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Original Article

The Effect of Memantine Versus Folic Acid on Cognitive Impairment in Patients with Schizophrenia: A Randomized Clinical Trial

Seyed Ahmad Hosseini[1], Zahra Sepehrmanesh[1], Hamidreza Gilasi[2], Fatemeh Sadat Ghoraishi[1*]

Abstract

Objective: Schizophrenia, as one of the most severe psychiatric diseases, has a chronic and debilitating process. The majority of patients with schizophrenia do not respond adequately to treatment with common antipsychotic drugs. Therapeutic problems induced by drug side effects as well as undesired results are major challenging issues regarding this disease. This study aimed at evaluating the effect of memantine supplementation on the improvement of cognitive symptoms in patients with schizophrenia.
Method: The present clinical trial was performed on 50 patients with acute schizophrenia who were admitted to Kargarnejad Psychiatric Hospital in Kashan in 2022 and who were diagnosed as schizophrenia cases at least three months ago. Patients were randomly divided into either the intervention group (n = 25) or the placebo group (n = 25). The intervention group received 5 mg of memantine per day for three months. The dose of memantine in this group was increased to the maximum of 20 mg per day. The placebo group received 1 mg of folic acid per day for three months. Moreover, an identical routine schizophrenia therapeutic regimen was administered to all patients. The effectiveness of memantine was evaluated using the Wechsler Adult Intelligence Scale (WAIS-III), which assessed cognitive ability in older adults over a 12-week follow-up period.
Results: The WAIS-III score in the 12th week of the study was significantly different between the placebo and intervention groups (P = 0.004), such that the score of the memantine group was higher than that of the placebo group. No significant difference was observed between the two groups in terms of drug side effects.
Conclusion: Memantine can be supplemented in the treatment of schizophrenia so as to improve the cognitive symptoms of this disorder. However, subsequent studies involving larger sample sizes and different doses seem to be necessary to provide more accurate results in this respect.

Key words: *Cognitive Symptoms; Folic Acid; Memantine; Schizophrenia*

1. Department of Psychiatry, Kashan University of Medical Sciences, Kashan, Iran.
2. Department of Epidemiology and Biostatistics, Faculty of Health, Kashan University of Medical Sciences, Kashan, Iran.

***Corresponding Author:**
Address: Department of Psychiatry, Kashan University of Medical Sciences, Kashan, Iran, Postal Code: 8713783976.
Tel: 98-36 155549111, Fax: 98-36 15550036, Email: ghoreishi_f@kaums.ac.ir

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Schizophrenia can be regarded as a chronic psychiatric disorder that is recognized by a combination of both negative and positive (delusions) symptoms that affect the patients' cognition, thinking, perception, and behavior through a number of complicated mechanisms, and it frequently leads to remarkable impairments (1). In addition to the main psychotic features, sleep disorders as well as drug side effects can have an enduring effect on the patients' quality of life. The lifetime prevalence of this disease is about 0.3-0.7% (2). While men and women have a similar prevalence of schizophrenia, most studies have demonstrated that its onset among females is typically 3-5 years later than its onset among males (3). The peak age for the onset of schizophrenia is 20-28 and 26-32 years for men and women, respectively (3). Schizophrenia is a chronic disease that accounts for about 50% of psychiatric hospital beds. In addition, the costs of schizophrenia were estimated to be $281.6 billion for the national health system of the United States in 2020 (4).

Although the pathogenesis of schizophrenia has not been specified so far, the dopamine theory of attention deficit hyperactivity disorder (ADHD) assumes that dopaminergic neurotransmission hyperactivity plays a major role in this regard. Therefore, recently, various types of antipsychotics have been clinically introduced which act on dopamine receptors. In fact, most conventional antipsychotics display the functional antagonistic activity at the D2 receptor (5, 6). However, many patients with schizophrenia do not respond adequately to the treatment using conventional antipsychotic drugs and keep on experiencing negative and positive symptoms, depression, cognitive impairments, and other symptoms. In theory, residual symptoms that are leftover following the treatment with conventional antipsychotic drugs are thought to be caused by a non-dopaminergic mechanism. In addition, drugs having different mechanisms of action are regarded as an auxiliary therapy for patients with schizophrenia and comprise inhibitors of serotonin reabsorption, serotonin receptor (5-HT2CR) antagonists, 5-HT6 and 5-HT3, alpha-7 nicotinic receptor agonists, γ-Aminobutyric acid (GABA) type B (GABAB) receptor antagonists, GABAA receptor agonists, muscarinic M1 receptor agonists, anti-inflammatory drugs including cannabinoids (e.g. cannabidiol), neurokinin-3 receptor antagonists, glutamatergic factors, and cholecystokinin agonists (7).

Glutamatergic dysfunction has been known to be involved in the schizophrenia pathogenesis for many years (8), and recently much attention has been devoted to address the role of N-methyl-D-aspartate receptor (NMDAR) in this respect (9, 10). Glutamate (Glu), as the major neurotransmitter within the human central nervous system (CNS), has a significant role in learning and memory, synaptic plasticity, and other cognitive functions (11). Moreover, schizophrenia may be associated with increased Glu levels in several areas of the brain (12). Among the NMDAR antagonist compounds, there has recently been a strong emphasis on amantadine-derived memantine as an anti-influenza agent, which is a non-competitive antagonist of NMDARs (13). Although phencyclidine and Ketamine are also "open-channel blockers" of NMDARs, they indicate less voltage dependence as well as slower kinetics than Mg^{2+} and memantine (14). Memantine, as the most reversible open-channel blocker, has a far strong dependence on the functional voltage (15). The mentioned features cause memantine not to influence the physiological activation of NMDARs while leading to the stable activation in pathological circumstances (16). Memantine and Mg^{2+} are voltage-dependent antagonists and can leave the channel of NMDA receptor due to strong synaptic depolarization. However, slower blockers such as phencyclidine and ketamine remain within the canal (17). Thus, memantine can not only detect but also block pathologically-active NMDARs while not affecting the typical function of physiologically-active receptors. The mentioned feature is not common for ketamine and phencyclidine.

Memantine was initially introduced by Eli Lilly and Company and was synthesized and registered in 1968. Today, considering the "glutamatergic hypothesis" of Alzheimer's disease (15) and its neuroprotective properties (18), memantine is recommended for patients with Alzheimer's disease in moderate to severe stages as well as for those who are not intolerant to Acetylcholinesterase inhibitors (AChEIs) (17). Preclinical studies have revealed that memantine targets many receptors within high concentrations. Some of these receptors include sigma-1 receptors, nicotinic acetylcholine receptors, serotonin receptors, etc.

There are some studies investigating the use of memantine in the treatment of positive and negative symptoms and cognitive disorders of patients with schizophrenia. However, the obtained findings are inconsistent. For example, John *et al.* reported that memantine is promising as an adjunctive therapy for treating schizophrenia (19), while Lee *et al.* declared no association between memantine treatment and remarkably-improved cognitive test scores (20). Although a meta-analysis in 2017 addressed the effects of memantine on schizophrenia, the number of eligible studies to be included in that review was limited (21). Therefore, considering the prevalence of schizophrenia, the socio-economic burden it imposes on the society, the therapeutic problems caused by drug side effects, and the failure to obtain the desired results, this study attempted to investigate the effect of memantine on the cognitive symptoms of patients with schizophrenia to shed better light on this issue.

Materials and Methods

Study design

This study enjoyed a double-blind randomized clinical trial design.

Patient enrollment

The study population included all the patients with schizophrenia diagnosed at least 3 months before the study who were admitted to Kargarnejad Psychiatric Hospital in the Iranian city of Kashan in 2022. All the patients were included in the study by the census method due to the small size of this population.

The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, text revision (DSM-5-TR), was used by one psychiatrist to assess all the clients. The included cases met the DSM-5-TR criteria for schizophrenia disorder.

The inclusion criteria were being diagnosed with schizophrenia according to the DSM-5 criteria, being within the age range of 18-50 years, and using common medications for schizophrenia since at least 3 months before the start of the study. The exclusion criteria were drug dependence and addiction, history of head trauma, history of seizures, severe liver and kidney dysfunctions, severe neurological disorders, depression, and the use of medications affecting cognitive symptoms.

Procedure

After obtaining the code of ethics from the ethics committee of Kashan University of Medical Sciences (approval code: IR.KAUMS.MEDNT.REC.1398.064), the clinical trial code from the Iranian Registry of Clinical Trial (Code: IRCT20190606043827N1), and the written consent from the 50 eligible patients, their demographic information such as gender, age, educational period, and duration of schizophrenia were recorded. Then, the patients were distributed into two groups of 25, employing the random allocation software (Figure 1).

All patients underwent identical routine antipsychotic treatments. In addition, the first group (memantine) received 5 mg of memantine daily for three months. It should be noted that based on the patient's response to treatment, if necessary, the mentioned dose was increased to a maximum daily dose of 20 mg. The second group (control) received 1 mg of folic acid as a placebo daily for three months.

It should be noted that in order to comply with the double-blindness criteria, both memantine and placebo were prepared by a single pharmacist before the start of the study. Since folic acid has been indicated to improve negative symptoms of schizophrenia without any effects on patients' cognition, this drug was used as the placebo (22). Both drugs were made in the same shape, color, size, and packaging, were coded with A and B labels, and provided to the researcher. The researcher used them in each of the two groups without knowing their type. In addition, the patient and statistician had no knowledge of the type of intervention in each group.

Furthermore, in order to ensure the correct and accurate use of drugs, patients were visited weekly, and the process of taking their medicines was checked.

Outcome measurement

Before the intervention, and at the 6th and 12th weeks during the intervention, the severity of the patients' symptoms was evaluated based on the Wechsler Adult Intelligence Scale (WAIS-III), which was designed and developed by Wechsler in 1987. WAIS-III is a set of objective composite tests, is performed individually, takes 20 to 45 minutes, and provides information on separate organic and functional memory disorders (23). Previous studies have assessed the validity and reliability of this scale by the test-retest method, and its Cronbach's alpha is more than 0.7 (24). The total score of the test indicates the memory performance; higher scores mean better memory performance, while lower scores mean weakness and defects in memory (23).

Moreover, drug side effects including headache, dizziness, and restlessness were evaluated and recorded at the 6th and 12th weeks during the intervention.

Statistical analysis

Finally, the collected data was entered into SPSS software (ver. 16). Data was reported as means ± standard deviation (SD) or frequency (percentage). According to the results of Kolmogorov-Smirnov (K-S) test indicating the normal distribution of the data, the Chi-squared test and the independent samples t-test were respectively used to compare the qualitative variables between the two groups and the means of the quantitative variables. In addition, repeated measures ANOVA was used to compare the mean Wechsler score over time over the 12 weeks of the intervention in each of the two groups. The significance level of less than 0.05 was considered in all analyses.

Results

In the current study, participants of the memantine group were 60% men and 40% women with the mean age of 33.8 ± 8.78 years; while in the control group, 76% were men and 24% were women with the mean age of 31.8 ± 9.53 years. The two groups were not significantly different in terms of age, gender, educational period, and duration of schizophrenia (P-value > 0.05) (Table 1).

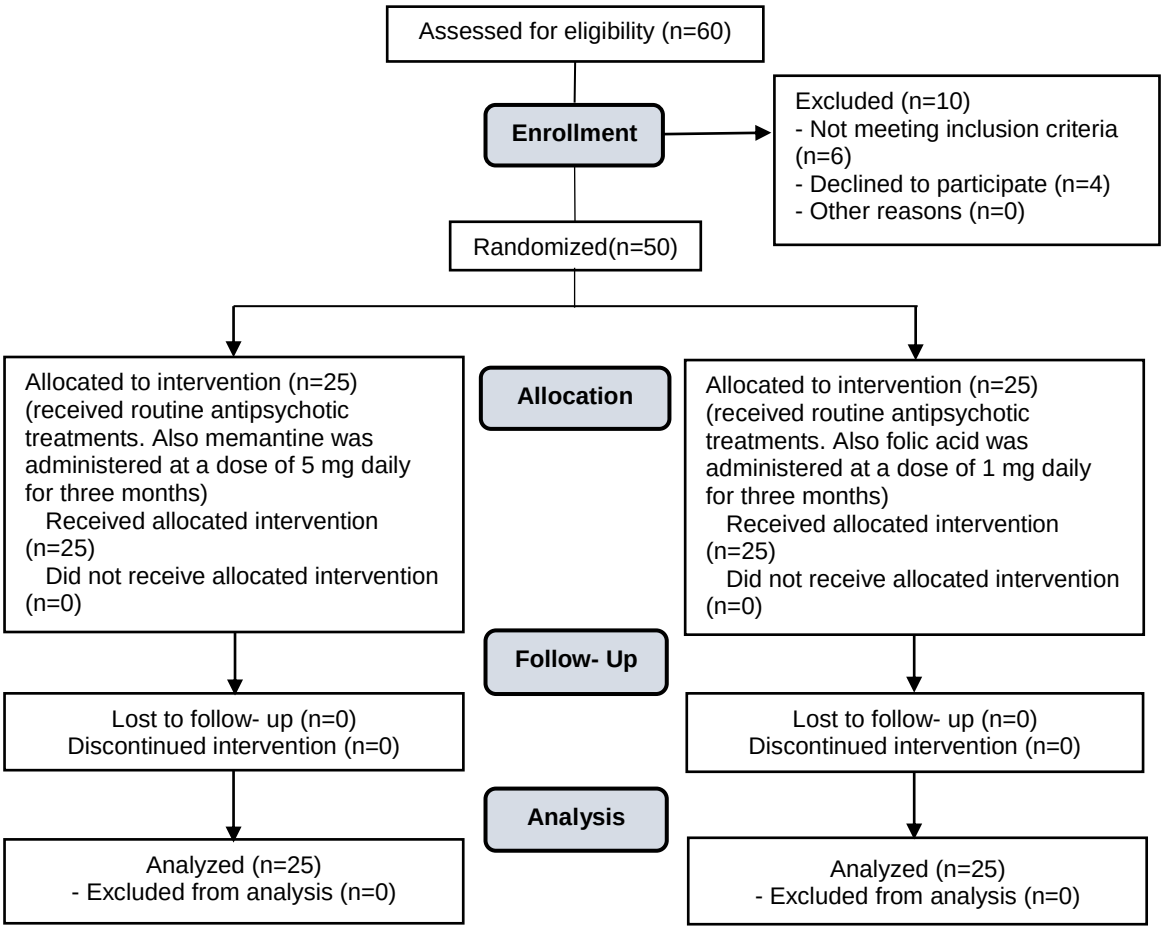

Figure 1. CONSORT Flow Diagram of Patients with Schizophrenia

Table 1. Patients' Demographic Characteristics in the Memantine and Control Groups

Variable		Memantine (n = 25)	Control (n = 25)	P-value
Gender	Male	15 (60%)	19 (76%)	0.363
	Female	10 (40%)	6 (24%)	
Age; year		33.8 ± 8.78	31.8 ± 9.53	0.299
Educational period; years		10.16 ± 3.46	8.44 ± 3.48	0.086
Duration of schizophrenia; months		161.28 ± 75.02	184.48 ± 100.04	0.358

Furthermore, the mean WAIS-III score was not significantly different between the two groups at the beginning of the study and the 6th week of the intervention (P-value > 0.05); however, this score was significantly higher in the 12th week in the memantine group, with the mean of 100.36 ± 27.66, than that of the control group with the mean of 84.72 ± 19.83 (P-value = 0.004). Moreover, the WAIS-III score increased significantly in the memantine group (F = 33.183, df = 2, P-value < 0.001) while it decreased insignificantly in the control group after the 12 weeks of the intervention (F = 1.236, df = 2; P-value = 0.102). The Bonferroni post hoc test revealed that the mean WAIS-III score in the memantine group at the beginning of the study was not significantly different from the mean score at the 6th week (P-value = 0.232); while the mean score had a significant increase in the 12th week, as compared to the beginning of the study (P-value = 0.015). In the control group, a two-by-two comparison did not indicate a significant difference in the mean values obtained at neither of the two times (P-value > 0.05) (Table 2, Figure 2).

The side effects in the memantine group included dizziness (16%), while dizziness and headache (8%) were reported in the control group. The two groups did not have a significant difference in terms of the occurrence of side effects (P-value = 0.456) (Table 3).

Table 2. Changes in the Mean Score of Wechsler Memory Test in Memantine and Control Groups

Variable	Follow up	Memantine (n = 25)	Control (n = 25)	P-value[1]
Wechsler memory test (WAIS-III)	Baseline	82.68 ± 21.98	88.56 ± 17.17	0.104
	Sixth week	88.96 ± 13.87	88.32 ± 10.74	0.391
	Twelfth week	100.36 ± 27.66	84.72 ± 19.83	0.004
F		33.183	1.236	
df		2	2	
P-value[2]		< 0.001	0.102	

1: The significance level obtained from the independent samples *t*-test comparing the mean score of WAIS-III between the two groups in each of the follow-up times
2: The significance level obtained from the Repeated Measures ANOVA comparing the mean score of WAIS-III over time within 12 weeks of the intervention in each of the two groups (F statistic and degrees of freedom (df) are also reported.)

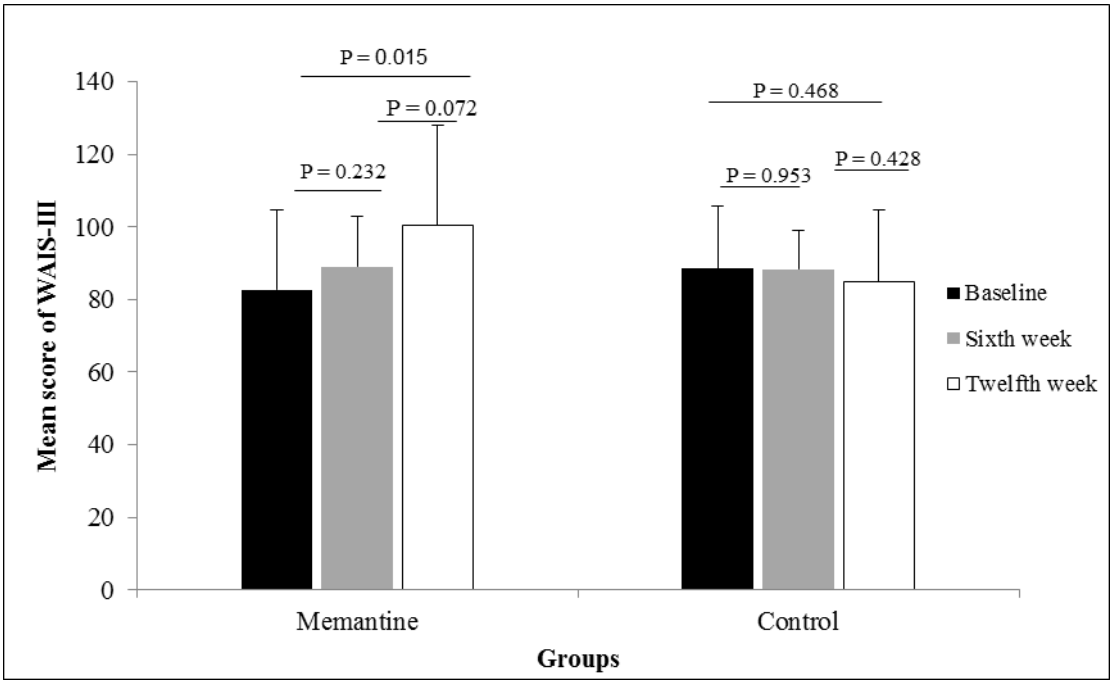

Figure 2. The Mean Score of the Wechsler Memory Test (WAIS-III) in the Memantine and Control Groups at the Follow-up Times

Table 3. Frequency Distribution of Drug Side Effects in the Memantine and Control Groups

Complications	Memantine (n = 25)	Control (n = 25)	P-value
Dizziness	4 (16%)	2 (8%)	
Headache	0 (0%)	2 (8%)	0.456
No side effects	21 (84%)	21 (84%)	

Discussion

The present study evaluated the effect of memantine on cognitive impairment of patients with schizophrenia receiving the routine treatment. The WAIS-III score at the 12th week of the study was significantly higher in the memantine group, as compared with the placebo group. In fact, over the 12 weeks of the intervention, the WAIS-III score increased significantly in the memantine group, while no significant change was found in the placebo group.

Consistent with the findings of this study, based on a 12-week randomized, double-blind, placebo-controlled trial, Mazinani *et al.* reported that memantine, as an adjunctive treatment beside risperidone, as compared with risperidone alone, significantly reduced cognitive symptoms (25). In a systematic review, Di Iorio *et al.*

revealed that increasing the use of memantine supplements played a significant role in the treatment of patients with schizophrenia, so that memantine can be considered as a promising complementary treatment in improving the symptoms of cognitive impairment in these patients (1). Another study also indicated that NMDA receptor antagonists such as memantine, as an adjunctive treatment, can improve the cognitive performance in patients with schizophrenia (26). Noteworthy is that, as shown by various studies, in addition to changes in the dopaminergic system, changes in the glutamatergic system as well as inflammation are involved in the occurrence and pathophysiology of schizophrenia (27). Therefore, a drug like memantine with two independent effects, i.e. changes in the glutamatergic system and its anti-inflammatory effect, may be effective in the treatment of the disease (14, 28, 29).

In fact, glutamatergic dysfunction has been identified in the pathogenesis of schizophrenia for many years (30) and, more recently, attention has been focused on the role of NMDAR (12, 28, 31), which is an ionotropic Glu receptor (iGluR). NMDARs can become overactive in a number of chronic neurological disorders. Excessive Ca2+ influx into the nerve cell due to the pathological activation of NMDAR results in cell death and cellular oxidative damage. The mentioned process is recognized as excitotoxicity. The over-stimulation of Glu receptors causes Glu-induced irritability in spite of the normal extracellular Glu levels (18). Among the NMDAR antagonist compounds, memantine has recently been highly emphasized. Actually, memantine is a non-competitive antagonist of NMDA receptors and also inhibits acetylcholine receptors (14). This drug is prescribed for treating moderate to severe dementia and is derived from amantadine (32). Furthermore, recent evidence shows that memantine preferentially occupies more surface areas of channel pores and has more psychotomimetic effects than NMDA receptors (33). According to conducted studies, memantine, unlike other receptor antagonists, does not seem to have an abuse potential (14). In addition to inhibiting NMDA receptors, memantine can also affect noradrenergic and serotonergic systems, so that it seems to play a significant role in memory performance (34).

Some studies, however, have reported results that contradict the findings obtained in this study and do not confirm the mechanism of memantine efficacy. For example, Krivey *et al.* revealed that memantine could not improve the cognitive function of patients with schizophrenia (35). Moreover, the results of a randomized controlled clinical trial addressing the effect of memantine used along with routine antipsychotics at a dose of 5-20 mg per day for eight weeks indicated that the patients' mean WAIS-III score based on the Wechsler criteria had no significant difference before and after the intervention. In fact, memantine cannot have a significant effect on the cognitive performance of patients with schizophrenia over eight weeks (36). It should be noted that the above studies followed up their patients for six or eight weeks, and comparing the results of these studies with the results that we obtained before the 12th week of this study shows consistency of the obtained results, as our study reported no significant change in the cognitive performance of these patients based on the WAIS-III score during the first six weeks. However, unlike the results of this study, Lieberman *et al.* stated that memantine was associated with more side effects than placebo, while there was no significant difference between the two groups in terms of side effects in our study and only four patients in each group suffered from headaches and dizziness (36). Furthermore, the results of the study by Lee *et al.* indicated that memantine supplementation did not result in the improvement of psychopathology and cognitive symptoms in patients with chronic schizophrenia. However, memantine was found to be well-tolerated in these patients (20).

When explaining the contradictions that exist between the results, it should be noted that differences in the dosages of the drug, the duration of treatment, and the duration of patients' follow-ups can play a noticeable role in the effectiveness of the drug; as John *et al.* pointed, in their study, to the long-term effect of memantine on obtaining a better treatment response (19). In addition, schizophrenia can be regarded as a complicated psychiatric disorder, whose onset, course, and outcome of treatment are affected by environmental, epigenetic, and genetic factors. Therefore, pharmaco(epi)genetic research can offer an imperative opportunity for improving patient care by predicting the drug side effects and patients' responses to the drug. Therefore, personalized medicine, ethnicity, and race may have a noteworthy effect on patients' response to memantine (37).

Limitation

Focusing on the Iranian population and having a long-term follow-up period, compared to many previous studies, can be considered as the strength of this study. Moreover, a longer treatment duration and follow-up period may be more effective in achieving better results by this drug. However, the small sample size was one of the most important limitations of this study, as we could not evaluate the effectiveness of the drug by adjusting the patients' basic variables in a multivariate regression model. Moreover, the different dosages of the drug could not be tested in this study to find the optimal effective dose. Furthermore, another limitation of this study was not evaluating the negative and positive symptoms of this disease by the Positive and Negative Syndrome Scale (PANSS). This study mainly addressed the cognitive function of the patients, as memory and neuro-cognitive disorders are the main disorders in schizophrenia. Considering the positive effect of memantine over a 12-week follow-up period, it can be

suggested to conduct studies that evaluate the cognitive function and the changes of positive and negative symptoms of these patients using the PANSS score.

Conclusion

The results of the current study showed that memantine can be considered a suitable supplement for treating cognitive symptoms with no side effects in patients with schizophrenia. Nonetheless, to obtain more accurate results, further multicenter studies involving larger sample sizes and different doses can be illuminative. According to the studies performed on its mechanism of action, it seems that memantine, as an NMDAR antagonist, can improve cognitive symptoms in schizophrenia.

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Conflict of Interest

None.

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