Memantine Treatment in Patients With Moderate to Severe Alzheimer Disease Already Receiving Donepezil
A Randomized Controlled Trial

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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 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

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-ADL19). 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-ADL19 (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.
MEMANTINE AND DONEPEZIL IN ALZHEIMER DISEASE

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 B12 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 Score9 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-ADL19) 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...
higher levels of cognitive ability. The SIB was assessed at baseline and all sub-
sequent 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 appropri-
ate for the assessment of later stages of dementia (ie, the level of indepen-
dence 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 was administered as an inter-
view to the patient's caregiver and
focused on the performance of each
activity of daily living during the pre-
vious 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 Impres-
sion 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 adminis-
tered according to the format of the Al-
zheimer Disease Cooperative Study–
Clinician’s Global Impression of
Change. The CIBIC-Plus is used to
assess the effect of medication on over-
all clinical status in patients with de-
mentia, incorporating caregiver observa-
tions as well as patient inter-
views. Change is rated on a scale from
1 (marked improvement) to 7 (marked
worsening). A global assessment of se-
verity of illness was made at baseline;
the CIBIC-Plus was assessed at all post-
baseline visits.

The NPI was designed to assess the
frequency and severity of behavioral
symptoms in patients with dementia,
based on an interview of the care-
giver.15 The 12-item version of the in-
strument 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 ob-
servable aspects of cognition, func-
tion, and behavior.16 A higher score re-
ffects worse function. The BGP care
dependency subscale reflects cogni-
tive and functional characteristics as-
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 out-
come.17 The FAST evaluates a pa-
tient's ability to perform daily and nec-
essary 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 ad-
ministered at baseline and the final visit.

Concomitant medications and vital
signs were recorded at every visit; ad-
verse events were recorded at baseline
and all subsequent visits; and labora-
tory tests, electrocardiograms, and physi-
ical 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 pa-
tients in each treatment group pro-
vided 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 random-
ized population consisted of all pa-
tients randomized into the study
(n=404); the safety population con-
sisted of all randomized patients who
received at least 1 dose of double-
blind study medication (n=403); the
modified intent-to-treat population
specied 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 in-
tent-to-treat population. Primary effi-
cacy analyses were conducted by us-
ing the last observation carried forward
(LOCF) approach for missing data im-
putation. Supportive analyses were per-
formed by using the observed case ap-
proach. Change from baseline was com-
pared between memantine and pla-
cebo 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 mea-
sures, the Cochran-Mantel-Haenszel
statistic using modified Ridit scores
(Van Elteren test) controlling for study
center was used to compare distribu-
tions between memantine and pla-
cebo groups. No interim analyses were
performed. SAS version 6.12 (SAS In-
itute, Cary, NC) was used for all
analyses.

RESULTS
Participants
The trial profile is summarized in
FIGURE 1. Of the 404 patients who en-
tered the study, 201 were randomized
to placebo and 203 were randomized
to memantine (1 in the memantine
group withdrew consent before receiv-
ing treatment). No patients were ex-
cluded during the placebo lead-in pe-
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 dis-
continued because of changes in ad-
ministration of donepezil.

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

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...and anti-inflammatory agents (21% and iolytics/neuroleptics (26% and 22%), reducing agents (23% and 25%), anx-
eral supplements (22% and 27%), lipid-
tine, respectively, were vitamins (74% and 73%), other (10% and 9%), and pulmo-
tvascular (20% and 23%), abdomen
(12% and 17%), head/neck (6% and 9%), other (10% and 9%), and pulmo-
ary (3% and 5%). The most frequent medication classes (>20%) used dur-
ting treatment with placebo and meman-
tine, 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%), anx-
lotics/neuroleptics (26% and 22%), and anti-inflammatory agents (21% and
24%). There were no statistically signifi-
cent differences between groups in the
umber or type of medical disor-
ders 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 treat-
ment with memantine vs treatment with
placebo were observed on all primary
and secondary outcome measures as pre-
sented. TABLE 2 summarizes primary
and secondary efficacy outcomes at week
24 and at end point, using both the ob-
erved case and LOCF analytical ap-
proaches.

Primary Outcomes
Analyses using the LOCF approach
showed a statistically significant ben-
et of memantine treatment vs treat-
ment with placebo on the SIB (P<.001)
and the ADCS-ADL 19 (P=.03), as did
analyses using the observed case ap-
proach (P<.001 for SIB; P=.02 for
ADCS-ADL 19 ). Post hoc analyses in-
cluding all randomized patients also
showed statistically significant ben-
etits 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 signifi-
cent differences between the meman-
tine and placebo groups at all visits be-
ginning at week 8; the mean SIB values
for the patients receiving memantine re-
mained above baseline throughout the
trial. Figure 2 also depicts the mean
change in total ADCS-ADL 19 from base-
line by visit and at end point by using
observed case and LOCF, respec-
tively, showing a statistically signifi-
cent difference (P<.05) from placebo
beginning at week 4.

Secondary Outcomes
A CIBIC-Plus score was used as a mea-
sure 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 un-
changed 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 significa-
tly lower for the memantine group
compared with the placebo group at
week 24 (P=.01 with observed case
analysis and P=.002 with LOCF), rep-
resenting fewer behavioral distur-
bances 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 ob-
erved 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 discontinu-
ation in 1.5% of patients in the pla-
celebo group and 2% in the meman-
tine group.

Adverse events occurred in 72% of
the placebo and 78% of the meman-
tine 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 oc-
curred 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=.09). By similar criteria, lower inci-
cences 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-

FIGURE 1.
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>
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<tr>
<th>Table 1. Baseline Demographic and Clinical Characteristics*</th>
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<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
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<tr>
<td>Age, mean (SD), y</td>
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<tr>
<td>Weight, mean (SD), kg</td>
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<tr>
<td>White race</td>
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<tr>
<td>MMSE score, mean (SD)</td>
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<tr>
<td>Duration of donepezil treatment, mean (SD), wk</td>
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<tr>
<td>Donepezil dose, mean (SD), mg</td>
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<tr>
<td>Any concurrent medical condition</td>
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<td>Any concurrent medication during treatment</td>
</tr>
<tr>
<td>Tocopherol</td>
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<tr>
<td>Multivitamins</td>
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<tr>
<td>Acetylsalicylic acid</td>
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<tr>
<td>Ascorbic acid</td>
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<tr>
<td>Paracetamol</td>
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<tr>
<td>Ginkgo biloba</td>
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<td>Calcium</td>
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*Data are No. (%) unless otherwise specified. One randomized patient discontinued the study prior to receiving any treatment and was not included in the analyses.

<table>
<thead>
<tr>
<th>Table 2. Efficacy Outcomes at Week 24 (Observed Case) and at End Point (LOCF)*</th>
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<tbody>
<tr>
<td><strong>Outcome Measure</strong></td>
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<tr>
<td>Placebo</td>
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<tr>
<td>SIB</td>
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<tr>
<td>Na of patients</td>
</tr>
<tr>
<td>ADCS-ADL-19</td>
</tr>
<tr>
<td>Na of patients</td>
</tr>
<tr>
<td>CIBIC-Plus†</td>
</tr>
<tr>
<td>NPI</td>
</tr>
<tr>
<td>Na of patients</td>
</tr>
<tr>
<td>BGP Care Dependency Subscale</td>
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</tbody>
</table>

*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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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. 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 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 (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—
Alzheimer Disease and Related Disorders Association criteria and who were not permitted to receive a cholinesterase inhibitor.\textsuperscript{7} Significant benefit of memantine treatment was observed on the ADCS-ADL\textsubscript{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\textsuperscript{7} were more cognitively impaired (mean baseline MMSE of 7.9\,), more functionally impaired (mean baseline ADCS-ADL\textsubscript{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).\textsuperscript{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 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.\textsuperscript{8} Preclinical studies show that memantine does not affect the inhibition of acetylcholinesterase by donepezil, nor does it bind to muscarinic receptors.\textsuperscript{19-21} Furthermore, in healthy volunteers, no pharmacokinetic or pharmacodynamic interactions were observed between memantine and donepezil.\textsuperscript{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.\textsuperscript{23,24}

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.\textsuperscript{25,26} Memantine may block pathological activation of NMDA receptors while dissociating from the NMDA re-

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

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

\textsuperscript{*}Patients may have reported more than 1 adverse event.
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Author Contributions: Dr Tariot had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tariot, Gergel. Acquisition of data: Tariot, Farlow, McDonald. Analysis and interpretation of data: Tariot, Farlow, Grossberg, Graham, McDonald, Gergel.

Drafting of the manuscript: Tariot, Farlow, Grossberg, Graham, Gergel.

Critical revision of the manuscript for important intellectual content: Tariot, Farlow, Grossberg, Graham, McDonald, Gergel. Statistical expertise: Gergel. Obtained funding: Gergel. Administrative, technical, or material support: Tariot, Farlow, Graham, McDonald, Gergel.

Study supervision: Tariot, Farlow, Graham, McDonald, Gergel.

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REFERENCES