Notice of correction 6/20/2011: In Figure 3B on page 1421, the memantine and the placebo scores have been correctly labeled.

Improvement of Negative and Positive Symptoms in Treatment-Refractory Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Trial With Memantine as Add-On Therapy to Clozapine

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Background: Glutamate deregulation may be involved in the neuropathology of schizophrenia, mainly through *N*-methyl-D-aspartate (NMDA) receptor dysfunction. Memantine, a drug approved by the FDA for the treatment of moderate to severe Alzheimer's disease, acts as a weak nonselective NMDA receptor antagonist. The aim of this study was to examine the efficacy of memantine as an adjunctive treatment to clozapine in patients with refractory schizophrenia.

Method: In this double-blind, placebo-controlled study, outpatients with refractory schizophrenia according to *DSM-IV* clinical criteria were randomly assigned, from March 2005 to February 2008, to receive either 20 mg/d memantine (n = 10) or placebo (n = 11), in addition to clozapine, for 12 weeks. The primary outcome measure was the total score on the 18-item Brief Psychiatry Rating Scale (BPRS) and BPRS subscales of positive and negative symptoms. Secondary outcomes were global severity of disease as measured by the Clinical Global Impressions scale (CGI), cognition as assessed by the Mini-Mental State Examination (MMSE), and extrapyramidal symptoms as assessed by the Simpson-Angus Scale (SAS).

Results: Twenty-one participants completed the study and were used in the analysis. Significant improvement ($P < .01$) on the total BPRS score, its subscales of positive (effect size [ES] = −1.38) and negative (ES = −3.33) symptoms, the CGI score (ES = 1.56), and the MMSE score was observed with memantine as compared with placebo. No significant changes in extrapyramidal symptoms were observed.

Conclusions: Memantine add-on to clozapine therapy was associated with improvement in negative and positive symptoms in refractory schizophrenia patients.

Trial Registration: clinicaltrials.gov Identifier: NCT00757978

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Schizophrenia is a highly debilitating[1] and multifaceted illness with positive, negative, and cognitive symptom domains. Standard treatments predominantly assist positive symptoms and may not adequately relieve other symptoms, particularly negative symptoms. Negative symptoms are a major contributor to functional impairment,[2] and conventional treatments are of limited benefit.[3] Clozapine, an atypical antipsychotic that is formally indicated for patients with schizophrenia whose symptoms are refractory to the other neuroleptics,[4] has a pharmacologic profile that shows results against positive and negative symptoms of schizophrenia. Clozapine seems to lack the cognitive side effects that are often seen with other psychoactive drugs, and it is able to increase the ability of the person to react to his or her environment and thereby to foster social rehabilitation. Nevertheless, about one-third of patients treated with clozapine still present significant residual symptoms, especially negative symptoms.[5] Adjunctive treatment, including antipsychotics, lamotrigine, antidepressants, and *N*-acetyl cysteine have been used to control negative symptoms.[6–10]

It has been suggested that glutamate deregulation may be involved in the neuropathology of schizophrenia, mainly through *N*-methyl-D-aspartate receptor (NMDAR) dysfunction. Memantine, a drug approved by the FDA for the treatment of moderate to severe Alzheimer's disease that acts as weak nonselective NMDAR antagonist, has been used off-label for various psychiatric disorders.[11–14] Our group has reported a case-series of memantine as adjunctive therapy to antipsychotic therapy that improved the negative symptoms of schizophrenia,[15] and Krivoy et al[16] reported improvement in negative symptoms in an open-label study of add-on therapy. A recent randomized, placebo-controlled trial with memantine as add-on therapy to

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atypical antipsychotics, in a nontreatment resistant cohort, failed to show improvement in positive and negative symptoms.[17]

We hypothesized that memantine, as an adjunct to clozapine in a treatment-resistant sample, would be effective for the treatment of negative symptoms of schizophrenia. The need for improved therapeutic strategies that more effectively treat this domain of symptoms remains critical.

METHOD

This study was a double-blind, placebo-controlled, randomized trial of memantine or placebo as adjunctive treatment to clozapine. The trial was registered with the US National Institutes of Health Clinical Trials Registry (NCT00757978).

The sample consisted of adult outpatients with schizophrenia in the Hospital de Clinicas de Porto Alegre, Brazil, aged between 18 to 65 years, and on clozapine treatment over the last 10 years for refractory schizophrenia, with partial remission of negative symptoms. The sample had a mean ± SD age of 34.67 ± 9.04 years , and the mean ± SD duration of illness was 18.56 ± 8.59 years; 19 of the 21 patients (90.5%) were male (Table 1).

All patients fulfilled *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition *(DSM-IV*),[18] criteria for schizophrenia [19] on clinical interview and were treated with clozapine. Exclusion criteria included any significant medical illness, use of any additional psychotropic agent except benzodiazepines, or substance abuse; female patients who were pregnant or at reproductive age and not taking contraceptives were also excluded. The Institutional Review Board of the Hospital de Clinicas de Porto Alegre approved the study. Informed written consent was received from all participants.

Individuals were assigned using simple randomization.[20] Treatment consisted of a 12-week trial of memantine or placebo, in addition to clozapine treatment as usual. Eligible patients were assigned to receive placebo or memantine (twice daily), with dosing titration as follows: week 1, 5 mg/d; week 2, 10 mg/d; week 3, 15 mg/d; weeks 4–12, 20 mg/d. Memantine was acquired from Apsen Farmaceutica S/A, Brazil (10 mg tablets). The primary domains assessed included (1) positive and negative symptoms of schizophrenia measured by the 18-item version of the Brief Psychiatry Rating Scale (BPRS),[21] (2) negative symptoms and (3) positive symptoms scores of the BPRS (negative symptoms scores are the sum of scores for items 3, 9, 13, and 16, and positive symptoms scores are the sum of scores for items 8, 11, 12, and 15 of the BPRS). Secondary outcomes included severity of the disease as measured by the Clinical Global Impressions scale (CGI)[22]; cognition as measured by the Mini-Mental State Examination (MMSE)[23]; and extrapyramidal symptoms as measured by the Simpson-Angus Scale (SAS).[24] All patient assessments were performed in both treatment conditions by a trained psychiatrist blinded to the patient's treatment condition. The assessments were conducted at baseline and at weeks 4, 8, and 12.

Table 1. Baseline Characteristics of the Patients Randomly Assigned to Memantine and Placebo Groups in a 12-Week Trial of Memantine as Add-On Therapy to Clozapine in Treatment-Refractory Schizophrenia

Characteristic	Treatment: Memantine Group (n = 10)[a]	Treatment: Placebo Group (n = 11)[a]	*P* Value
Age, y	34.60 ± 9.99	34.73 ± 8.57	.97
Male sex, n (%)	8/10 (80)	11/11 (100)	.21
Duration of illness, y	18.56 ± 8.59	17.18 ± 8.29	.89
Body mass index, kg/m^2	25.68 ± 2.87	28.48 ± 4.40	.10
Weight, kg	76.18 ± 13.09	86.04 ± 17.74	.17
Clozapine dose, mg/d	540.00 ± 211.87	659.09 ± 185.55	.17
BPRS total score	37.10 ± 8.18	43.18 ± 7.17	.08
BPRS positive symptoms score[b]	7.20 (3.33)	9.45 (4.64)	.22
BPRS negative symptoms score[c]	13.90 (1.79)	14.82 (1.94)	.28
MMSE score	22.30 ± 4.57	24.73 ± 3.58	.19
CGI score	5.40 ± 0.57	5.82 ± 0.87	.20
SAS score	6.40 ± 3.37	7.09 ± 3.33	.64

[a]Data presented as mean ± SD for all categories except male sex.
[b]BPRS positive symptoms score is the sum of scores for questions 8, 11, 12, and 15 of the BPRS.
[c]BPRS negative symptoms score is the sum of scores for questions 3, 9, 13, and 16 of the BPRS.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, MMSE = Mini-Mental State Examination, SAS = Simpson-Angus Scale.

The demographic characteristics of the patients in the memantine and placebo groups were compared. Sex was examined using the χ^2 test. The continuous variables from the demographic characteristics were analyzed using an unpaired *t* test. Between-group differences for outcome measures at baseline were calculated using unpaired *t* tests.

Analyses were conducted for the intent-to-treat sample (n = 21). Overall efficacy of treatment was assessed by conducting a 2-way analysis of covariance (ANCOVA), controlling for pretreatment scores on all major outcome measures by treatment condition at termination. All outcomes were assessed at baseline and at weeks 4, 8, and 12 for the memantine and placebo groups. A repeated-measures analysis of variance (ANOVA) was used to examine changes over time in the outcome measures. ANOVA was conducted on each of the outcome measures of interest; the number of time categories was the same for both groups, ranging from baseline to week 12 for all the outcomes considered. Greenhouse-Geisser estimates were used throughout to control for any sphericity. The statistical significance of the interaction between time and treatment was used to demonstrate a treatment effect. An α level of .05 (2-sided) was considered statistically significant. Post hoc data analyses were done with the Bonferroni *t* test, using the appropriate

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mean square error from the ANCOVA to establish a protected 1.25% type I error (0.05/4). Effect size (ES) *d* was calculated using the method of Cohen.

The required sample size was determined using the assumption that a clinically meaningful difference between the 2 treatment groups would be 10 points in total BPRS score with a pooled standard deviation of 8.0. All analyses were done using SPSS version 16.0 for Windows (SPSS Inc, Chicago, Illinois).

RESULTS

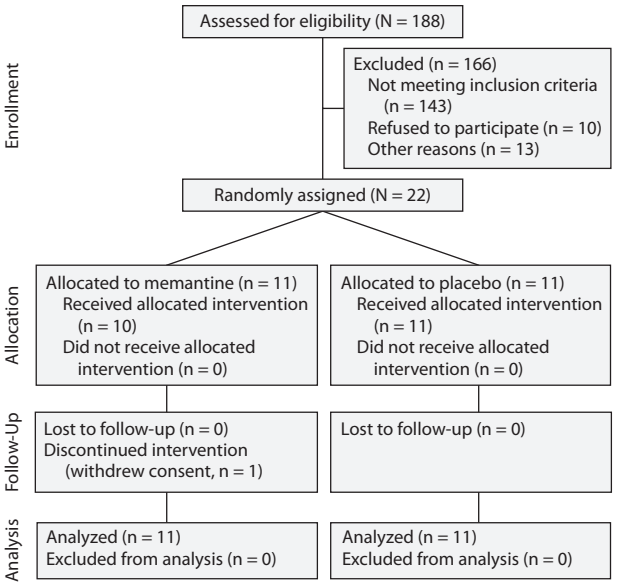
Of 422 schizophrenic outpatients who underwent screening from January 2006 through March 2008, 188 (44.5%) were treated with clozapine and initially eligible for baseline assessment, and 143 (33.9%) were determined to be ineligible. Thus, 45 (10.7%) of those undergoing screening were eligible and of these, 10 (22.2%) refused to participate (Figure 1). The most common reasons for refusal were related to the requirements intrinsic to a research protocol, including not wanting to be randomly assigned to placebo.

The treatment and placebo groups did not differ significantly in background demographic characteristics (Table 1). The placebo group had slightly more severe scores on the rating scales, including the BPRS, and the mean dose of clozapine was higher in the placebo group, but the differences in these baseline parameters were not significant.

Of the 22 participants initially enrolled in the study, 21 completed the full protocol (Figure 1). One patient in the memantine group discontinued the treatment during week 2 and withdrew consent. At baseline, there were no significant group differences in positive and negative symptoms on the BPRS total, BPRS positive, or BPRS negative symptom scores. On the BPRS total and on its positive symptoms and negative symptoms subscales, patients who received memantine, compared with those who received placebo, reported significantly greater decreases in BPRS total score (week 12, 19.00 vs 43.18, $P = .001$), positive symptoms score (week 12, 4.10 vs 9.18, $P = .007$), and negative symptoms score (week 12, 6.10 vs 13.55, $P = .001$). ESs for the differences in treatment outcomes are shown in Table 2.

The repeated-measures ANOVA showed a statistically significant interaction between treatment and time for BPRS total score, BPRS positive symptoms score, and BPRS negative symptoms score ($P = .001$ for all 3 outcomes). Post hoc pairwise contrasts of the treatment means at all time points revealed significant differences between mean scores, with memantine reducing the BPRS total mean score by 20.25 points more than placebo (95% CI for the difference, −27.61 to −12.89; $P < .001$; Figure 2). For BPRS positive and negative symptoms, the memantine groups showed reduced mean scores of 3.27 and 7.58 when compared to the placebo group (95% CI for the difference, −5.27 to −1.27, $P < .003$; 95% CI, −9.65 to −5.51, $P < .001$, respectively).

Figure 1. Flow Diagram of Patient Allocation in a 12-Week Trial of Memantine as Add-On Therapy to Clozapine in Treatment-Refractory Schizophrenia[a]



[a]Endpoints were completed for 95.45% of randomly assigned patients.

The secondary outcomes assessed were the scores on the CGI, the MMSE, the SAS, and weight. Patients receiving memantine, compared with those receiving placebo, reported significantly greater improvement in overall functioning on the CGI ($P < .001$) at week 12 (Table 2). At week 12, patients who received memantine as compared with those who received placebo were rated as significantly less ill. The ES for the CGI was −1.56 (95% CI, −2.54 to −0.58). The repeated-measures ANOVA showed that patterns in variation of mean global severity of disease during the 12 weeks of treatment were significantly different between the 2 conditions (treatment-by-time interaction, $P = .002$; Figure 3). The memantine group showed a difference of 1.25 points reduction in their mean scores compared to the placebo group (95% CI, −1.99 to −0.50; $P = .002$) on the CGI.

At week 12, patients who received memantine, compared with those who received placebo, showed a significantly greater improvement in their cognitive symptoms scored by the MMSE ($P = .001$). The repeated-measures ANOVA showed that patterns in variation of mean overall social functioning during the 12 weeks of treatment were significantly different between the 2 conditions (treatment-by-time interaction, ($P < .001$; Figure 3). The memantine group had a 6.12-point greater increase in mean score compared to the placebo condition (95% CI, 4.45–7.79).

The other 2 secondary outcomes, extrapyramidal symptoms as measured by the SAS score and weight, were not significantly different (Table 2). Four patients, 1 receiving memantine, and 3 placebo, complained of nausea and dizziness.

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Table 2. Clinical Outcomes According to Treatment Assignment With Memantine Versus Placebo in a 12-Week Trial of Memantine as Add-On Therapy to Clozapine in Treatment-Refractory Schizophrenia

	Treatment			
Outcome	Memantine Group (n = 10)[a]	Placebo Group (n = 11)[a]	ES (95% CI)	*P* Value
BPRS total score[b]				
Baseline	37.10 (8.18)	43.18 (7.17)		.085
Week 12[c]	19.00 (7.20)	43.18 (9.93)	−2.75 (−3.94 to −1.55)	.001
BPRS positive symptoms score[b]				
Baseline	7.20 (3.33)	9.45 (4.64)		.220
Week 12[c]	4.10 (2.88)	9.18 (4.54)	−1.38 (−2.33 to −0.43)	.007
BPRS negative symptoms score[b]				
Baseline	13.90 (1.79)	14.82 (1.94)		.275
Week 12[c]	6.10 (2.28)	13.55 (2.02)	−3.33 (−4.65 to −2.01)	.001
CGI score[b]				
Baseline	5.82 (0.87)	5.40 (0.52)		.200
Week 12[c]	4.10 (0.74)	5.73 (1.19)	−1.56 (−2.54 to −0.58)	.001
MMSE score[d]				
Baseline	22.30 (4.57)	24.73 (3.58)		.190
Week 12[c]	28.20 (3.33)	23.73 (3.16)	1.32 (0.38 to 2.27)	.005
SAS score[b]				
Baseline	6.40 (3.37)	7.09 (3.33)		.640
Week 12[c]	5.40 (2.71)	6.36 (2.77)	−0.34 (−1.20 to 0.53)	.430
Weight, kg				
Baseline	76.18 (13.09)	86.04 (17.74)		.170
Week 12[c]	77.25 (13.09)	84.41 (15.53)	−0.48 (−1.34 to 0.39)	.270

[a]Data are presented as mean (SD).
[b]Smaller values denote better outcomes.
[c]Analyses at week 12 were performed with ANCOVA using the pretreatment score (baseline) as covariate.
[d]Greater values denote better outcomes.
Abbreviations: ANCOVA = analysis of covariance, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, ES = effect size, MMSE = Mini-Mental State Examination, SAS = Simpson-Angus Scale.

DISCUSSION

This trial supports the use of memantine as adjunctive therapy to clozapine in patients with treatment-resistant schizophrenia. Our trial successfully demonstrated significant differences in both negative and positive symptoms between the placebo and memantine groups. This study also supports the role of the NMDA system in the pathophysiology of schizophrenia.

Although clozapine is a highly effective treatment for refractory schizophrenia,[4] up to one-third of patients taking clozapine remain consistently symptomatic.[5] Glutamate neurotransmission has been strongly implicated in the pathophysiology of schizophrenia.[25–28] Reduced activation of the NMDAR subtype may play a major role in negative symptoms of schizophrenia.[29] Blocking active NMDA channels in healthy volunteers impairs cognitive functioning, creating cognitive deficits similar to those seen in schizophrenia.[30,31] Studies have also demonstrated that noncompetitive NMDAR antagonists, such as dissociative anesthetics like phencyclidine and ketamine, reproduce the cardinal symptomatic features of schizophrenia.[32] Alteration in peripheral glutamate receptor linkage to second messenger intracellular calcium is also reported in schizophrenia.[33,34]

Clozapine increases the expression of NMDARs and also glutamate metabotropic receptors (mGluRs).[35] The hyperexpression of mGluR is associated with brain-derived neurotrophic factor (BDNF) production in glial neurons, increasing this neurotrophin.[35,36] There is also a close relationship between NMDARs and mGluRs, particularly mGluR5, which modulates NMDA expression.[35]

Chronic clozapine treatment has a unique property that elevates mGluR5 expression in animal models; elevated mGluR5 expression, in turn, improves glutamatergic tonus by modeling the NMDA glutamatergic system.[35] In this complex panel, chronic clozapine treatment in our sample may have prepared a special glutamatergic environment in which memantine played the main role in clinical improvement. This environment can explain both patient improvement with the memantine/clozapine association and negative results with other associations.[17]

Several studies suggest that clozapine interacts with the NMDAR complex.[37–43] Clozapine may affect the glycine site of the NMDAR or mildly inhibit the glycine transporter. The inhibitory action of clozapine on dopaminergic neurons may account for its beneficial effects in ameliorating symptoms of schizophrenia and may suggest further studies to investigate a role for the glycine site of the NMDAR as a target for novel antipsychotics.[37,40] Under a condition in which the NMDA/glycine site is saturated by the endogenous ligands (glycine or D-serine), an antagonistic action of clozapine would prevail, leading to increased firing activity.[38] In contrast, when a high degree of blockade of the NMDA/glycine site is present, an agonistic action of clozapine is more prominent, thereby decreasing impulse

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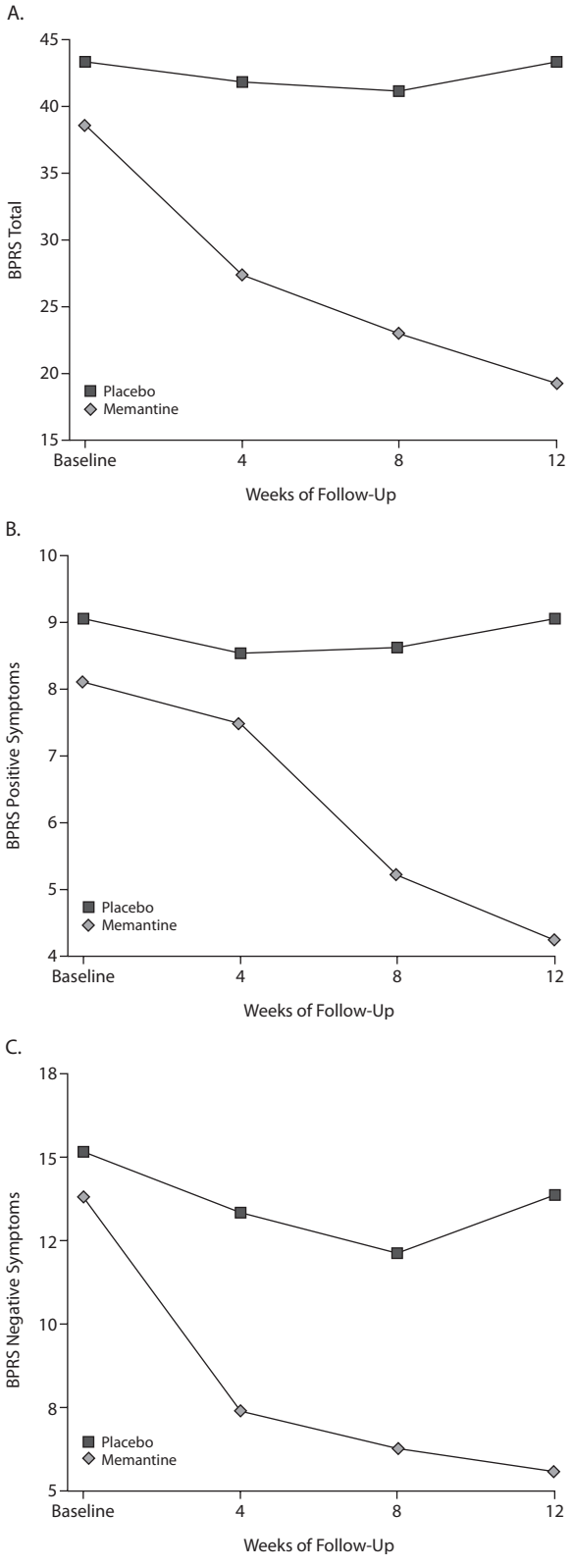
Figure 2. Mean Brief Psychiatry Rating Scale (BPRS) Total (A), Positive Symptoms (B), and Negative Symptoms (C) Scores for the Placebo and Memantine Groups a 12-Week Trial of Memantine as Add-On Therapy to Clozapine in Treatment-Refractory Schizophrenia



activity.[37] Thus, clozapine appears to stabilize dopaminergic neurons, dampening both hyperactivity and hypoactivity via an agonistic and antagonistic action, respectively, at the NMDA/glycine site.[37–43]

On the other hand, recent clinical data also support partial agonistic action at the NMDA/glycine site by clozapine. D-Cycloserine, in combination with traditional or second-generation antipsychotics, improves symptoms of schizophrenia. A unique interaction between clozapine and the glycine site of the NMDAR may explain the paradoxical worsening in negative symptoms when d-cycloserine is added to clozapine in patients with schizophrenia.[39]

Our results are therefore in line with the glutamatergic hypothesis of schizophrenia, according to which glutamate plays a central role in the core schizophrenic symptoms.[44,45] *N*-Acetyl cysteine, which, in addition to increasing glutathione, increases glutamate via cysteine-glutamate exchange, improving negative symptoms of schizophrenia.[46] Our study supports the initial hypothesis posited by Andreasen et al[47] that improving glutamatergic tonus in some brain areas, such as prefrontal, thalamic, and cerebro-cerebellar regions,[47] by NMDA partial activation could be responsible for the improvement of negative and possibly positive symptoms in our patients.

An interesting finding of this trial was the improvement of positive symptoms without worsening of psychosis in the active treatment group, suggesting that memantine has broader actions than previously realized. Improvement of positive symptoms may be due to the unique properties of memantine. Memantine is a fast off-rate (low affinity) type of uncompetitive NMDAR antagonist that blocks only pathological receptor activity and could theoretically restore abnormal neurons to a homeostatic state. Some studies indicate that memantine exerts its effect on NMDAR activity by binding at or near the $Mg2^{+}$ site within the ion channel. Due to its interaction with external $Mg2^{+}$, and based on mutational analysis of the NMDAR by others,[48] the specific site of memantine action is assumed to be near the external $Mg2^{+}$ blocking site at the selectivity filter region of the NMDAR-associated channel. This region is formed by asparagine (N) residues at the "N-site" of NR1 and "N + 1 site" of NR2 subunits. Compared with physiologic blockage by external $Mg2^{+}$, a common explanation for the safety and effectiveness of memantine has been that memantine represented "better magnesium", manifesting a somewhat slower unblocking rate, moderate voltage dependence, and slightly higher affinity. Reversal of hyperactivity induced by the NMDAR antagonist MK-801 is predictive of antipsychotic activity, particularly the activity of atypical antipsychotics. MK-801–induced hyperactivity is reversed by selective 5-HT_{2A} inverse agonists/antagonists and by atypical antipsychotic drugs having 5-HT_{2A} inverse agonist/antagonist activity and clozapine is the masterpiece of this mechanism.[49–51] Consistent with the potent clozapine interaction with 5-HT_{2A} receptors, after systemic administration

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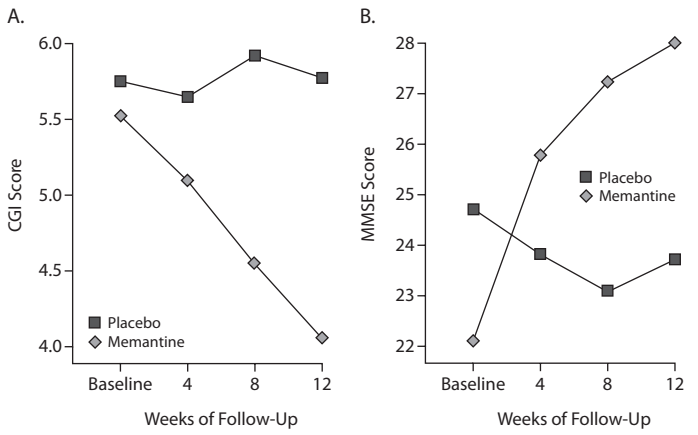
Figure 3. Mean Clinical Global Impressions (CGI) Scores (A) and Mean Mini-Mental State Examination (MMSE) Scores (B) for the Placebo and Memantine Groups in a 12-Week Trial of Memantine as Add-On Therapy to Clozapine in Treatment-Refractory Schizophrenia[a]



[a]For A, $P = .002$, and for B, $P < .001$. $P < .0125$ (.05/4) considered significant, repeated measures ANOVA.

(intraperitoneally), both *N*-desmethylclozapine and clozapine reduced MK-801–induced hyperactivity in mice and rats, respectively.[36,52]

Memantine can prevent neuronal damage in several models of neurodegeneration.[53] This effect has been attributed to inhibition of NMDAR activity. Meisner et al[54] reported an interaction between memantine and BDNF, possibly due to an effect of memantine on nonneuronal BDNF-producing cells, activating extra synaptic NMDARs and promoting neuronal functioning.

Although there is a link between BDNF and dopamine, we cannot know if there is a causative relationship, and we cannot postulate that the effects of memantine are solely due to BDNF up-regulation, but this possibility is suggested by the novel neuroprotective pharmacologic action of memantine in neurodegenerative disorders and schizophrenia.[54]

There is evidence that oxidative stress is increased in patients with schizophrenia.[45,55–58] As previously reported, memantine may be considered a neuroprotective drug by virtue of its increasing BDNF levels and preventing dopamine deficit. Thus, memantine may act like antipsychotics[59] by chronically reducing neuronal oxidative stress in treated patients[15] and decreasing neuroprogression and neuronal death.

There is no current, effective treatment for negative symptoms in schizophrenia. Considering our scarce treatment options, memantine can be considered an extremely promising medication for adjunctive treatment, in particular as an adjunct to clozapine. Lieberman et al[17] did not report efficacy of memantine as adjunctive to atypical antipsychotics other than clozapine. It is nevertheless possible that there is a synergic interaction between both drugs, and treatment-refractory disease signaled by clozapine use, may respond in a differential manner with memantine as an add-on therapy to clozapine.

There are some limitations to this study. First, at baseline the placebo group had slightly more severe symptoms on the BPRS and its subscales; this discrepancy might have resulted in the overestimation of the efficacy of the memantine; to correct for this potential error, adjustment for baseline was done using ANCOVA. Second, serum clozapine levels have not been measured; the only information available was the drug daily dose. However, clozapine doses were equivalent between the 2 studied groups. As far as we are aware, clozapine metabolism is extensively hepatic,[60] in contrast to memantine metabolism, in which excretion occurs in urine by active tubular secretion.[61] Moreover, there is no pharmacokinetic interaction between clozapine and memantine.[60] Third, since the study had only 12 weeks of follow-up, studies with a longer follow-up are necessary to determine the efficacy of memantine and its role as long-term maintenance for refractory schizophrenia adjunctive to clozapine. Fourth, the MMSE is not the most sensitive measure of cognition, and future studies should use formal cognitive testing. In addition, this was a trial of memantine add-on to clozapine in refractory schizophrenia; its positive results cannot be generalized to patients with less severe symptoms and without clozapine use. As a tautology, less refractory patients are more likely to respond to therapy, and the effects of memantine may be greater in nonrefractory individuals.

This is the first randomized clinical trial showing benefit of adjunctive treatment with memantine as add-on to clozapine therapy. This study supports the use of memantine as an adjunctive therapy for schizophrenia. However, our findings need to be replicated in a larger sample size and over a longer follow-up in order to better evaluate the potential benefits of this adjunctive treatment. Lastly, this trial adds to the evidence base supporting a key role of glutamate in the pathophysiology of schizophrenia.

Drug names: clozapine (FazaClo, Clozaril, and others), ketamine (Ketalar and others), lamotrigine (Lamictal and others), memantine (Namenda).

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