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The effect of add-on memantine on positive, negative and depressive symptoms of schizophrenia: a double-blind, randomized, controlled trial

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Background. Although antipsychotics are the mainstay treatment of schizophrenia, they don't adequately address residual positive, negative and depressive symptoms. The aim of the present study is to assess the effect of adjunctive memantine treatment on positive, negative and depressive symptoms of schizophrenia.

Methods. This randomized, placebo-controlled study was conducted in Noor Hospital, Isfahan, Iran, 2013-2014; 32 patients in maintenance treatment were included in each group, using block sampling; inclusion criteria were age 18-65 years, normal intellectual ability, being diagnosed with schizophrenia for the past two years, being treated with fixed doses of atypical antipsychotic for at least three months before randomization. Exclusion criteria were pregnancy, breast feeding, having received electro-convulsive therapy in the past two weeks, drug or substance abuse and dependence, psychiatric/ neurological comorbidities, and sensitivity to memantine. Patients in the intervention group were treated with memantine plus atypical antipsychotic; while in the control group, patients received placebo and atypical antipsychotic. Patients were assessed by Positive and Negative Symptom Scale (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS) initially and every four weeks to the end of the 12th week. Data were analyzed in SPSS 17.0 using t-test, chi square, analysis of variance (ANOVA), and analysis of covariance (ANCOVA).

Results. Positive symptoms ($p=0.028$), negative symptoms (0.004), general psychopathology ($p<0.001$), depressive symptoms ($p<0.001$) and total symptom severity ($p<0.001$)

decreased significantly in patients receiving add-on memantine.

Conclusion. This study shows that, add-on memantine would be helpful, in the adjunctive treatment of depressive, positive, negative and general symptoms in patients with schizophrenia.

Keywords: Memantine, Schizophrenia, Depression, Psychopathology, Treatment, n-methylaspartate

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Efecto de la terapia adyuvante con memantina en el control de los síntomas positivos, negativos y depresivos de la esquizofrenia: estudio aleatorizado, doble ciego y controlado

Antecedentes. Aunque los fármacos antipsicóticos son el pilar básico del tratamiento de la esquizofrenia, no resuelven adecuadamente los síntomas residuales positivos, negativos y depresivos. El objetivo del presente estudio es evaluar el efecto del tratamiento adyuvante con memantina sobre los síntomas positivos, negativos y depresivos de la esquizofrenia.

Métodos. Este estudio aleatorizado, controlado con placebo se ha realizado en el hospital Noor en Isfahan, Irán, de 2013 a 2014. En cada grupo se seleccionaron al azar 32 pacientes con tratamiento de mantenimiento. Los pacientes fueron seleccionados como muestreo en bloque. Los criterios de inclusión fueron: edad de 18 a 65 años, con capacidad mental normal, diagnosticados de esquizofrenia durante los últimos dos años y tratados con dosis fijas de antipsicóticos atípicos al menos durante los tres meses pre-

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vios a la aleatorización. Los criterios de exclusión incluyeron embarazo, lactancia, tratamiento electroconvulsivo en las últimas dos semanas, abuso y dependencia de sustancias, comorbilidad de trastornos psiquiátricos o neurológicos e hipersensibilidad a la memantina. Los pacientes del grupo de intervención recibieron un fármaco antipsicótico atípico más memantina, mientras que el grupo control recibió el antipsicótico atípico más placebo. Los pacientes fueron evaluados por la Escala de Síntomas positivos y negativos (PANSS) y la Escala de Depresión de Calgary para la Esquizofrenia (CDSS) al inicio y luego cada cuatro semanas hasta el final en la duodécima semana. Los datos se analizaron con SPSS-17 utilizando test t, test de ji cuadrado, análisis de varianza (ANOVA) y análisis de covarianza (ANCOVA). **Resultados.** En el grupo al que se añadió Memantina los síntomas positivos ($p=0,028$), los síntomas negativos ($0,004$), la psicopatología general ($p<0,001$), los síntomas depresivos ($p<0,001$) y la gravedad general de los síntomas ($p<0,001$) disminuyeron significativamente.

Conclusión. Este estudio muestra que la adición de memantina podría ser útil como tratamiento adyuvante de los síntomas depresivos, positivos, negativos y síntomas generales en pacientes esquizofrénicos.

Palabras clave: Memantina, Esquizofrenia, Depresión, Psicopatología, Tratamiento, n-metilaspártato

INTRODUCTION

Schizophrenia is a major mental disorder, causing acute exacerbation, chronic functional impairment and life-long disability.^{1,2} Dimensions of schizophrenia are categorized as positive and negative symptoms, disorganization, depressive symptoms and cognitive impairment.³ Around 1% of the population is afflicted by the illness and it is among the ten medical conditions yielding highest disability.⁴

Depressive symptoms occur frequently in schizophrenia. Globally, patients with schizophrenia described feeling lower level of happiness than general population.¹ Almost 25% of patients with schizophrenia experience depressive disorder, and many more suffer sub-threshold depressive states.³ Depression may be identified during any phase of the disease, as in prodromal, psychotic or post-psychotic phases.³ It is also estimated that 50% of patients with schizophrenia have comorbid depression.^{3,4} Patients with schizophrenia are at increased risk of developing depression in comparison to general population.^{3,4} The impact of comorbid depression represents in heavier burden, increased suffering and poor function. Moreover, the presence of depressive symptoms in

the residual course can accelerate the re-emergence of psychosis.³

Administration of antipsychotics is still the anchor treatment for the disorder; however, it does not ameliorate functional morbidity, cognitive deficit, and residual positive and negative symptoms sufficiently.^{5,6} Although most atypical antipsychotics appear to have antidepressant properties they have not proven to be effective, when used alone, for the treatment of persistent depressive conditions in schizophrenia.³ Therefore, generally, clinicians prefer combination treatments for patients with schizophrenia.^{5,7}

On the other hand, adjunctive antidepressants may be beneficial for the treatment of depression in schizophrenia. However, an important limitation in their utility is that they can intensify side effects of antipsychotics, such as akathisia, somnolence, weight gain and sexual problems.³

Glutamate dysregulation is considered a prominent element in the neurochemical correlates of schizophrenia, considering that N-methyl-D-aspartate (NMDA) receptor hypo-functioning results in excessive glutamate activity and, consequently, in neuronal cell death.^{8,9} Therefore, agents targeting NMDA-mediated glutamate system, including D-serine, D-alanine, D-cycloserine and sarcosine, have been the subject of studies for treatment of schizophrenia and other major psychiatric conditions.¹⁰⁻¹³ Memantine is an uncompetitive NMDA blocker which has been approved for the treatment of Alzheimer's disease. It was introduced as having few side effects and high tolerability.⁷ Memantine also seems to act as a neuroprotective factor in schizophrenia, as it inhibits excessive NMDA-receptor activity without disrupting its normal function.^{7,14} It has also been studied as an adjunctive treatment in depression, obsessive-compulsive disorder and other psychiatric conditions in previous trials. However, to our knowledge, no studies have focused on the effect of memantine on depressive symptoms of schizophrenia.¹⁵⁻¹⁷

Several studies have focused on adjunctive use of memantine in schizophrenia, which revealed equivocal results. In some studies, adjunctive memantine treatment has been reported to decrease positive and negative symptoms, and to improve cognitive and functional level in patients with schizophrenia; interestingly, no serious side effects were reported.^{7,18} On the other hand, other studies did not find any benefit in add-on memantine treatment for different aspects of psychopathology in schizophrenia.¹⁹ Adjunctive memantine was even reported to increase adverse effects of baseline antipsychotic treatment.⁵

The aim of the present study is to assess the effect of adjunctive memantine treatment on positive, negative and depressive symptoms of schizophrenia.

METHOD AND MATERIAL

This randomized, placebo-controlled trial was conducted in Noor Hospital affiliated to Isfahan University of Medical Sciences (IUMS), Isfahan, Iran, from June 2013 to November 2014. The study was approved by the research and ethics committee of Isfahan University of Medical Sciences. The codes of Helsinki declaration are observed. The IRCT registration number was 19320.

64 patients were selected through sequential sampling among inpatient cases of schizophrenia. The diagnosis was based on clinical interview and DSM-IV-TR criteria. Inclusion criteria were as the following: age 18-65 years, normal intellectual ability, being diagnosed with schizophrenia for the past two years, being treated as out-patient with fixed doses of atypical antipsychotic for at least three months before randomization. Exclusion criteria were pregnancy, breast feeding, having received ECT in the past two weeks, psychiatric hospitalization during the past three months, drug or substance abuse and dependence, comorbidity of other psychiatric disorders or neurological conditions, and sensitivity to memantine. Patients were assessed through the following scales:

Positive and Negative Symptom Scale (PANSS)

PANSS is a scale of symptom severity in schizophrenia, first published in 1987. It requires a rather brief interview. PANSS assesses three domains through 30 different questions; each symptom can be rated from 1 to 7. Positive symptoms, including hallucinations and delusions, are assessed through seven questions; likewise, severity of negative symptoms, like blunted affect, are measured through seven items; finally, general psychopathology, like guilt feelings, somatic concern and uncooperativeness, is evaluated in 16 different questions. The total minimum and maximum scores are 30 and 210, respectively. PANSS is highly valid and reliable; the overall alpha-coefficients for Positive and Negative scales were 0.73 and 0.83, respectively.²⁰

Calgary Depression Scale for Schizophrenia (CDSS)

CDSS is a semi-structured, goal-directed interview which is specifically designed to measure the level of depressive symptoms regardless of positive, negative and extrapyramidal symptoms in schizophrenia, and appears to be sensitive to change. It is available in 38 languages including Farsi, and is 82% specific and 85% sensitive for predicting the presence of major depressive episode in patients with schizophrenia. It includes nine items each rated from 0-3. Score 6 is considered as the cut-off.²¹

In the beginning, written informed consents were obtained from family or guardian. According to their sequence, patients were allocated in random blocks. Each block embraced two patients, one allocated to intervention group and the other allocated to the control. Patients in the intervention group were treated with memantine plus atypical antipsychotic, while in the control group, patients received placebo and atypical antipsychotic. Memantine administration was initiated at 5 mg daily (Osve, Tehran, Iran); the dosage was increased at weekly intervals by 5 mg and finally up-titrated to 20 mg daily within 4 weeks, and then continued for 12 weeks. The other group received similar amount of placebo. Both intervention and control groups were on a stable dosage of atypical antipsychotic regimen for at least three months before randomization. All patients were assessed by means of PANSS and CDSS initially and every four weeks to the end of the 12th week. Memantine and placebo were packed and alphabetically labeled in the pharmacology laboratory. Therefore, both patients and the clinicians who conducted the interviews and assessed patients were blinded as to patients' group allocation.

STATISTICAL ANALYSIS

SPSS 17.0 (SPSS Statistics for Windows, Chicago: SPSS Inc.) was used for statistical analysis. PANSS and CDSS scores were analyzed using ANOVA. Age, duration of schizophrenia, and number of prior psychiatric admission were compared through t-tests, while the differences between other demographic features were measured by means of chi-square; results were presented as mean (SD) and as number (percentage). Also, ANCOVA was conducted to determine differences between memantine and placebo on mean changes of PANSS and CDSS scores, controlling for age, sex, type of antipsychotic, mean duration of illness, and baseline scores of CDSS and the three domains of PANSS.

RESULTS

Totally, 64 patients were included in the study; four patients dropped out in the process. All demographic data are demonstrated in table 1. The analysis of demographic information, including age, education, marital status, illness duration and history of hospitalization, did not reveal any significant differences between the two groups (Table 1). There were 18 missing responses for social status, five for marital status, and six for education level.

At baseline, no univariate differences were found between the two groups, with regard to depressive severity ($p=0.510$). However, the two groups showed differences regarding general psychopathology and total symptom severity ($p=0.026$).

Table 1	Baseline characteristics of patients		
Characteristics	Memantine	Placebo	<i>p</i>
Marital status, n (%)			
single	21 (75)	16 (59.3)	0.214 ^f
other	7 (25)	11 (40.7)	
Age, years, Mean (SD)	32.3 (9.9)	34.2 (10.6)	0.471 [*]
Gender, n (%)			
female	12	16	0.301 ^f
male	18	14	
Education level, n (%)			
Primary	23 (79.3)	17 (68)	0.528 ^f
High school certificate	4 (13.8)	4 (16)	
College/university	2 (6.9)	4 (16)	
Living condition, n (%)			
With parents	10 (47)	9 (43)	0.468 ^f
With one parent	7 (33)	6 (28)	
With spouse	2 (9)	5 (23)	
Independently	2 (9)	1 (4)	
Years of illness, Mean (SD)	7.9 (6.4)	10 (6.9)	0.285 [*]
Frequency of prior admission, Mean (SD)	3 (3.4)	1.5 (6)	0.414 [*]
Baseline antipsychotic treatment, n (%)			
Risperidone	15 (50)	16 (53.3)	0.205 ^f
Olanzapine	10 (33.3)	7 (23.3)	
Clozapine	4 (13.3)	5 (16.6)	
Aripiprazole	1 (3.3)	2 (6.7)	

^{*}t-test, ^fchi-square; n: number, SD: standard deviation

Patients receiving intervention had a significant decrease in the CDSS (depression) scores, in the 4th, 8th and 12th week; while the control group had an increase in CDSS score in the 4th week, and then followed a decrease in the 8th and 12th week. The two groups were significantly different in this regard ($p < 0.001$) (Table 2, Figure 1).

Positive, negative and general psychopathology decreased in both groups, according to PANSS; the decrease was more remarkable in the intervention group; particularly, differences were significant, in the following domains: positive symptoms ($p = 0.028$), negative symptoms (0.004), general psychopathology ($p < 0.001$), and total symptom severity ($p < 0.001$) (Table 3, Figure 2). The results of repeated measure ANOVA shows that neither CDSS ($p = 0.426$) nor total PANSS score ($p = 0.486$) was influenced by the passage of time.

Also, a significant difference was detected in patients receiving memantine, versus placebo, in mean changes of CDSS scores in the 4th, 8th and 12th week using ANCOVA, controlling for age, sex, type of antipsychotic, mean duration of illness, and baseline scores of CDSS and baseline scores in the three domains of PANSS ($p < 0.05$). The results of ANCOVA, controlling for aforementioned covariates showed significant difference in the mean changes of scores in the three domains of PANSS, in patients receiving memantine versus placebo, in the 4th, 8th and 12th week ($p < 0.05$).

The reported side effects were constipation ($n = 2$), headache ($n = 2$) and dizziness ($n = 1$), which were mild to moderate in severity. No serious or severe adverse effects were reported during the study.

DISCUSSION

The present study shows that memantine, as an add-on to atypical antipsychotics, could reduce depressive, positive, negative and general symptoms in schizophrenia.

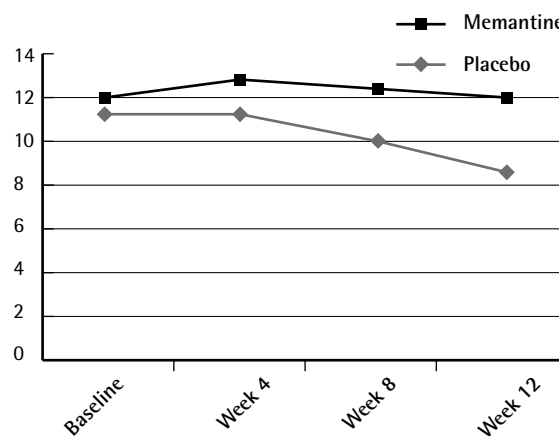


Figure 1

Comparison of depressive symptoms between add-on memantine and add-on placebo, based on CDSS (Calgary Depression Scale for Schizophrenia)

	Memantine, CDSS Mean (SD)	Placebo, CDSS Mean (SD)	Between-group p^*	ANCOVA P
Baseline	11.3 (4.5)	12.1 (5.2)		0.023
Week4	11.2 (4.1)	12.9 (4.8)		0.032
Week8	10.0 (3.9)	12.4 (4.5)		0.011
Week12	8.8 (3.4)	12.0 (4.8)	<0.001	0.003
Within-group p^*	0.426			

** p derived from ANOVA (analysis of variance), SD: Standard Deviation. CDSS: Calgary Depression Scale for Schizophrenia*

	PANSS, Mean (SD)			ANCOVA P
	memantine	Placebo	Between-group p	
Positive Subscale	Baseline	25.4 (4.3)	26.9 (3.6)	
	Week4	23.9 (4.3)	26.4 (3.6)	
	Week8	22.6 (4.3)	24.9 (4.0)	
	Week12	21.3 (4.2)	23.9 (3.8)	0.028
	Within-group p	0.128		0.038
Negative Subscale	Baseline	26.8 (3.7)	28.5 (4.3)	
	Week4	25.1 (4.0)	27.6 (4.7)	
	Week8	23.3 (4.0)	26.6 (4.4)	
	Week12	21.4 (3.8)	25.5 (4.0)	0.004
	Within-group p	0.933		0.004
General Psychopathology Subscale	Baseline	55.5 (6.6)	59.6 (7.1)	
	Week4	53.6 (6.7)	58.9 (7.1)	
	Week8	51.9 (6.6)	57.6 (7.4)	
	Week12	50.2 (6.7)	56.1 (5.9)	<0.001
	Within-group p	0.790		0.003
Total Symptom Severity	Baseline	107.4 (13.0)	114.9 (12.5)	
	Week4	102.7 (13.2)	113 (13.0)	
	Week8	97.9 (13.0)	109.1 (13.7)	
	Week12	93.0 (13.1)	105.9 (11.3)	<0.001
	Within-group p	0.486		0.002

SD: Standard Deviation, ANCOVA: analysis of covariance

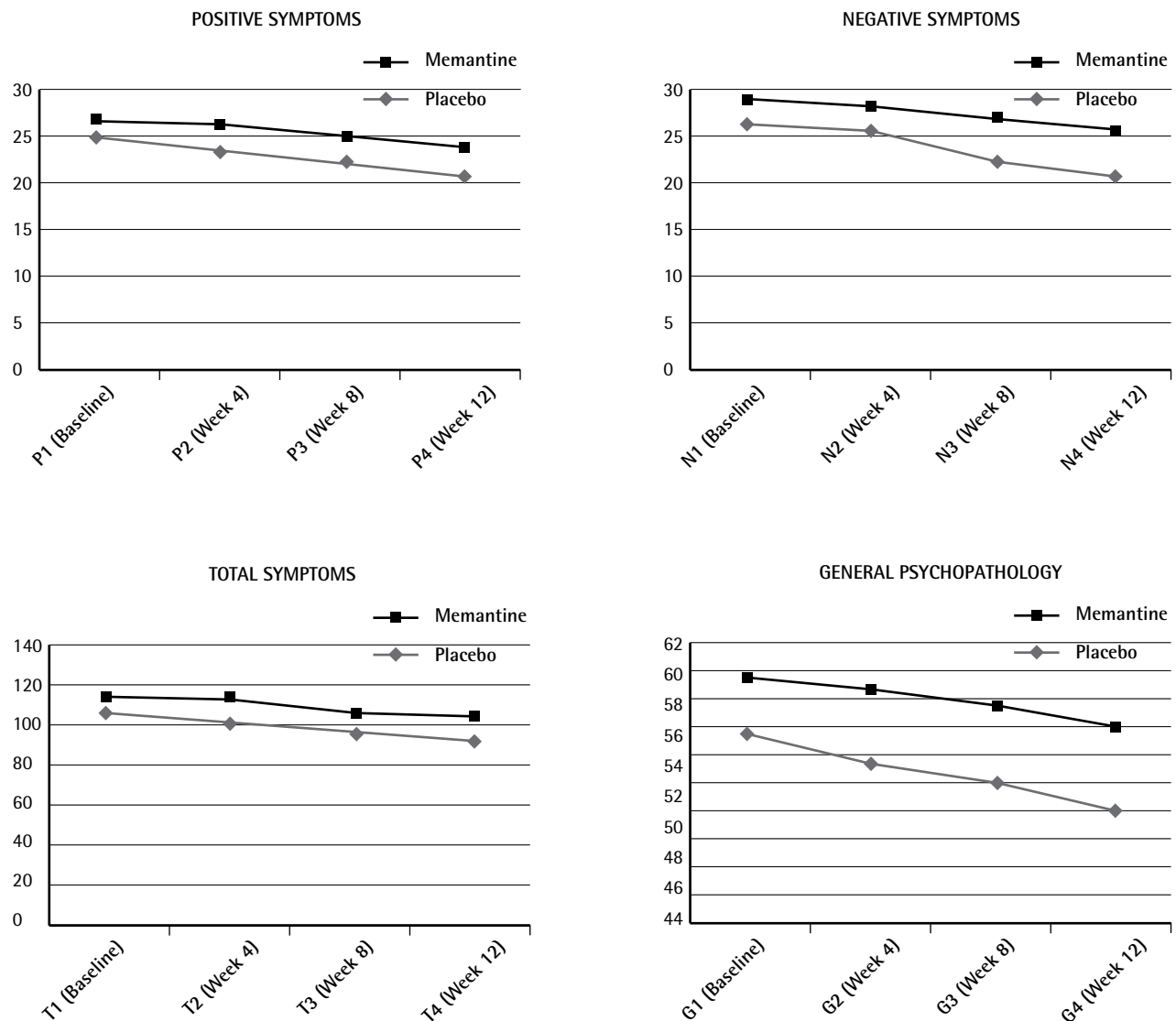


Figure 2

Comparison of positive, negative, total symptoms and general psychopathology between add-on memantine and add-on placebo, based on PANSS (Positive and Negative Symptom Scale)

Likewise, recently, Paraschakis reported that adjunctive memantine results in improvement of negative and cognitive symptoms in schizophrenia.¹⁸ In a case series study by John et al., NMDA was found to be clinically effective in treatment of positive and/or negative symptoms, cognitive and functional domains in patients with schizophrenia.⁷ Similarly, Rezaei et al. found that addition of memantine to risperidone can develop significant improvement in negative features of schizophrenia.²² Also, in a double-blind controlled study on refractory schizophrenia, De Lucena et al. showed significant improvement in both positive and negative symptoms.²³ Furthermore, in a six-week open-label trial on seven patients,

Krivoy et al. showed that an increasing dose of adjunctive memantine can yield improvements in negative symptoms and clinical status of schizophrenia.²⁴

However, some studies do not support such effective role for memantine; as Fakhari et al. presented that adding memantine to risperidone did not have any significant effect on positive and negative symptoms of schizophrenia.¹⁹ Also, Lieberman et al. showed no efficacy as an adjunctive treatment in patients with schizophrenia and residual psychopathology, who are maintained on atypical antipsychotics. The authors stated not only no therapeutic benefits with

the addition of memantine, but also worsening of psychotic symptoms and causing other side effects. The authors also mention that no clinical relevance was found between psychotic exacerbation and memantine administration.⁵ In the current study, our findings revealed neither exacerbation of psychotic symptoms, nor significant adverse effects.

The effect of memantine as an antidepressant had previously been studied in other mental conditions; but, to our knowledge, no studies have focused on the effect of memantine on depressive symptoms of schizophrenia. As an uncompetitive antagonist of NMDA receptor, memantine is hypothesized to play an antidepressant, similar to that of ketamine.^{14,25,26} However, the antidepressant effects of memantine have not been fully supported. Omranifard et al. found that co-administration of memantine did not show any significant benefit over placebo in elderly patients with depression.¹⁵ Besides, in randomized controlled trial, Smith et al. detected no significant statistical or effect size differences between memantine and placebo augmentation in patients with resistant major depressive disorder. Despite the abovementioned findings, our current study revealed a significant effect by adjunctive memantine on depressive symptoms of schizophrenia. Our finding can be explained through the neuroprotective role of memantine in schizophrenia.⁷ The antidepressant aspects of memantine can be viewed in terms of NMDA receptor blockade. Memantine like ketamine blocks NMDA receptor excessive function, modulating glutamate transmission via its post-synaptic action.¹⁵ Also, the amelioration of depressive symptoms can be explained through the potential benefits of memantine on cognitive and functional aspects, leading to better quality of life.⁷

Although our current study suggests the benefit of add-on memantine to atypical antipsychotics for treatment of depressive, positive, negative and general symptoms in schizophrenia, regarding the short duration of treatment in the present study, heterogeneous baseline treatment, further studies are required to confirm the results.

CONCLUSION

The present study shows that, memantine can be effective, as an add-on to atypical antipsychotics, in the treatment of depressive, positive, negative and general symptoms in patients with schizophrenia. Considering the safety and tolerability, memantine can be an option for adjunctive treatment in this regard.

Limitations

The study was performed in inpatient setting which makes the results less generalizable. Moreover, the reason of admission was neither studied nor adjusted in both groups.

The two groups had baseline differences in general psychopathology and total symptom severity; however, the results were statistically adjusted for base line differences. Also, changes in cognitive profile of patients were not assessed in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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