients with moderate Alzheimer's

Table 2. Results of the Efficacy Analysis.*

Measure	Base Line		Analysis with Last Observation Carried Forward (Change from Base Line at End Point)			Analysis of Observed Cases (Change from Base Line at Week 28)		
	Memantine	Placebo	Memantine	Placebo	P Value†	Memantine	Placebo	P Value†
CIBIC-Plus‡								
Score	NA	NA	4.5±1.12	4.8±1.09	0.06	4.4±1.12	4.7±1.13	0.03
No. of patients	126	126	118	118		97	84	
ADCS-ADLsev§								
Score	26.8	27.4	-3.1±6.79	-5.2±6.33	0.02	-2.5±6.27	-5.9±6.78	0.003
No. of patients	126	126	124	123		97	84	
SIB								
Score	65.9	68.3	-4.0±11.34	-10.1±13.50	<0.001	-4.5±11.48	-10.2±12.66	0.002
No. of patients	126	126	124	123		96	83	
MMSE								
Score	7.7	8.1	-0.5±2.40	-1.2±3.02	0.18	-0.6±2.61	-0.9±3.09	0.68
No. of patients	126	126	124	124		97	82	
FAST¶								
Score	2.8	2.8	0.2±1.24	0.6±1.39	0.02	0.1±1.24	0.5±1.38	0.007
No. of patients	126	126	121	118		97	84	
GDS								
Score	5.5	5.6	0.1±0.47	0.2±0.48	0.11	0.1±0.49	0.2±0.48	0.16
No. of patients	126	126	121	119		97	84	
NPI								
Score	21.4	19.5	0.5±15.76	3.8±16.06	0.33	0.1±15.92	2.9±16.13	0.60
No. of patients	126	126	120	119		97	84	

* CI denotes confidence interval, CIBIC-Plus Clinician's Interview-Based Impression of Change Plus Caregiver Input, NA not applicable, ADCS-ADLsev Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (modified for severe dementia), SIB Severe Impairment Battery, MMSE Mini-Mental State Examination, FAST Functional Assessment Staging, GDS Global Deterioration Scale, and NPI Neuropsychiatric Inventory. The analysis with the last observation carried forward was performed with the intention-to-treat population. For this analysis, the numbers of patients fulfilling the intention-to-treat criteria are given in parentheses. The observed-cases analysis was performed with 181 patients observed at week 28. Plus-minus values are means ±SD.

† P values are based on the Wilcoxon-Mann-Whitney test for between-treatment comparisons.

‡ The CIBIC-Plus is a change score. By design the base-line score, "no change," is set at 4.00. Higher values at subsequent measurements indicate worsening. The end-point and week 28 values are actual mean ratings. The 95 percent confidence intervals for the differences between groups were -0.51 to 0.02 for the change from base line at the end point and -0.69 to -0.03 for the change from base line at week 28.

§ The 95 percent confidence intervals for the differences between groups were 0.49 to 3.78 for the change from base line at the end point and 1.45 to 5.28 for the change from base line at week 28.

¶ The FAST scores were calculated by enumerating the FAST stages and substages as follows: stage 3 (a score of -2) through 5 (0) and substage 6a (1) through substage 7f (11).¹⁷

|| The NPI scores are from the patient assessments.

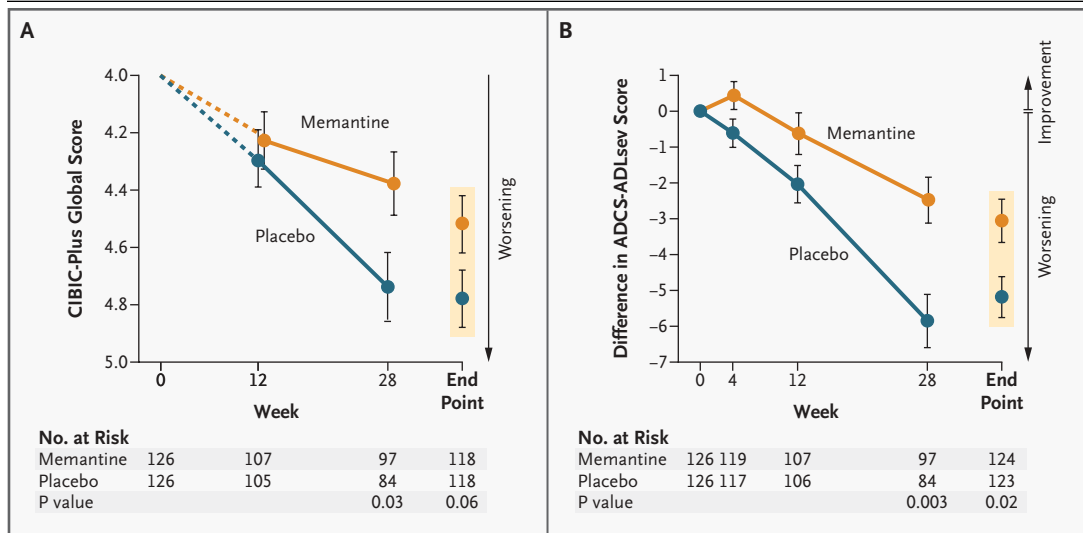


Figure 1. Primary Efficacy Variables.

The mean (\pm SE) scores at each specified time in the observed-cases analysis are shown. The boxes indicate the mean (\pm SE) at the end point in the analysis with the last observation carried forward in the intention-to-treat population. Panel A shows the change from base line in the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) global scores. Panel B shows the change from base line in the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory, modified for severe dementia (ADCS-ADLsev).

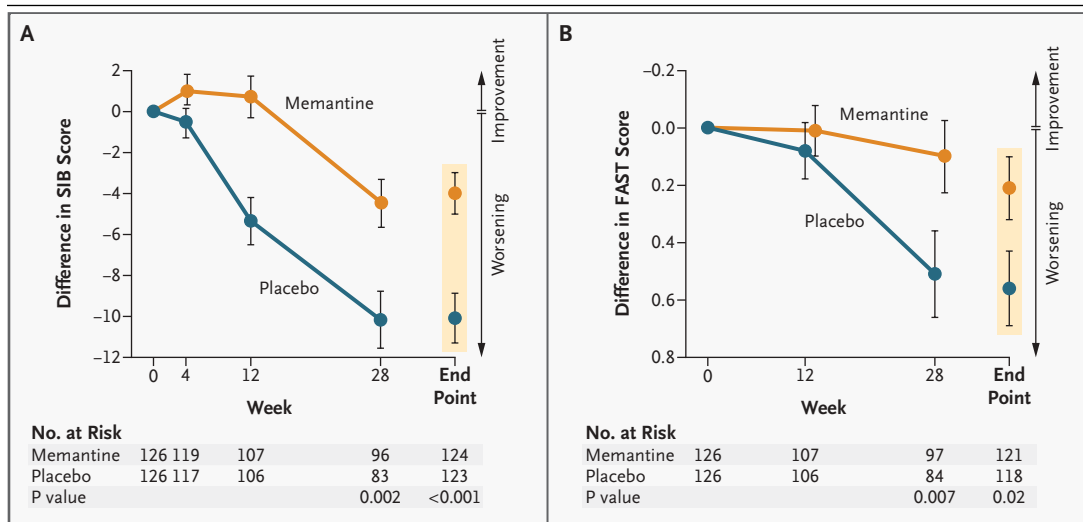


Figure 2. Other Efficacy Variables.

The mean (\pm SE) scores at each specified time in the observed-cases analysis are shown. The boxes indicate the mean (\pm SE) at the end point in the analysis with the last observation carried forward in the intention-to-treat population. Panel A shows the change from base line in Severe Impairment Battery (SIB) scores. Panel B shows the change from base line in Functional Assessment Staging (FAST) scores, calculated by enumerating the stages and substages as follows: stage 3 (-2) through stage 5 (0) and substage 6a (1) through substage 7f (11).

disease (Mini-Mental State Examination score, 10 to 14) and those with severe Alzheimer's disease (Mini-Mental State Examination score, less than 10). A benefit of memantine as compared with placebo was suggested for all outcome measures in both groups.

The required caregiver time, as assessed by the Resource Utilization in Dementia score, was analyzed in the intention-to-treat population with the last observation carried forward. The result was statistically significant, indicating that caregivers spent less time with patients receiving memantine (difference between treatment groups, 45.8 hours per month; 95 percent confidence interval, 10.37 to 81.27; $P=0.01$).

SAFETY AND TOLERABILITY

As expected in this population with moderate-to-severe illness, the majority of patients had adverse events during the study (84 percent with memantine and 87 percent with placebo). However, most adverse events were mild to moderate in severity and were either not related or unlikely to be related to the study medication (Table 3). The incidence rates for the frequently reported adverse events in the memantine group were no more than 2 percent higher than in the placebo group. There were no clinically relevant differences between patients in the memantine and placebo groups in base-line assessments of clinical laboratory values, electrocardiographic results, or measurements of vital signs.

More patients receiving placebo than patients receiving memantine discontinued the study prematurely because of adverse events (22 [17 percent] vs. 13 [10 percent]). Agitation was the most common reason for discontinuation (7 percent of those receiving placebo and 5 percent of those receiving memantine). Serious adverse events were reported in 23 patients receiving placebo (18 percent) and 16 patients receiving memantine (13 percent). There were seven deaths, two of which occurred in the memantine group. Two of these patients died within the 30-day period after the last dose of study medication. Most of the serious adverse events, including all of the deaths, were considered to be unrelated to the study medication.

DISCUSSION

This study provides evidence that modulation of NMDA receptors to reduce glutamate-induced excitotoxicity alleviates the symptoms of Alzheimer's

Table 3. Most Frequently Reported Adverse Events.*

Adverse Event	Memantine (N=126)	Placebo (N=126)
	<i>no. of patients (%)</i>	
Any adverse event	106 (84)	109 (87)
Agitation	23 (18)	40 (32)
Urinary incontinence	14 (11)	14 (11)
Urinary tract infection	7 (6)	17 (13)
Insomnia	13 (10)	10 (8)
Diarrhea	12 (10)	10 (8)

* Adverse events occurring in at least 10 percent of the patients in either treatment group are reported.

disease. This novel neurochemical approach is distinct from the cholinomimetic mechanism of all currently approved treatments for Alzheimer's disease.

This trial studied patients whose moderate-to-severe Alzheimer's disease compromised their ability to perform both instrumental and basic activities of daily living independently.¹⁷ More than 95 percent of patients were in Functional Assessment Staging stage 6. All patients had difficulty putting on clothing independently, and many also had difficulties with handling the mechanics of bathing and toilet use, and some patients also had difficulties maintaining continence. The significant differences observed in favor of the memantine group on the ADCS-ADLsev, the Functional Assessment Staging ratings, and the Severe Impairment Battery suggest reduced decline in these critical capacities, which was apparent in the global assessment of the patients (CIBIC-Plus in the observed-cases analysis).

The clinical relevance of treatment effects has been an issue in all trials of medication for Alzheimer's disease. Point differences between drug- and placebo-treated patients on quantitative scales do not necessarily indicate that these effects are clinically meaningful. Response analyses (rates of individual response) are often performed to illustrate the clinical relevance of results. In the present study, a significant difference in the predefined criterion for a response, which incorporated multiple end points, was observed. The treatment effects seen in the areas of cognition and function seemed to translate into improvements in the patients' behavior (less agitation in the adverse-events reports) and

mitigation of the burden on caregivers (fewer hours spent assisting the patient).

The results of the present study cannot be directly compared with those of studies of other anti-dementia drugs (tacrine, donepezil, rivastigmine, and galantamine); virtually all published studies with these compounds have been performed in patients with mild-to-moderate Alzheimer's disease. An exception is a recent study of donepezil by Feldman et al.²⁷ However, even that study included patients with less severe disease (the mean Mini-Mental State Examination score at base line was 12) than those in the present trial, whose mean Mini-Mental State Examination score at base line was less than 8. The treatment effects of memantine in the present study and donepezil in the study by Feldman et al. are of similar size for the common end points, the CIBIC-Plus and the Severe Impairment Battery. Cholinergic compounds have gastrointestinal side effects, whereas the tolerability of memantine in this study was found to be excellent. Future studies will need to examine whether memantine treatment and cholinergic treatment may ultimately prove to be complementary or even synergistic.

There are notable limitations to this study. The dropout rate for the total study population was 28 percent, which is probably attributable to the relatively severe stage of disease in the study patients. The withdrawal rate was higher in the placebo group (33 percent) than in the memantine group (23 percent). The failure to obtain information at week 28 for the majority of patients who discontinued the study prematurely limits the interpretation of the results. However, the average duration of randomly assigned therapy for patients in this 28-week trial was 24 weeks for both study groups. In three analyses, the effects of different strategies for replacing missing observations for all patients assigned to treatment were investigated, and the results did not change materially. Thus, our data indicate that memantine reduces decline in patients with moderate-to-severe Alzheimer's disease.

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APPENDIX

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