Antidepressant Augmentation Using the *N*-Methyl-D-Aspartate Antagonist Memantine: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Objective: Intravenous *N*-methyl-D-aspartate (NMDA) antagonists have shown promising results in rapidly ameliorating depression symptoms, but placebo-controlled trials of oral NMDA antagonists as monotherapy have not observed efficacy. We conducted a randomized, double-blind, placebo-controlled trial of the NMDA antagonist memantine as an augmentation treatment for patients with *DSM-IV* major depressive disorder.

Method: Adult outpatients with major depressive disorder and partial response or nonresponse to their current antidepressant (as indicated by a 17-item Hamilton Depression Rating Scale score of ≥ 16 at baseline) were randomized (from July 2006–December 2011) to add memantine (flexible dose 5–20 mg/d, with all memantine group participants reaching the dose of 20 mg/d) (n = 15) or placebo (n = 16) to their existing treatment for 8 weeks. The primary outcome, change in Montgomery-Asberg Depression Rating Score (MADRS), was evaluated with repeated-measures mixed effects models using last-observation-carried-forward methods. Secondary outcomes included other depression and anxiety rating scales, suicidal and delusional ideation, and other adverse effects.

Results: 84% of participants completed the trial, including 93% of participants receiving memantine. Participants receiving memantine did not show a statistically or clinically significant change in MADRS scores compared to placebo, either over the entire study (β = 0.133, favoring placebo, *P* = .74) or at study completion (week 8 mean [SD] MADRS score change = −7.13 [6.61] [memantine]; −7.25 [11.14] [placebo]; *P* = .97). A minimal to small effect size (comparing change to baseline variability) favoring placebo was observed (Cohen *d* = 0.19). Similarly, no substantial effect sizes favoring memantine nor statistically significant between-group differences were observed on secondary efficacy outcomes.

Conclusions: This trial did not detect significant statistical or effect size differences between memantine and placebo augmentation among nonresponders or poor responders to conventional antidepressants. While the small number of participants is a limitation, this study suggests memantine lacks substantial efficacy as an augmentation treatment for major depressive disorder.

Trial Registration: ClinicalTrials.gov identifier: NCT00344682

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N-methyl-D-aspartate (NMDA) antagonists have garnered intense interest as a novel therapy for depression since the pivotal findings that ketamine infusions produce rapid, robust, and sustained improvement in depression symptoms.[1,2] However, ketamine's use is limited by the requirement for intravenous administration, the transient dissociative and perceptual disturbances that frequently accompany its administration,[3] and the challenges of preserving recovery of symptoms over longer than a few weeks after a single infusion.[4] The NMDA antagonist memantine, while of lower affinity, faster-dissociating, and exhibiting other pharmacologic differences than ketamine,[5] also has fewer side effects and is orally administered. Memantine is also already approved by the US Food and Drug Administration (FDA) for treatment of another neuropsychiatric disorder, Alzheimer's dementia, making it an attractive candidate for investigation.

An initial trial of memantine as monotherapy for depression was terminated early when memantine treatment failed to separate from placebo based on response or remission rate.[6] Although this monotherapy trial did not demonstrate benefit, there are animal findings suggesting that noncompetitive NMDA receptor antagonists such as memantine work synergistically in combination with antidepressants,[7] providing a rationale for evaluating memantine specifically as an augmentation treatment. In this article, we report the results of a randomized trial testing the hypothesis that memantine would have greater efficacy than placebo in reducing symptoms of major depressive disorder when used to augment antidepressant treatment.

METHOD

We conducted an 8-week randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov identifier: NCT00344682) of memantine augmentation treatment in outpatients at the University of Massachusetts Medical School, Worcester, Massachusetts, from July 2006 to December 2011. Participants who were incomplete responders or nonresponders to their current antidepressant were randomized 1:1 to add on either flexibly dosed memantine (5–20 mg/d) or placebo to their current antidepressant using a block randomization design by the University of Massachusetts Medical School Investigational Pharmacy. A printed list computer generated from the Web site www.randomization.com was used, with allocation concealed from participants, research staff, and investigators. All participants began on 5 mg/d, and the dose was increased by 5 mg/d at weekly intervals, as tolerated, to a maximum dose of 20 mg/d. In the absence of limiting adverse effects, this dose was achieved approximately 22 days into the 8-week (56-day) trial.

Clinical Points

- This placebo-controlled, double-blind randomized trial, although small, did not find efficacy for the oral *N*-methyl-D-aspartate antagonist memantine as an augmentation treatment in major depressive disorder.
- This study joins a placebo-controlled monotherapy trial and several other randomized controlled trials in suggesting a lack of efficacy for memantine against depression symptoms.

The original target recruitment was 25 patients per study arm. However, the study was terminated prior to full enrollment in 2012 at funder request, resulting in a final enrollment of 31 patients. The study was approved by the University of Massachusetts School of Medicine Institutional Review Board.

Study Population

Study participants were recruited through clinician referral and posted and radio advertising, with the majority of patients recruited through clinician referral within our single-site, tertiary-care medical center. Inclusion criteria included adults aged 18 to 85 years; the ability to provide written informed consent; diagnosis of a current or partially remitted major depressive episode according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (*DSM-IV-TR*)[9] criteria using the Mini-International Neuropsychiatric Interview (MINI)[10]; and a Hamilton Depression Rating Scale (17 item)[11,12] score of ≥ 16. Participants received 1 or more of the following medications at the following stable dosages for the previous 25 days or more prior to study entry: mirtazapine (≥ 15 mg/d); fluoxetine, paroxetine, or citalopram (≥ 20 mg/d); paroxetine controlled release (≥ 25 mg/d); sertraline or desvenlafaxine extended release (≥ 50 mg/d); duloxetine (≥ 60 mg/d); fluvoxamine extended release (≥ 100 mg/d); venlafaxine or venlafaxine extended release (≥ 150 mg/d); fluvoxamine (≥ 200 mg/d); or bupropion or bupropion sustained release (≥ 300 mg/d). These dosages were based on "adequate treatment" definitions drawn from the Antidepressant Treatment History form,[13] except for paroxetine controlled release, fluvoxamine extended release, desvenlafaxine extended release, and duloxetine. For these antidepressants, approximately comparable dosages were determined by the study investigators. Participants were not permitted to make antidepressant dosage changes during the 8 weeks of trial participation. Written informed consent was obtained from all participants prior to any study assessments.

Exclusion criteria included a *DSM-IV-TR*[9] diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorder, current mood stabilizer or antipsychotic use (except lithium as an augmentation agent for major depressive disorder); a history of alcohol or drug abuse or dependence within 6 months prior to study enrollment; a history of electroconvulsive therapy within 3 months prior to study enrollment; a history of seizures; Mini-Mental State Examination[14] score of < 21 (indicating moderate dementia); or active suicidal ideation, defined as either a score of 2 on item 4 or 5 of the Beck Scale for Suicide Ideation[15] or a score of 3 on the Quick Inventory of Depressive Symptomatology-self-report scale (QIDS-SR) suicidal thoughts item.[16] To maximize generalizability, only medications clearly contraindicated for use with memantine (eg, other NMDA antagonists, such as amantadine or dextromethorphan) were restricted. There were no restrictions on established anxiolytic or insomnia treatments or upon initiation or continuation of psychotherapy. Prespecified criteria for termination of participation in the trial ("rescue criteria") were as follows: occurrence of a score of 3 on the QIDS-SR suicidal thoughts item, a score of 5 or 6 on the Montgomery-Asberg Depression Rating Scale (MADRS)[8] suicidal thoughts item (item 10), a worsening of > 35% on MADRS score from baseline, or active alcohol abuse or illicit substance use.

Procedures

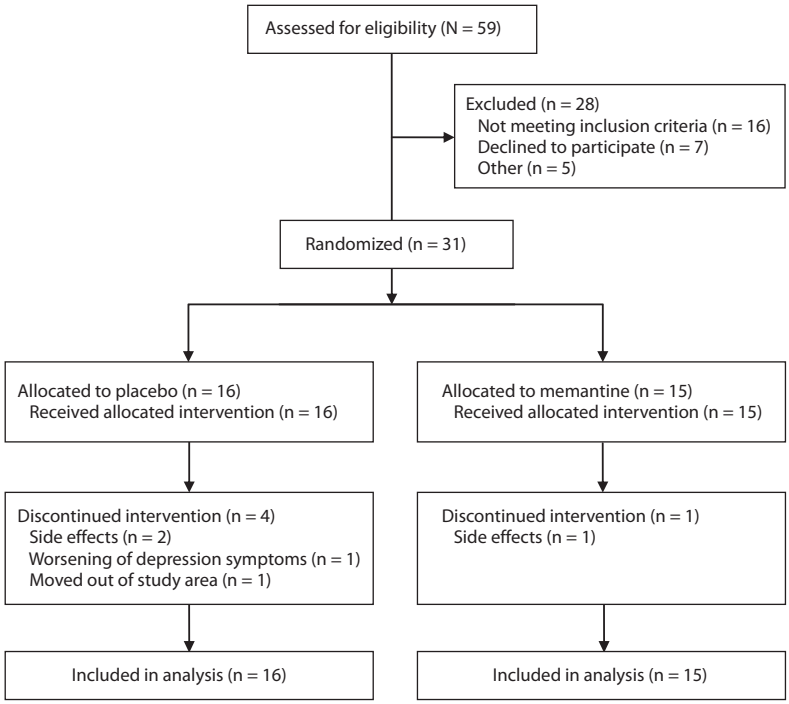
Patients were evaluated by a research psychiatrist and a research coordinator at each study visit. Study drug and placebo were dispensed from the investigational pharmacy. Participants were evaluated at baseline and at weeks 1, 2, 3, 4, 6, and 8 using the MADRS and the self-rated QIDS-SR. Adverse events were recorded at each visit. At baseline and at weeks 4 and 8, the Hamilton Anxiety Rating Scale[17] and the Schedule for Affective Disorders and Schizophrenia[18] delusional severity item were also administered. At baseline and at 8 weeks, and as needed during the protocol, the Beck Scale for Suicide Ideation was administered. Brief (approximately 45 minutes) cognitive testing was also performed at baseline and week 8 (results not reported here).

After completion of the trial, participants were tapered off their study drug over 1–3 weeks. All patients, research staff, and clinical investigators remained blinded throughout the trial, with the exception of an unintentional unblinding of 1 of the principal investigators (E.G.S.) for a single participant receiving placebo who had completed the trial.

Statistical Analysis

We used *t* tests and Fisher exact tests, as appropriate, to describe demographic and clinical differences between the 2 treatment groups. The primary outcome was change in MADRS score over repeated measures (1 baseline and 6 treatment assessments), using participants' most recently observed MADRS scores for any missing assessments through study completion at 8 weeks (last observation carried forward [LOCF]). Secondary depression outcomes included change over repeated measures in MADRS score, using no imputation ("observed case" analysis) (ie, all available observations were used but no values were imputed for missing values), and change in QIDS-SR score (LOCF). Each analysis used intent-to-treat, repeated-measures, mixed-effects models with random intercepts and random slopes. Other secondary efficacy outcomes included change in Hamilton Anxiety Rating Scale score (LOCF) and MADRS

Figure 1. Screening, Randomization, and Disposition of Patients With Major Depressive Disorder Incompletely Responding to Antidepressant Therapy Who Were Randomly Assigned to Treatment Augmentation With Memantine or Placebo



response rate (defined as 50% reduction in MADRS score from baseline) and remission rate (defined as a MADRS score of 12 or less) at week 8, analyzed by Fisher exact tests. Safety analyses included change in the Beck Scale for Suicide Ideation and Schedule for Affective Disorders and Schizophrenia delusional scale, comparing baseline score to the maximum score obtained during treatment.

Results of "guess tests" (ie, guesses of treatment assignment made after trial completion) were analyzed by Fisher exact tests. All tests were 2-tailed, considered significant at $\alpha = .05$, and conducted using Stata/IC 12.1 for Mac (StataCorp, College Station, Texas), except the power estimates (Stata/IC 10.0 for Windows). Statistical power ($\alpha = .05$, $\beta = .80$) was estimated post hoc in terms of projected detectable effect size using estimates of mean changes, standard deviations, and correlations between observations from the data we obtained using an alternate repeated-measures design (repeated-measures analysis of covariance).

RESULTS

Of 59 patients screened by phone or in person, 31 (53%) were randomized to receive memantine (n = 15) or placebo (n = 16). All randomized participants received study medication and had at least 2 postbaseline assessments, and 84% of the participants completed the trial (Figure 1). One hundred percent of memantine and 50% of placebo recipients received a study medication dose of 20 mg/d during some portion of the trial. One participant receiving memantine dropped out due to side effects, while 4 participants receiving placebo dropped out due to adverse effects, worsening of depression symptoms, or movement out of the area. Although study enrollment was terminated early, randomization balanced patients effectively on all measured confounders (Table 1).

No significant differences were found between memantine augmentation and placebo augmentation in our primary end point of change in MADRS score (LOCF) across all the repeated measures ($\beta = 0.133$, $P = .74$) (Table 2A), with the nonsignificant and modest score differences observed favoring placebo (Figure 2A). An alternative, observed case analysis of the MADRS data was also nonsignificant ($\beta = 0.497$, $P = .212$) (Figure 2B).

Mean (SD) MADRS score change (LOCF) for memantine recipients at week 8 was −7.13 (6.61); mean MADRS score change for placebo recipients was −7.25 (11.14) (Table 2B). A Cohen *d* effect size for change in MADRS score from baseline through week 8 of 0.19 (favoring placebo) was observed. A larger, although nonsignificant, change in MADRS score from baseline through study completion favoring placebo was observed for the nonimputed, observed case mixed model (−7.13 [6.61] [memantine] vs −10.75 [10.46] [placebo]), resulting in a medium-sized effect size (Cohen $d = 0.69$) favoring placebo. Both of these effect size estimates are larger than what simple comparisons of the change scores between memantine and placebo might suggest, since score changes for each treatment group were being compared to that group's baseline standard deviation[19] (which is a narrow ± 6.92 points for placebo recipients). A comparison of effect sizes based on final MADRS scores for the memantine and placebo groups would produce much more modest effect sizes favoring placebo (Cohen $d = 0.02$ [LOCF] and Cohen $d = 0.25$ [observed case]). A post hoc secondary analysis comparing baseline to week 8 MADRS change for patients with the greatest baseline depression severity also did not reveal differences favoring memantine (Table 2B).

Similarly, no statistically significant differences were observed for the other secondary depression outcome (QIDS-SR) in repeated-measures analysis ($\beta = -0.246$, $P = .22$) or at week 8 comparison (accompanied by a negligible effect size of −0.04). However, the QIDS-SR results do directionally favor memantine, and the difference in score change at week 8 shows a smaller, although still nonsignificant, *P* value than the MADRS outcomes ($P = .14$). Nevertheless, the changes in depression rating scales over time (Figure 2A–C) suggest a lack of substantial efficacy for memantine compared to placebo as measured by either QIDS-SR or MADRS.

The secondary end points of response and remission based on MADRS score also yielded nonsignificant results: 13.3% (n = 2) of participants receiving memantine had a response or remission by 8 weeks versus 18.8% (n = 3) of

Table 1. Baseline Characteristics of Patients With Major Depressive Disorder Assigned to Memantine or Placebo Augmentation of Antidepressant Treatment

Characteristic	Memantine Augmentation (n = 15)		Placebo Augmentation (n = 16)		*P* Value[a]
Demographics					
Gender (female), n %	8	53.33	11	68.75	.473
Age, mean SD, y	54.80	6.17	49.75	11.68	.147
Education, mean SD, y[b]	13.82	2.44	14.78	2.28	.380
Physiologic measure					
Body mass index, mean SD[c]	28.41	5.34	27.98	4.82	.834
Baseline and concomitant antidepressant treatment, n %[d]					
SSRIs	10	66.67	11	68.75	> .999
Citalopram/escitalopram	5	33.33	4	25.00	.704
Fluoxetine	4	26.67	2	12.50	.394
Fluvoxamine	0	0.00	1	6.67	> .999
Paroxetine	0	0.00	2	12.50	.484
Sertraline	1	6.67	2	12.50	> .999
SNRIs	3	20.00	4	25.00	> .999
Duloxetine	2	13.33	1	6.25	.600
Venlafaxine/desvenlafaxine	1	6.67	3	18.75	.600
Bupropion	4	26.67	3	18.75	.685
Mirtazapine	1	6.67	1	6.25	> .999
Tricyclic antidepressant[e]	2	13.33	0	0.00	.226
Desipramine[e]	2	13.33	0	0.00	.226
Combination treatment (receiving > 1 antidepressant)	4	26.67	3	18.75	.685
≥ Minimum adequate dose[f]	10	66.67	12	75.00	.704
Length of preceding antidepressant treatment, mo[g]					
≤ 3	2	16.67	1	8.33	> .999
≤ 12	6	0.50	3	0.25	.400
Other psychiatric medications (intended to treat depression), n %					
Dopaminergic stimulants	1	6.67	2	12.5	> .999
Nondopaminergic stimulants	1	6.67	2	12.5	> .999
Clinical rating scale score (baseline), mean SD					
Hamilton Depression Rating Scale (17-item)	22.60	4.73	21.69	5.47	.624
Montgomery-Asberg Depression Rating Scale	27.47	8.32	27.38	6.95	.974
Quick Inventory of Depressive Symptomatology, Self-Report	15.73	7.01	12.31	4.16	.107
Hamilton Anxiety Rating Scale[h]	23.33	6.81	24.07	9.17	.805
Mini-Mental State Examination	29.00	1.51	28.87	1.13	.786
Beck Scale for Suicide Ideation	2.27	4.33	1.63	3.07	.636

[a]Calculated by *t* test for continuous variables and Fisher exact test for dichotomous variables.
[b]Data missing for 11 participants: 4 assigned to memantine and 7 assigned to placebo.
[c]Data missing for 5 participants: 2 assigned to memantine and 3 assigned to placebo.
[d]Since antidepressant treatment at baseline did not change during the study, the same Table information applies to antidepressant treatment received throughout the study. Percentages do not equal 100% since some participants were receiving more than 1 antidepressant.
[e]Participants were required to be receiving a nontricyclic antidepressant, but 2 patients received desipramine in combination with a nontricyclic antidepressant.
[f]Determined as the length of time participants had been receiving their antidepressant of longest duration.
[g]Data missing for 7 participants: 3 assigned to memantine and 4 assigned to placebo.
[h]Data missing for 1 participant, assigned to placebo.
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

participants receiving placebo (Fisher exact test, $P > .999$). These results produce a nonsignificant number needed to treat favoring placebo of approximately 18.

No significant differences were observed when using the Hamilton Anxiety Rating Scale or the suicidal or delusional thinking scales or in any reported adverse effects (Table 3). Two serious adverse effects were reported that required hospitalization, both involving worsening of preexisting respiratory problems judged probably unrelated to study medication (1 participant received memantine and 1 participant received placebo).

The integrity of blinding was assessed through "guess tests" administered to participants, research coordinators, and study psychiatrists. No group was able to accurately distinguish memantine from placebo ($P > .05$ for all results), with the highest proportion of correct guesses only 57.1% (observed among participants receiving memantine).

DISCUSSION

In this placebo-controlled, flexibly-dosed randomized trial in which all participants assigned memantine received the highest approved dosage (20 mg/d), no statistically significant differences were observed between memantine and placebo as augmentation agents in incomplete responders or nonresponders to conventional antidepressants. The primary outcome, repeatedly measured change in MADRS

Table 2. Rating Scale Outcomes for Patients Assigned Memantine or Placebo Augmentation of Antidepressant Treatment

Rating Scale	β Coefficient[a]	*P* Value[b]
A.Rating Scale Changes From Mixed Effects Models Incorporating All Repeated Measures		
Primary outcome		
Change in MADRS score (LOCF; time × treatment interaction)	0.133[c]	.742
Secondary outcome		
Change in MADRS score (observed case analysis[d]; time × treatment interaction)	0.497[e]	.212
Change in QIDS-SR score (LOCF; time × treatment interaction)	−0.246[f]	.216

B. Rating Scale Changes (participant's final score minus baseline score) and Effect Sizes at Week 8/Study Termination	Memantine Augmentation (n = 15)		Placebo Augmentation (n = 16)			
	Mean	SD	Mean	SD	*P* Value[g]	Effect Size[h]
Primary outcome						
MADRS score (LOCF)[i]	−7.13	6.61	−7.25	11.14	.97	0.19
Secondary depression outcome						
MADRS score (observed case)[j]	−7.13	6.61	−10.75	10.46	.28	0.69
QIDS-SR score (LOCF)	−6.47	5.25	−3.69	5.00	.14	−0.04
Secondary anxiety outcome						
Hamilton Anxiety Rating Scale (LOCF)[k]	−4.13	5.11	−5.53	7.29	.55	0.00

[a]Negative coefficient equals greater decrease in the memantine group compared to the placebo group; positive coefficient equals greater decrease in the placebo group compared to the memantine group.
[b]Significance of treatment × time interaction term.
[c]The full model including this interaction term was 24.669 − 0.551 × treatment group − 0.776 × study week + 0.133 × treatment group × study week.
[d]Observed case equals all rating scale observations used, but observations were not carried forward (ie, no imputation).
[e]The full model including this interaction term was 25.351 − 1.149 × treatment group − 1.170 × study week + 0.497 × treatment group × study week.
[f]The full model including this interaction term was 11.030 + 2.276 × treatment group − 0.405 × study week − 0.246 × treatment group × study week.
[g]Calculated by *t* test of difference in mean score at week 8 minus mean score at baseline (for the observed case analysis, using the value for each participant at study completion if prior to week 8).
[h]Effect size *d* calculated as d_{IGPP} (IGPP = independent group, prebaseline and postbaseline) per formula and recommendations provided by Feingold[19]: *d* = mean change (memantine group)/$SD_{\text{memantine group at baseline}}$ − mean change (placebo group)/$SD_{\text{placebo group at baseline}}$. (SDs at baseline are provided in Table 1.) A positive effect size indicates a lower final mean score for placebo recipients than memantine recipients.
[i]A post hoc exploratory subanalysis was also performed examining change in mean MADRS score (LOCF) observed in participants with the greatest initial depression severity (baseline MADRS score ≥ the median baseline score): −8.56 (95% CI, −13.28 to −3.28) (9 memantine recipients), −11.00 (95% CI, −23.65 to 1.65) (7 placebo recipients).
[j]Observed case equals all rating scale observations used, but observations not carried forward (no imputation). Therefore, rating scale score changes and effect sizes relate to the value at termination of study participation, whenever it occurred (ie, not necessarily at week 8).
[k]Baseline observation for 1 participant receiving placebo is missing (baseline mean determined without this participant), but week 8 observation for this participant was included in the analysis.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.

score, was statistically nonsignificant (*P* = .74) (although limited sample size restricts power) and had a minimal effect size at week 8 (Cohen *d* = 0.19), favoring placebo. The MADRS observed case repeated-measures analysis was also nonsignificant (*P* = .21), with a larger week 8 effect size favoring placebo. Response and remission rates were also nonsignificant and slightly favored placebo.

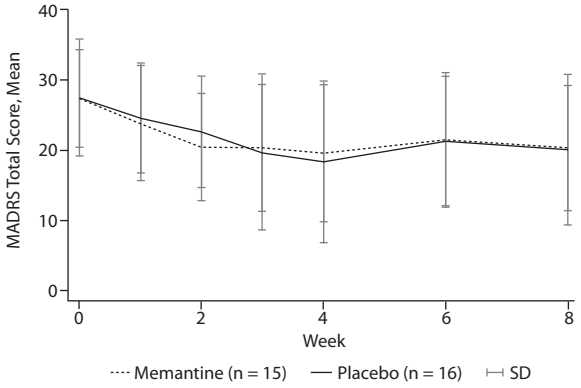
In contrast, change in self-rated depression (QIDS-SR) was also nonsignificant but favored memantine both in repeated-measures analysis and at week 8. However, interpretation of the change in QIDS-SR score is most likely complicated by the fact that this outcome had the greatest (albeit nonsignificant) baseline imbalance of any rating scale (3.4 points). This difference may have facilitated the observation of greater changes in QIDS-SR in the memantine group. The memantine group's baseline scores were also more variable (SD = 7.01 [memantine] vs SD = 4.16 [placebo]), resulting in an effect size observed at week 8 that was negligible (*d* = −0.04), despite the more sizable changes in QIDS-SR score observed for the memantine group.

Given the early termination of our trial, we derived post hoc power estimates for our final sample size, taking into account our repeated-measures design (which boosts power).[20] We estimate that our trial most likely had an ability to discriminate a Cohen *d* effect size of approximately 0.53. This is less power than would be desired. However, while both this study and the previous placebo-controlled trial[6] of memantine monotherapy in major depressive disorder were limited by an almost identically small sample size, it may be notable that both trials observed multiple outcomes that numerically favored placebo.

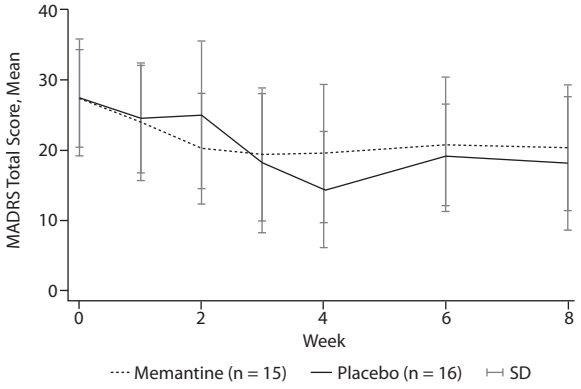
With a sample size falling between a typical phase 1 and phase 2 trial, our investigation might be viewed as consistent with the recently proposed "quick win, fast fail" approach to drug evaluation.[21] This approach emphasizes the value of small studies for boosting efficiency in drug development through a focus on detecting substantial effect sizes, not

Figure 2. Depression Rating Scale Scores for Patients With Major Depressive Disorder Assigned to Memantine or Placebo Augmentation of Antidepressant Treatment

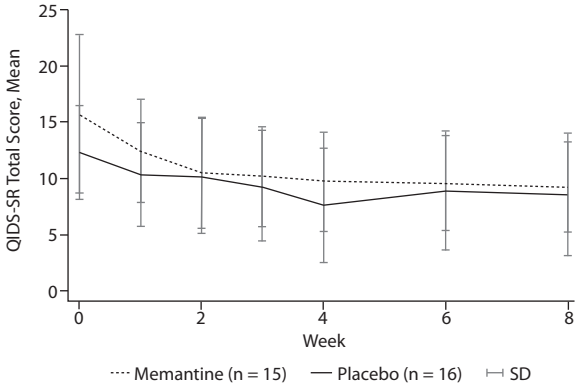
A. Primary Outcome: MADRS (LOCF)



B. Secondary Outcome: MADRS ("observed case" [no imputation])



C. Secondary Outcome: QIDS-SR (LOCF)



Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.

statistical significance, although type II errors (ie, failure to identify valuable interventions) are possible.[21] For this trial, the observations that the observed drug versus placebo difference was minimal, few participants dropped out, and maximum titration of possible dose was achieved for all memantine-receiving participants would all likely lessen the chances of type II error.

Limitations of our trial design beyond sample size included the fact that participants could be receiving any one of a substantial number of existing antidepressants, although specific antidepressants appeared to be generally balanced between treatment groups (Table 1). We also did not limit the amount of response participants may have already had to their antidepressant (as long as baseline Hamilton Depression Rating Scale [17 item] score was ≥16) nor imposed limits on the length of time participants could have received their current antidepressant (beyond a minimum of 25 days). This 25-day period was intended to replicate the earliest point (approximately 30 days) at which patient-provider discussions might occur about next steps in pharmacotherapy for patients experiencing an incomplete response or nonresponse to antidepressants. A longer preceding treatment requirement could have yielded lower placebo response rates and reduced the chance some participants were still experiencing change in depression produced by their concomitant antidepressant; however, these concerns are considerably mitigated by the observation that, for the 77% of participants for whom information on duration of current antidepressant treatment was available, only 3 of 24 (12.5%) had received antidepressants for 3 months or less prior to trial enrollment (16.7% of memantine and 8.3% of placebo recipients [Table 1]).

Like most,[6,22,23] but not all,[24] prior trials of memantine for depression, our dosing did not exceed the maximum dose approved for human use (20 mg/d). A small pilot study (n = 8),[24] in which 37.5% of the participants received doses of memantine of 30–40 mg/d, reported a much higher rate of treatment responders (62.5%) than either our trial (13.3%) or the placebo-controlled monotherapy trial.[6] However, this pilot study's open-label design and requirement of prior positive response to antidepressant treatment may have considerably boosted responses independent of any effects from higher dosage. Furthermore, in deciding whether to evaluate dosages of memantine that are higher than currently approved, the research community may need to consider emerging toxicologic literature reporting NMDA antagonist–associated neurotoxicity in some animal models of the developing brain. This literature has prompted FDA hearings to discuss the relevance to human anesthetic use of NMDA antagonists, especially in children.[25–27] Two major reservations concerning the relevance of these animal safety studies have been raised: the first involves the need to employ excessive doses compared to human use and the second concerns the use of "unrealistically long" (ie, multiday) exposures.[25] The first consideration (concerning dosing) is likely to be generally pertinent to typical psychiatric use of oral NMDA antagonists (and it may be additionally reassuring that psychiatric use of NMDA antagonists are being investigated in adults, not children). However, the logic of the second consideration (duration of exposure) is not as reassuring in the context of the likely psychiatric use of oral NMDA antagonists, since ongoing exposures of some duration are usually intended.

Strengths of our study include the generally good balance achieved on measured participant characteristics despite small sample size, the generally low dropout rate, the

Table 3. Adverse Events in Patients With Major Depressive Disorder Assigned Memantine or Placebo Augmentation of Antidepressant Treatment

	Memantine Augmentation (n = 15)		Placebo Augmentation (n = 16)		*P*
Adverse Event	n	%	n	%	Value[a]
Psychiatric					
Anxiety	3	20.00	3	18.75	> .999
Irritability	2	13.33	2	12.50	> .999
Emotional lability	2	13.33	2	12.50	> .999
Hypomania/mania	0	0.00	2	12.50	.484
Internal sensation of speed or rapid thoughts	0	0.00	3	18.75	.226
Restlessness	1	6.67	1	6.25	> .999
Passive suicidal ideation	2	13.33	1	6.25	.600
Active suicidal ideation	1	6.67	2	12.50	> .999
Unusual belief/perception[b]	1	6.67	0	0.00	.484
General					
Headache	5	33.33	5	31.25	> .999
Back pain	1	6.67	1	6.25	> .999
Generalized aches	0	0.00	1	6.25	> .999
Diaphoresis	1	6.67	3	18.75	.600
Chills	0	0.00	2	12.50	.484
Clammy hands	0	0.00	1	6.25	> .999
Feeling flushed/hot	0	0.00	1	6.25	> .999
Increased menstrual pain	0	0.00	1	6.25	> .999
Dizziness	1	6.67	5	31.25	.172
Light-headedness	3	20.00	0	0.00	.101
Balance or gait problems	1	6.67	3	18.75	.600
Leg weakness	1	6.67	2	12.50	> .999
Falls	0	0.00	1	6.25	> .999
Dermatologic					
Rash	0	0.00	2	12.50	.484
Pruritus	0	0.00	1	6.25	> .999
Worsened acne	0	0.00	1	6.25	> .999
Skin lesion	1	6.67	0	0.00	.484
Sleep and energy					
Insomnia/disturbed sleep	4	26.67	5	31.25	> .999
Worsened sleep apnea	0	0.00	1	6.25	> .999
Nightmares	0	0.00	1	6.25	> .999
Sleepwalking	1	6.67	0	0.00	.484
Sedation/somnolence	4	26.67	4	25.00	> .999
Fatigue	4	26.67	6	37.50	.704
Cognitive					
Confusion/decreased mental clarity	2	13.33	2	12.50	> .999
Mild dissociative symptoms	2	13.33	1	6.25	.600
Gastrointestinal					
Nausea	1	6.67	6	37.50	.083
Vomiting	0	0.00	1	6.25	> .999
Dyspepsia	1	6.67	1	6.25	> .999
Taste perversion	0	0.00	1	6.25	> .999
Perceived weight gain	0	0.00	1	6.25	> .999
Perceived weight loss	0	0.00	1	6.25	> .999
Carbohydrate craving	0	0.00	2	12.50	.484
Decreased appetite	1	6.67	1	6.25	> .999
Dry mouth	1	6.67	0	0.00	.484
Constipation	1	6.67	1	6.25	> .999
Cardiopulmonary/thoracic					
Heart palpitations	1	6.67	1	6.25	> .999
Difficulty breathing	1	6.67	1	6.25	> .999
Chest pain	1	6.67	0	0.00	.484
Neurologic					
Paresthesia/neuropathy exacerbation	1	6.67	1	6.25	> .999
Facial twitching	1	6.67	0	0.00	.484
Dyskinesia	0	0.00	1	6.25	> .999
Sensory					
Tinnitus	1	6.67	0	0.00	.484
Eye photosensitivity	0	0.00	1	6.25	> .999
Infectious/potentially infectious					
Upper respiratory infection symptoms	0	0.00	2	12.50	.484
Sore throat	0	0.00	1	6.25	> .999
Conjunctival swelling	0	0.00	1	6.25	> .999
Head pressure/ear pressure	0	0.00	1	6.25	> .999
Ear pain/jaw pain	0	0.00	1	6.25	> .999

[a]Fisher exact test.
[b]One participant receiving memantine endorsed a vague fear of imminent harm repeatedly during an everyday event but maintained it had existed for months prior to study entry, although it was not detected on the baseline screening of unusual thoughts.

success of blinding, the success in titrating all memantine recipients to maximum dose, and the use of a repeated-measures design.

To our knowledge, this trial is the only randomized placebo-controlled trial of memantine as an augmentation agent added to antidepressant treatment. Two other placebo-controlled trials have reported a lack of efficacy for memantine as an augmentation agent in other psychiatric conditions (bipolar depression[22] and schizophrenia[28]). A placebo-controlled trial[29] of memantine as a prophylactic monotherapy for depressive symptoms among elderly patients requiring physical rehabilitation also failed to demonstrate efficacy.

In conclusion, this randomized trial did not detect statistically significant differences between augmentation of conventional antidepressants with memantine and placebo and also did not detect substantial effect sizes favoring memantine. While this study's small sample size is a limitation, its findings suggest that memantine lacks substantial efficacy as an augmentation treatment for major depressive disorder.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), ketamine (Ketalar and others), lithium (Lithobid and others), memantine (Namenda), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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Potential conflicts of interest: **Dr Smith** currently receives research support from a Department of Veterans Affairs Health Services Research and Development Career Development Award for work separate from this study and has received funding (not in the last 12 months) from Forest Research Institute for a separate study concerning antidepressants and blood pressure. **Dr Deligiannidis** has received research support from UMass Medical School. **Dr Patel** has served on the speaker's bureau of Sunovian and Merck and, following completion of this study, serves as a speaker for Otsuka. **Dr Rothschild** has received research support from the National Institute of Mental Health, Cyberonics, Takeda, and St. Jude Medical; has served as a consultant to Allergan, GlaxoSmithKline, Eli Lilly, Noven, Pfizer, Shire, and Sunovian; has received royalties for the Rothschild Scale for Antidepressant Tachyphylaxis (RSAT); and has received royalties from American Psychiatric Press for *Psychoneuroendocrinology: The Scientific Basis of Clinical Practice* (2003), *Clinical Manual for Diagnosis and Treatment of Psychotic Depression* (2009), *The Evidence-Based Guide to Antipsychotic Medications* (2010), and *The Evidence-Based Guide to Antidepressant Medications* (2011). **Mss Ulbricht** and **Landolin** report no financial relationships with commercial interests or other conflicts to disclose.

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Role of sponsor: The sponsor had no role in the study design or conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation or approval of the manuscript. Forest Research Institute had an opportunity to review the final manuscript, but no modifications were requested or made.

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