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Daily Oral Memantine Attenuated the Severity of Borderline Personality Disorder Symptoms: A Double-Blind Placebo-Controlled, Randomized Clinical Trial

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Abstract

Background: Borderline personality disorder (BPD) has been considered a psychiatric disorder, the effective pharmacological treatments for which have not been well established.
Objectives: This study aimed to assess the efficacy of memantine (10 mg/day) in reducing BPD severity and cognitive impairment.
Methods: The BPD patients diagnosed by psychologists were included and divided into the placebo (n = 19) and memantine (n = 20) groups. Included participants were randomized, double-blinded, and stabilized on the medication and psychotherapy for at least four weeks. The patients in the memantine group received oral memantine (10 mg/day) for four weeks. The severity of BPD was assessed by a self-reported questionnaire named Borderline Evaluation of Severity Over Time (BEST). Moreover, the Wisconsin test was carried out to assess executive function.
Results: The mean score of the BEST test significantly decreased in week eight post-treatment in the memantine group. In addition, a significant decrease in this score was indicated in the memantine group compared to the placebo group in week eight. The mean total score of the BEST test was not significantly different before and after the placebo administration. There was no significant difference in the Wisconsin subscales, including the number of wrong answers and categories achieved after memantine or placebo administration. Perseverative errors rose after the administration of memantine. Adverse side effects did not occur in any of the participants.
Conclusions: Our findings suggested the potential therapeutic effects of memantine for BPD. Furthermore, we found that a low dose of meantime might be preferable to prevent the side effects.

Keywords: Borderline Personality Disorder, Memantine, Mood Disorder, N-Methyl-D-aspartate, Wisconsin

1. Background

Borderline personality disorder (BPD) is characterized by disability in affect regulation, impulse control, self-image, and interpersonal relationships. Mood disorders, anxiety, substance abuse, attention deficit hyperactivity disorder, and cognitive impairments, such as executive functions, have been considered the most common comorbidities of BPD (1). Most patients have reported adverse life events during childhood, but the neurobiological mechanisms of BPD are poorly understood (2). The hyperactivity of the hypothalamic-pituitary-adrenal axis and impairment of serotonergic, glucocorticoid, aminergic, and glutamatergic systems might be involved in the pathophysiology of BPD (3).

N-Methyl-D-aspartate (NMDA) signaling pathways are critical in some neurodevelopmental alterations and neurological disorders (4). Over-activation of NMDA receptors following environmental stimulations, including chronic

stress or social separation, involves the dysfunction of the hippocampus, amygdala, prefrontal, and cingulate cortex (5). High glutamate concentration in the anterior cingulate cortex exacerbates impulsivity and has been considered a diagnostic biomarker of BPD (6). Although psychotherapy is known as the primary treatment of BPD, some pharmacological treatments, including neuroleptics and selective serotonin reuptake inhibitors, have been prescribed to control severe symptoms (6). Furthermore, the improving effects of some NMDA modulators, namely lamotrigine, and topiramate, have been reported on anger, affective instability, and impulsivity of BPD (7).

Memantine, an uncompetitive voltage-dependent NMDA-receptor blocker, has been introduced as an effective medication to improve moderate to severe dementia in Alzheimer's disease (8). Some clinical trials have reported the potential efficacy of memantine in treating other neurological and neuropsychiatric disorders, such as peripheral neuropathy, depression, and schizophrenia (9, 10).

2. Objectives

A clinical trial in 2018 reported the improving effect of memantine at a dose of 20 mg/day on BPD symptoms (10). In that study, some patients had headaches, fatigue, or dizziness as the adverse effects of treatment. In our study, as the second clinical trial, to avoid any unwanted side effects, the efficacy of a low dose of memantine (10 mg/day) on the severity of BPD and the impairment of executive function was evaluated.

3. Methods

3.1. Ethics Approval

The Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC.1399.1185) approved the study protocol. After a complete explanation of the research process, written consent was obtained from the participants.

3.2. Participants

This randomized, double-blind, placebo-controlled clinical trial was performed on females or males aged 16 - 45 years referred to the Iran Psychiatric Hospital, Tehran, Iran (affiliated with Iran University of Medical Sciences, Tehran, Iran), and met the inclusion criteria. The sampling process was performed during Murch 2021-June 2022. BPD patients were diagnosed by psychologists based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for BPD. The participants were randomized, double-blind, and stabilized on medication and psychotherapy for at least four weeks.

The inclusion criteria were men and women aged 16 - 45 years, diagnosis of BPD, and ability to read and write in Persian. Exclusion criteria were neurological disorders, brain trauma, epilepsy, pregnancy, addiction, using drugs that might interact with memantine, and some psychotic conditions, such as schizophrenia, bipolar, psychotic depression, and mental retardation. Subjects who did not meet the mentioned conditions or were unwilling to complete a questionnaire were excluded.

Included participants were randomized by permuted block method and four blocks. In each block, 12 participants (six for the placebo group and six for the memantine group) were included and were matched in terms of three variables, age, gender, and education, with a ratio of 1:1. The outcome assessor, data analyzers, and randomizers were separate individuals, all of whom were blinded to allocation. The allocated group of each participant was printed sequentially and enveloped in a non-transparent and sealed envelope similar in appearance, using the random permuted block. The allocation was not within the reach of the subjects and outcome assessors. The outcome assessor, randomizer, and statistical analyzer were separate individuals, and all of them were blinded to allocation. Memantine and placebo tablets were similar in size, shape, color, and odor.

3.3. Interventions

Participants included in this study were divided into memantine (n = 20) and placebo groups (n = 19). Patients in the two groups were matched by age, gender, and education level. The details of the participants are shown in Table 1. Patients were stabilized on medication and psychotherapy in weeks 1 - 4 and then received a placebo or memantine (10 mg/day) in the placebo and memantine groups in weeks 5 - 8, respectively.

3.4. Outcomes

Changes in the severity of BPD symptoms and executive function as the main primary outcomes were assessed by the Borderline Evaluation of Severity Over Time (BEST) questionnaire and the Wisconsin Card Sorting Test (WCST), respectively.

The severity of BPD was assessed by the self-reported questionnaire named BEST. The acceptable BEST Persian version with high face and content validity and reliability has been published (11). Participants completed the BEST questionnaires in the baseline and weeks 2, 4, 6, and 8 of the trial. The BEST questionnaire contains fifteen items

Table 1. Analysis of Participants' Details by Chi-Square and Fisher's Exact Test [a]

Characteristics	Groups		Total	P-Value
	Placebo (n = 19)	Memantine (n = 20)		
Age, mean ± SD	27.42 ± 7.28	26.85 ± 8.63	27.12 ± 7.90	0.825
Gender				0.605
Male	12 (63.2)	11 (55.0)	23 (59.0)	
Female	7 (36.8)	9 (45.0)	16 (41.0)	
Education level				0.423
high school diploma or less	12 (63.2)	15 (75.0)	27 (69.2)	
University education	7 (36.8)	5 (25.0)	12 (30.8)	
Marital status				0.661
Single	16 (84.2)	16 (80.0)	32 (82.1)	
Married	2 (10.5)	4 (20.0)	6 (15.4)	
Divorced	1 (5.3)	0 (0.0)	1 (2.6)	
Employment				0.658
Employed	4 (21.1)	6 (30.0)	10 (25.6)	
Unemployment	14 (73.7)	12 (60.0)	26 (66.7)	
Homemaker	1 (5.3)	2 (10.0)	3 (7.7)	
History of psychiatric disorders				0.487
No	0 (0.0)	2 (10.0)	2 (5.1)	
Yes	19 (100.0)	18 (90.0)	37 (94.9)	
Hospitalization history				0.005
No	11 (57.9)	3 (15.0)	14 (35.9)	
Yes	8 (42.1)	17 (85.0)	25 (64.1)	
Suicide attempts				0.634
No	10 (52.6)	9 (45.0)	19 (48.7)	
Yes	9 (47.4)	11 (55.0)	20 (51.3)	

[a] Values are expressed as No. (%) unless otherwise indicated.

and three subscales, each scored from 1 to 5 on a Likert scale. The subscale A with eight items assesses thoughts and feelings during the past month. Subscale B, with four items, addresses negative behaviors during the past month. Items in subscales A and B are rated based on severity (1: None/slight; 5: Extreme). Subscale C with three items evaluates positive behaviors. The items in subscale C are rated based on their frequencies (1: Almost never; 5: Almost always). The total score of the severity of the disorder is obtained by subtracting the scores of subscale C from the sum of the scores of subscales A and B. The resulting scores are between -3 to 57. Finally, a correction factor of 15 is added to change the range to a positive direction. The final range of the scale is 12 - 72, which indicates BPD's low to high severity (12). The total score of the BEST difference between the baseline and weeks 2, 4, 6, and 8 among the two groups was the first outcome measured.

Moreover, the executive function of participants as the other outcome was measured by WCST. The WCST was performed at the baseline and end of the intervention (week 8) to assess executive function. This test was developed by Berg to evaluate flexibility in thinking and shifting to a new response to changing environmental contingencies (13). It is used as a measure of executive function (14). The WCST consists of four stimulus cards, and the subject receives two sets of 64 response cards. The subject should match

response cards to the stimulus cards and receive feedback on whether he/she is right or wrong on each trial.

The computer-based Wisconsin test designed by the Sinai Research Institute of Cognitive Behavioral Sciences was used. The acceptable software of the Persian version with high face and content validity and reliability has been published (15). The participants were trained to match the suggested card to the four stimulus cards. The correctness or incorrectness of each trial was displayed on the monitor. The results of different subscales in WCST, including the number of wrong answers, perseverative errors, and categories achieved, were recorded (16). To assess the executive function of participants, each scale was compared at the baseline and the end of the trial in the placebo and memantine groups. Furthermore, side effects were assessed using a systematic questionnaire in both groups before and after medication administration.

3.5. Sample Size and Statistical Analysis

Based on the first clinical placebo-controlled trial published in 2018, the sample size with a power of 80% and a significance level of 5% was calculated (10). Assuming a 20% dropout rate, the sample size was 24 per group. The data were adjusted by the history of hospitalization and baseline variables as the main cofounders.

The comparison among categorical variables was made by the two-tailed Fisher's exact test. The score changes in different time points within each group were analyzed by Repeated Measures ANOVA. Furthermore, the mean ± SD of the BEST score was compared at each time point between groups using the independent samples *t*-test. The probability values less than 0.05 were considered significant. The statistical software SPSS version 22 was used for data analysis.

4. Results

4.1. Participants

Sixty-four patients were enrolled in the study. Sixteen patients did not meet the inclusion criteria. Forty-eight participants were included and randomly divided into the placebo and memantine groups. Twenty patients in the memantine group and 19 patients in the placebo group completed the study (Figure 1). No one of the dropouts met adverse effects or drug interactions. The details of the characteristics are mentioned in Table 1.

The results of chi-square and Fisher's exact tests showed no statistically significant difference in the frequency distribution of variables (gender, education level, marital status, employment status, history of psychiatric disorders, and history of suicide attempts) between the two groups ($P > 0.05$). However, a significant difference was noted in the history of hospitalization ($P = 0.005$). In addition, the results of the two-sample independent *t*-test showed that the mean age was not significantly different between the two groups at a 95% confidence level ($P = 0.825$).

4.2. Adverse Side Effects

Adverse events were recorded during the study. Mild side effects were indicated in both placebo and memantine groups; however, they did not lead to treatment discontinuation. There was no significant difference in the frequency of side effects between the two groups (Table 2).

4.3. Severity Assessment of BPD

The mean total score of BEST was assessed in the placebo and memantine groups at different treatment time points (baseline, weeks 2, 4, 6, and 8; Table 3).

The mean ± S.E.M of BEST score significantly decreased after daily oral memantine received in week 8 compared to baseline ($P < 0.001$). There was no significant difference before and after the placebo administration. Moreover, the mean total score of BEST in the memantine group was compared to the placebo by independent samples *t*-test (Table 3). A significant reduction was indicated in the eighth week in the memantine group compared to the placebo group ($P < 0.001$). There was no significant difference between the groups on the baseline and weeks 2, 4, and 6.

The details of ANCOVA statistical analysis of unadjusted and confounder-adjusted estimates with 95% confidence interval are mentioned in Tables 4 and 5, respectively. The hospitalization history and baseline variables were adjusted by the cofounders.

4.4. Wisconsin Subscale Scores

Wisconsin subscales, including the number of wrong answers, perseverative errors, and categories achieved, were compared in each group on the baseline and week 8 (beginning and end of the trial) (Table 6). There was no significant difference in none of the wrong answers and categories achieved subscales before and after medication administration in the placebo and memantine groups. However, perseverative errors significantly increased in the memantine group before and after medicine administration ($P < 0.05$). The details of ANCOVA statistical analysis of unadjusted and confounder-adjusted estimates with 95% confidence interval are mentioned in Tables 7 and 8, respectively. The hospitalization history and baseline variables were adjusted as cofounders.

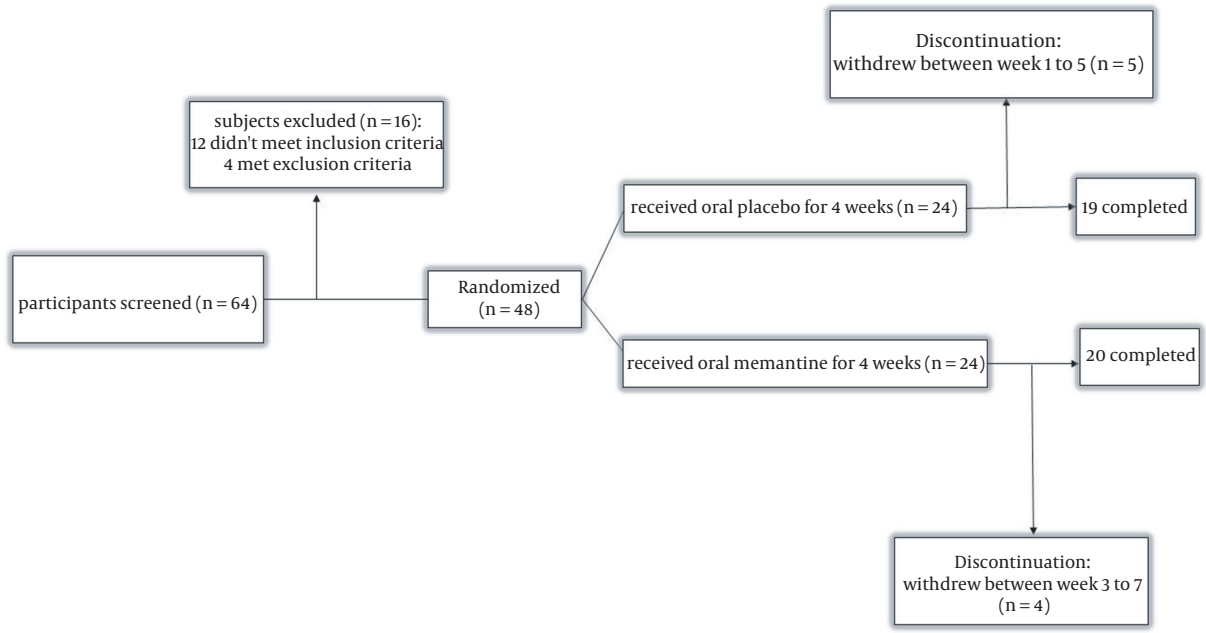

Figure 1. Trial participants' flow-diagram

Table 2. Frequency of Side Effects

Side Effects	Placebo, No. (%)	Memantine, No. (%)	P-Value
Somnolence	1 (5.2)	2 (10)	0.82
Tiredness	2 (10.5)	1 (5)	0.83
Headache	0 (0)	0 (0)	0.99
Decreased appetite	1 (5.2)	2 (10)	0.82
Vomiting	0 (0)	0 (0)	0.99
Dizziness	0 (0)	1 (5)	0.85
Diarrhea	0 (0)	0 (0)	0.99

Table 3. BEST Scores

Time Points	Placebo	Memantine	P-Value *	Adjusted P-Value $
Baseline best	39.26 ± 1.98	38.49 ± 3.39	0.390	
Week 2	38.67 ± 2.78	37.13 ± 3.82	0.162	0.479
Week 4	40.80 ± 3.65	39.46 ± 4.96	0.347	0.208
Wee 6	40.35 ± 2.73	38.34 ± 4.44	0.098	0.426
Week 8	39.76 ± 2.65	31.05 ± 4.07	< 0.001	< 0.001
P-value #	0.106	< 0.001		

[a] Values are presented as mean ± SEM. *, independent samples *t*-test; #, repeated measures ANOVA; $ analysis of covariance.

Table 4. ANCOVA Statistical Analysis of Unadjusted Estimates with a 95% Confidence Interval of BEST Scores

Parameter	B	Std. Error	*t*	P-Value	95% Confidence Interval	
					Lower Bound	Upper Bound
Week 2						
Intercept	37.134	0.751	49.465	<0.001	35.613	38.655
Group						
Placebo	1.534	1.076	1.427	0.162	-0.645	3.714
Memantine	0	-	-	-	-	-
Week 4						
Intercept	39.461	.957	41.216	< 0.001	37.521	41.401
Group						
Placebo	1.337	1.372	0.975	0.336	-1.442	4.117
Memantine	0	-	-	-	-	-
Week 6						
Intercept	38.350	0.813	47.161	< 0.001	36.702	39.997
Group						
Placebo	1.999	1.165	1.716	0.095	-0.362	4.359
Memantine	0	-	-	-	-	-
Week 8						
Intercept	31.046	0.772	40.231	< 0.001	29.482	32.610
Group						
Placebo	8.718	1.106	7.885	< 0.001	6.477	10.958
Memantine	0	-	-	-	-	-

5. Discussion

In this double-blind, placebo-controlled clinical trial, we examined a low dose of memantine (10 mg/day) for eight weeks to improve BPD symptoms. Our data showed a significant decrease in the mean score of BEST on week 8 compared to weeks 2 and 4 in the memantine group. In addition, a significant decrease in this score was indicated in the memantine group compared to the placebo group on week 8.

The therapeutic effect of memantine on BPD was in the same direction as other different psychiatric disorders. Based on reported studies, memantine prevented stress-induced problems and caused mood stabilization in bipolar disease (17-19). Moreover, memantine could diminish disinhibition, irritability, aggression, and false impression in Alzheimer's disease (20). Irritability in patients with autism and mania in patients with bipolar disorder were significantly improved by memantine (21, 22). In addition, the efficacy of memantine at a higher dosage (20 mg/day) has been reported to improve BPD symptoms; however, more than 40% of participants experienced some adverse effects, including mild headache, fatigue, or dizziness (10).

In this regard, our data showed that a low dose of memantine (10 mg/day) for 8 weeks could effectively improve BPD symptoms while the side effects of the medication were decreased. However, the participants were not matched in terms of hospitalization history, and the data were adjusted by this confounder variable. More participants with a history of hospitalization were included in the memantine group indeliberately. Although the history of hospitalization might be related to the severity of the disorder, the relation between the history of hospitalization and the severity of the disorder was not assessed in our study. This bias has been carried out unintentionally, and more assessment would be necessary in future studies.

In a 12-week study on memantine monotherapy in adults with ADHD with 10 mg daily, some participants had mild adverse effects, such as systolic blood pressure and mood and visual problems (23). Therefore, a follow-up longer than 8 weeks in future studies seems to help determine the presence or extent of side effects at a low dose (10 mg/day) of memantine in BPD patients.

Executive function deficits are one of the most common cognitive problems among BPD patients and are as-

Table 5. ANCOVA Statistical Analysis of Confounder-adjusted Estimates with 95% Confidence Interval of BEST Scores [a]

Parameter	B	Std. Error	*t*	P-Value	95% Confidence Interval	
					Lower Bound	Upper Bound
Week 2						
Intercept	51.858	7.191	7.211	< 0.001	37.258	66.457
Baseline best	-0.350	0.185	-1.888	0.067	-0.725	0.026
Hospitalization history	-1.535	1.200	-1.279	0.209	-3.972	0.902
Group						
Placebo	1.179	1.165	1.012	0.479	-1.185	3.543
Memantine	0	-	-	-	-	-
Week 4						
Intercept	18.235	9.094	2.005	0.053	-0.227	36.697
Baseline best	0.520	0.234	2.221	0.033	0.045	0.995
Hospitalization history	1.496	1.518	0.986	0.331	-1.585	4.578
Group						
Placebo	1.529	1.473	1.038	0.347	-1.461	4.519
Memantine	0	-	-	-	-	-
Week 6						
Intercept	28.256	8.159	3.463	0.001	11.692	44.821
Baseline best	0.245	0.210	1.167	0.251	-0.181	0.671
Hospitalization History	0.808	1.362	0.593	0.557	-1.957	3.573
Group						
Placebo	2.133	1.321	1.614	0.098	-0.549	4.816
Memantine	0	-	-	-	-	-
Week 8						
Intercept	40.981	7.639	5.365	< 0.001	25.474	56.489
Baseline best	-0.226	0.197	-1.148	0.259	-0.625	0.173
Hospitalization history	-1.497	1.275	-1.174	0.248	-4.086	1.091
Group						
Placebo	8.271	1.237	6.686	< 0.001	5.759	10.782
Memantine	0	-	-	-	-	-

[a] The hospitalization history and baseline variables have been considered cofounders.

sociated with self-harm behaviors, impulsivity, and social functions (24-26). Memantine has been reported to ameliorate cognition disturbances in Alzheimer's, epilepsy, and breast cancer (11, 27). On the other hand, it fails to improve cognition in Parkinson's disease or Down syndrome (28). In the current study, we evaluated the effect of memantine on the cognitive impairments of BPD subjects, and our results showed that memantine could not improve cognitive executive disabilities. Some research indicated that a dose-dependent steady-state plasma level of memantine is needed to achieve desirable cognition (29, 30). Therefore, to achieve a potential improvement in executive cognitive functions in BPD patients. The prescription of memantine for more extended periods is needed in future stud-

Table 6. Wisconsin Subscales Scores

Wisconsin Subscales	Placebo	Memantine	P-Value *	Adjusted P-Value $
Wrong answers				
Before	30.11 ± 10.00	36.70 ± 3.44	0.012	
After	32.00 ± 9.63	33.80 ± 8.92	0.549	0.222
Difference between before and after	1.89 ± 5.34	-2.90 ± 9.14	0.053	
P-value #	0.140	0.172		
Perseverative errors				
Before	9.84 ± 6.62	4.70 ± 3.95	0.005	
After	9.00 ± 6.86	7.70 ± 7.22	0.284	0.118
Difference between before and after	-0.84 ± 2.67	3.00 ± 5.97	0.007	
P-value #	0.186	0.037		
Achieved categories				
Before	2.53 ± 1.90	3.85 ± 1.87	0.017	
After	2.89 ± 2.18	3.20 ± 2.50	0.344	0.160
Difference between before and after	0.37 ± 1.67	-0.65 ± 2.76	0.720	
P-value #	0.35	0.114		

[a] Values are presented as mean ± SEM. *, independent samples *t*-test; #, paired samples *t*-test; $, analysis of covariance.

Table 7. ANCOVA Statistical Analysis of Unadjusted Estimates with a 95% Confidence Interval of WCST Subscales Results

Parameter	B	Std. Error	*t*	P-Value	95% Confidence Interval	
					Lower Bound	Upper Bound
After Treatment, Wrong Answers						
Intercept	33.800	2.074	16.297	0.000	29.598	38.002
Group						
Placebo	-1.800	2.971	-0.606	0.548	-7.821	4.221
Memantine	0	-	-	-	-	-
After Treatment Achieved Categories						
Intercept	3.200	0.526	6.080	0.000	2.134	4.266
Group						
Placebo	-0.305	0.754	-0.405	0.344	-1.833	1.223
Memantine	0	-	-	-	-	-
After Treatment, Preservative Error						
Intercept	7.700	1.576	4.886	0.000	4.507	10.893
Group						
Placebo	1.300	2.258	0.576	0.284	-3.275	5.875
Memantine	0	-	-	-	-	-

Table 8. ANCOVA Statistical Analysis of Confounder-adjusted with 95% Confidence Interval of WCST Subscales Results [a]

Parameter	B	Std. Error	*t*	P-Value	95% Confidence Interval	
					Lower Bound	Upper Bound
After Treatment, Wrong Answers						
Intercept	10.361	7.290	1.421	0.164	-4.438	25.160
Before right answers	0.720	0.168	4.284	0.000	0.379	1.062
Hospitalization history	-3.528	2.824	-1.249	0.220	-9.262	2.206
Group						
Placebo	1.437	2.981	0.482	0.222	-4.614	7.488
Memantine	0	-	-	-	-	-
After Treatment Achieved Categories						
Intercept	0.539	1.085	0.496	0.623	-1.665	2.743
Before achieved categories	0.816	0.163	5.000	0.000	0.484	1.147
Hospitalization history	-0.564	0.697	-0.808	0.425	-1.980	0.852
Group						
Placebo	0.533	0.701	0.759	0.160	-0.891	1.957
Memantine	0	-	-	-	-	-
After Treatment, Preservative Error						
Intercept	2.498	1.866	1.338	0.189	-1.291	6.286
Before preservative error	0.952	0.154	6.183	0.000	0.640	1.265
Hospitalization history	0.854	1.893	0.451	0.655	-2.989	4.698
Group						
Placebo	-3.231	2.016	-1.603	0.222	-7.324	0.862
Memantine	0	-	-	-	-	-

[a] Hospitalization history and baseline variables were considered cofounders.

ies. Moreover, we only used WCST to examine the executive function and cognition of our participants. Perhaps, the assessment of different subdomains of executive functioning through related tests, namely the listening span task (LST), Eriksen flanker task (FT), or letter fluency task (LFT) (31), in future studies can be helpful to gain more precise results. In addition, the inclusion of more participants with a history of hospitalization in the memantine group, which might indicate a more severe disorder, might be involved in the lack of effectiveness of memantine in WCST. Therefore, matching the participants regarding hospitalization history in future investigations is recommended.

Memantine, at a higher dosage, has affected serotonin, sigma-1, and nicotinic acetylcholine receptors, as well as serotonin and dopamine uptake. Lower dosage administration acted as an NMDA receptor blocker, especially in the CNS (32). It has been indicated that the hypo-activation of NMDA receptors triggered neural toxicity that might originate from GABAergic neurons disinhibition since diazepam and barbiturates suppressed ketamine-induced psychosis (32). The neurotoxicity severity depends on the type and dosage of NMDA receptor antagonist (33, 34). Memantine, as a low-affinity antagonist, had fewer side effects than other NMDA receptor blockers. In addition, our findings proposed that a low dose of memantine administration might reduce the probability of general side effects occurrence.

In conclusion, memantine as an NMDA antagonist seems to be effective in improving some symptoms of BPD (35). Our findings suggested that a low dose of memantine might be considered a new pharmacological approach to improve some BPD symptoms without adverse effects.

5.1. Limitations

Some limitations in our research should be considered in future studies. Considering delayed response in some psychiatric disorders, and individual differences in response to medications, a longer follow-up than 8 weeks seems to be beneficial for achieving stronger and clear efficacy of treatment on the severity of symptoms and cognitive functioning of patients (36). Moreover, we only used WCST to examine the executive function and cognition of our participants. Using more tests to examine different aspects of cognition can further strengthen and clarify the results. In addition, matching the participants in terms of hospitalization history should be considered in the future.

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Footnotes

Authors' Contribution: Conception and design of research: Fariba Karimzadeh; Data and sample collection: Homa Mohammadsadeghi, Maryam Soleimannejad; Analysis and interpretation of data: Mohammadreza Shalbafan, Mehrdad Eftekhar Ardebili; Preparation of the manuscript: Samira Ramazi, Nooshin Ahmadirad; Pharmacological observation: GelarehVahabzadeh; Critical revision of the manuscript for important intellectual content: Fariba Karimzadeh.

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Data Reproducibility: The dataset presented in the study is available on request from the corresponding author.

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