Memantine Augmentation of Sertraline in Severity of Symptoms and Cognitive Function Among Patients with Obsessive-Compulsive Disorder: A Double-Blind Placebo-Controlled, Randomized Clinical Trial

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Abstract

Background: Medications currently recommended for the treatment of Obsessive-Compulsive Disorder (OCD) usually decrease the severity of the symptoms by 20–30%, and 40–60% of OCD patients do not achieve satisfactory treatment. In this study, the main objective was to investigate the effectiveness of memantine, which is a non-competitive N-Methyl-D-aspartate (NMDA) receptor antagonist, as an adjunct therapy to sertraline, a selective serotonin reuptake inhibitor (SSRI), to improve severity of symptoms and cognitive function among patients with obsessive-compulsive disorder.

Methods: 70 patients who based on Diagnostic and Statistical Manual of Mental Disorders (DSM–5) criteria were diagnosed with OCD, and had a Yale-Brown obsessive compulsive scale (Y-BOCS) score of more than 21, were recruited in a placebo controlled, double-blinded, parallel-group, clinical trial of 12 weeks to receive either memantine (10 mg twice daily) and sertraline (100 mg daily initially followed by 200 mg daily after week 4) or placebo and sertraline. The primary outcome was OCD symptoms measured by the Y-BOCS, moreover, the executive function and the cognition of participants was measured by the Wisconsin Card Sorting Test (WCST).

Results: Y-BOCS score in total, obsession and compulsion subscales significantly dropped in both groups; however, there was not a significant difference between them. In comparison of cognition, memantine group showed a greater response in number of categories subscale in the WCST (p value<0.001). No major adverse effects were observed in any of the groups.

Conclusion: Our findings suggest a probable effect of memantine as adjuvant therapy to sertraline on cognitive function of patients with OCD as well as its safety and tolerability in comparison with placebo. Nevertheless, the current results don`t support the efficacy of memantine as an adjunctive agent to sertraline for improving severity of symptoms among patients with OCD.

Trial registration: The trial was registered at the Iranian Registry of Clinical Trials on 2019-10-04 (www.irct.ir; IRCT ID: IRCT20170123032145N4).

Background

Obsessive-Compulsive Disorder (OCD) affects 1–3% of worldwide population (1, 2). OCD is characterized by recurrent, unwanted and intrusive thoughts, urges or images which causes anxiety and discomfort, and/or by repetitive behaviors or mental acts that tries to prevent or reduce the associated anxiety(3, 4). If left untreated, the course is chronic (5). OCD impairs quality of life severely and causes impairment in all aspects of function(6, 7). It has shown that patients with OCD have significant differences, with the control group, in tests related to verbal memory, psychomotor speed and global attention, visuospatial and executive functions, indicating poorer performance(8, 9). Cognitive impairments, particularly deficiencies in executive functions and information processing, considerably suppress patient's abilities to gain, maintain and relearn the skills needed for suitable performances and association between poorer

neuropsychological performance and real-life functioning has been shown in OCD patients(10, 11). Apart from the public health impact, OCD also results in a considerable economic burden(12).

Currently, selective serotonin reuptake inhibitors (SSRIs) and/or cognitive behavioral therapy (CBT), are considered to be first-line treatments for OCD (13, 14). Notwithstanding the effectiveness of CBT as a non-pharmacological treatment, it has several disadvantages such as delayed clinical response, limited access, and high cost(15). SSRIs usually reduce the Obsessive-Compulsive Disorder symptoms by as much as 20–30% and in only 40–60% of patients with OCD Satisfactory treatment is obtained(16, 17).

The cortico-striato-thalamo-cortical (CSTC) circuits, driven by the excitatory neurotransmitter glutamate, are described to be involved in OCD(18). Glutamate has an important role in many physiological processes including memory, cognition and learning(19). The striatum is an important brain region in the pathophysiology of OCD and is responsible for motor and cognitive actions(20). Glutamatergic neurons are the most abundant neurons in cell migration within the striatum and migration is also tightly controlled by glutamate(21). Some studies have shown that glutamatergic over-activity, increased glutamate levels in cerebrospinal fluid (CSF), and polymorphism of N-methyl-D-aspartate (NMDA) receptor's gene coding, play a part in OCD occurrence(22–25). Due to high proportion of resistance to SSRI treatment, the focus has shifted to the effect of glutamate and the CSTC brain circuit(26). Also there is evidence suggesting that the temporal lobe (TL) has an important role in the brain pathogenesis of OCD(27–29).

Memantine is a non-competitive NMDA receptor antagonist approved for Alzheimer's disease in many countries, with a good safety profile, being studied in a variety of psychiatric disorders(30). It may decrease hyperactivity of the direct pathway of CSTC(26). Memantine has a targeted de-excitation effect in the temporal lobes on the glutamatergic system and connected brain regions, that might further reduce OCD symptoms(28). The specific effect of memantine on temporal lobe can be even more helpful in certain patients and subtypes with specific deficits in cognition and maladaptive compensatory memory processes(26).

Open-label studies(31), single (32) and double-blind randomized controlled trials (RCTs)(33, 34) show benefits of adding memantine to ongoing SSRI in treatment of OCD. As methodological issues exist with each of these trials and inconsistent findings, and lack of studies on effect of memantine on cognitive impairments in OCD patients(20), this study aimed to investigate the benefits of memantine augmentation therapy with sertraline in reduction of OCD symptoms and cognitive impairments in OCD patients compared to sertraline plus placebo.

Methods

Trial setting and design

A 12-week, randomized, double-blind, placebo-controlled, parallel-group trial was performed at the outpatient clinics of Iran Psychiatric Hospital and Tehran Institute of Psychiatry (affiliated with Iran

University of Medical Sciences, Tehran, Iran).

Participants were randomized to groups with a random permuted block method (ratio of 1:1 and blocks of four). 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 in reach of the participants and outcome assessors. The outcome assessor, randomizer, and statistical analyzer each were separate individuals and all of them were blinded to allocation. Additionally, memantine and placebo tablets were similar in size, shape, color, and odor.

Participants

Patients, aged 18–60 years, with a clinical diagnosis of OCD based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria, were screened for the study (35). Those with a Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥ 21 (moderate to-severe OCD) were included (36).

The patients attending to the clinics were consecutively checked for the inclusion criteria and recruited until the sample size was achieved. All of the patients enrolled in the study were assessed with a structured clinical interview designed in accordance with the DSM-5 by an expert psychiatrist (35).

The exclusion criteria were :1) comorbid axis I disorders; 2) a life threatening psychiatric symptoms (such as suicidal ideation); 3) serious medical or neurological conditions; 4) mental retardation (based on clinical judgment); 5) substance dependence (other than nicotine) 6) pregnancy/breast feeding; 7) history of severe allergy to or contraindication for the use of memantine or sertraline; 8) history of complete response with sertraline 9) history of previous psychosurgery for OCD; 10) history of treatment-refractory OCD. During the conduction of the trial, patients were not permitted to participate in any psychotherapeutic treatment. Furthermore, patients were excluded if they used any psychotropic drugs in the last 6 weeks.

Interventions

Eligible participants were randomized to receive either memantine, 10mg twice per day, or placebo for 12 weeks. All participants, regardless of group assignment, 100 mg/day for 4weeks and then gradually increased to 200mg/day. To minimize the side effects, the dosage of sertraline was slowly increased every week.

Outcome

Y-BOCS was used for assessment of patients at baseline and at weeks 0, 4, 8, and 12 of therapy. Y-BOCS provides a rating scale for severity of obsessive-compulsive symptoms (34–36). This clinician-rated scale contains 10 questions, each item rated from 0 (no symptoms) to 4 (extreme symptoms)(37). The psychometric properties of the Persian version of Y-BOCS are approved in previous studies (14, 16, 36).

The total score of the Y-BOCS difference between the baseline and the week 12 among the two groups was the primary outcome measure of the trial.

We used Wisconsin Card Sorting Test (WSCT) to examine participant's executive function at weeks 0 and 12 of therapy. The WCST was developed by Berg and Grant to assess flexibility in thinking and shifting to a new response to changing environmental contingencies(38). It is used as a measure of executive function(39, 40). 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 whether he or she is right or wrong on each trial. Important scales in the WCST include the number of categories achieved, the number of perseverative errors, and the number of set-loss errors(41).

The difference of each scale of the WCST between baseline and the end of the trial between the two groups were measured to assess the executive function and cognition of participants.

Moreover, adverse effects were monitored each four weeks using a systematic questionnaire and three open questions to include any other side effects not included in the questionnaire. In case of observation of any serious adverse effects during the course of therapy, a physician assessed the potential role of the medication in inducing the adverse effects and omitted the patient from the trial.

Missing data was imputed with last observation carried forward (LOCF) method.

Sample size and statistical analysis

With a between-group difference of five points in Y-BOCS score, type I error of 5% and power of 90%, using G-power 3.1.9.2 we calculated a sample size of 58 (29 in each group). Considering a drop-out rate of 20%, our final sample size was calculated 70 (35 in each group).

IBM SPSS Statistic 16.5 (IBM Corporations, Somers, New York, USA) was used for the statistical analysis. Continuous variables were reported as mean ± SD and categorical variables as n (%). Mean differences (MDs) between groups were reported as MDs (95% confidence interval (CI)). Fisher's exact test, or $\chi 2$-test was used for the comparison among categorical variables. The independent samples t-test was conducted for the comparison of continuous variable values, respectively. The comparison of Y-BOCS total and subscale score changes and WCST scale scores in and between groups during the 12-week course of study was achieved by performing General linear model repeated measures. Whenever sphericity of the data could not be assumed using the Mauchly's test of sphericity, the homogeneity of the variance is tested with Levene's test. Score changes from baseline in the participants of each group was examined using the paired sample t-test. A p-value level of $\leqslant 5\%$ was defined as significant.

Results

Participants

One hundred and four patients were screened primarily, while 70 patients were recruited (randomly assigned to groups of memantine+sertraline or placebo+sertraline), and 53 patients completed the trial. Trial flow diagram and number of dropouts are represented in Figure 1. None of the dropouts was in regard of adverse effects or substance use. In first 4weeks there were 35 patients in memantine group and 30 patients in placebo group that the Baseline characteristics of each group are summarized separately in Table 1.

Table 1

Baseline characteristics of participants in first 4weeks

		Treatment Group				
		memantine+sertraline (n=35)		placebo+sertraline (n=30)		P value
		Mean±SD	Count (%)	Mean±SD	Count (%)	
Age (years)		35.03±11.35		334.83±10.30		
Gender	Female		27 (77.1%)		17 (56.7%)	0.07
	Male		8 (22.9%)		13 (43.3%)	
Education	Illiterate		0 (0.0%)		1 (3.3%)	0.30
	Primary		1 (2.9%)		2 (6.7%)	
	Secondary		9 (25.7%)		5 (16.7%)	
	High school diploma		9 (25.7%)		13 (43.3%)	
	University Education		16 (45.7%)		9 (30.0%)	
Marital status	Single		18 (51.4%)		11 (36.7%)	0.08
	Married		14 (40.0%)		17 (56.7%)	
	Divorced		0 (0.0%)		2 (6.7%)	
	Separated		3 (8.6%)		0 (0.0%)	
Employment	Employed		18 (51.4%)		18 (60.0%)	0.71
	Unemployed		7 (20.0%)		4	

				(13.3%)	
	Housewife		10 (28.6%)	8 (26.7%)	
Previous treatment	Yes		4 (11.4%)	2 (6.7%)	0.50
	No		31 (88.6%)	28 (93.3%)	
Y-BOCS score (week 0)	Total	27.88±5.65	30.11±5.79		0.12
	Obsession	15.07±2.57	15.53±2.50		0.46
	Compulsion	12.70±4.30	14.57±3.81		0.07
WCST score (week 0)	Error	22.89±9.85	22.09±10.63		0.80
	Categories	3.36±1.77	3.90±1.86		0.35
	Perseveration	6.15±5.54	7.88±9.02		0.47
SD: standard deviation; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale.					

Y-BOCS total score

The baseline Y-BOCS total score's difference was not significant between the groups (MD (95% CI) = -2.23(−5.07–0.61), p-value=0.12, Table 1). Total Y-BOCS score changes from baseline in memantine group at fourth and 12th week of the study was MD (95% CI) = 4.85 (1.77–7.92) (p-value<0.001) at week 4 and MD (95% CI) = 16.66 (13.62–19.69) (p-value<0.001) at 12th week, respectively. Similarly, participants in the placebo group experienced significant Y-BOCS total score drop at fourth and 12th week into the trial (MD (95% CI) = 7.88 (4.48–11.27) (p-value <0.001) in the 4th week and MD (95% CI) = 20.61 (17.35–23.86) (p-value<0.001) in the end) General linear model repeated measures revealed no significant difference for the time between memantine and placebo groups (p-value= 0.71) (Figure 2).

Y-BOCS obsession subscale score

The baseline Y-BOCS obsession subscale score was not significantly different among treatment groups (MD (95% CI) =-0.46 (-1.72-0.80), p-value=0.46 (Table1)). Obsession Y-BOCS score changes from baseline in memantine group at fourth and 12th week of the study were MD (95% CI) = 2.62 (1.20–4.03) (p-value<0.001) at week 4 and MD (95% CI) = 8.88 (7.38–10.37) (p-value<0.001) at 12th week, respectively. Similarly, participants in the placebo group experienced significant Y-BOCS total score drop at 12 weeks into the trial, while their score change mean differences were MD (95% CI) = 10.23 (8.82–11.63) (p-value

<0.001) and in the 4th week (MD (95% CI) = 3.80 (2.13–5.46) (p-value<0.001)) respectively. The time×treatment group interaction analysis by general linear model repeated-measures revealed no significant difference between groups (p-value= 0.33) (Figure 3).

Y-BOCS compulsion subscale score

The baseline Y-BOCS compulsion subscale score was not significantly different among treatment groups (MD (95% CI) =-1.87 (-3.89_0.15), p-value=0.07 (Table1)). Compulsion Y-BOCS score changes from baseline in both groups at 4th and 12th week of the study. Memantine group difference in 4th was MD (95% CI) = 2.33 (0.15–4.50) (p-value 0.03) and MD (95% CI) = 7.80 (5.77–9.82) (p value< 0.001) in the 12th week and placebo group experienced significant Y-BOCS compulsion score drop at week (4 MD (95% CI) = 4.15 (2.07–6.28) (p-value<0.001)) and in week 12 (MD (95% CI) = 10.42 (8.34–12.49) (p-value<0.001)), respectively but the time×treatment group interaction analysis by general linear model repeated-measures revealed no significant difference (p-value=0.87) (Figure 4).

Table 2

Comparison of Yale-Brown obsessive-compulsive scale (Y-BOCS) subscales score change from baseline for treatment groups

Y-BOCS subscale score reduction		Treatment group					
		memantine+sertraline			placebo+sertraline		
		Mean±SD	MD (95% CI)	p-Value	Mean±SD	MD (95% CI)	p-Value
Total	Week 4	23.03±6.42	4.85 (1.77-7.92)	<0.001	22.23±6.88	7.88 (4.48-11.27)	<0.001
	Week 12	11.22±6.26	16.66 (13.62-19.69)	<0.001	9.5±6.34	20.61 (17.35-23.86)	<0.001
Obsession	Week 4	12.55±3.01	2.62 (1.20-4.03)	<0.001	11.73±3.67	3.80 (2.13-5.46)	<0.001
	Week 12	6.29±3.33	8.88 (7.38-10.37)	<0.001	5.3±2.76	10.23 (8.82-11.63)	<0.001
Compulsion	Week 4	10.37±4.16	2.33(0.15-4.50)	0.03	10.42±4.15	4.15 (2.01–6.28)	<0.001
	Week 12	4.90±3.42	7.80 (5.77–9.82)	<0.001	4.15±3.92	10.42 (8.34–12.49)	<0.001

WCST number of errors subscale score

The baseline WCST number of errors subscale score did not significantly differ among treatment groups (MD (95% CI)=0.80 (-5.78-7.38), p-value=0.80 (Table1)). WCST number of errors score reduced in memantine group (MD (95% CI)=5.21 (-1.11-11.53)) between week 0 to 12 but the difference was not significant. (p-value=0.10). It did not change significantly in placebo group in the course of the trial. (MD (95% CI)=-0.29 (-5.73-6.32), p-value=0.92) and general linear model repeated measures revealed no significant difference between two groups (p value= 0.53) (Figure 5).

WCST number of categories subscale score

The baseline WCST number of categories subscale score did not significantly differ among treatment groups (MD (95% CI)=-0.54 (-1.70-0.62), p-value=0.35 (Table1)). WCST number of categories score changed significantly between week 0 to 12, in memantine group ((MD (95% CI)=-1.48 (-2.62- -0.33), p-

value=0.01) but it did not change significantly in placebo group.(MD (95% CI)=0.19 (-0.93-1.31), p-value=0.73) and general linear model repeated measures revealed significant difference between two groups (10.938 (1.38)=0.77 p-value<0.001) (Figure 6).

WCST number of perseverative errors subscale score

The baseline WCST number of perseveration subscale score did not significantly differ among treatment groups (MD (95% CI)=-1.73 (-6.58-3.12), p-value=0.47 (Table1)). WCST number of perseveration score did not change significantly between week 0 to 12, in both groups. (MD (95% CI)=2.05 (-1.43-5.53), p-value=0.24 in memantine group and MD (95% CI)=2.12 (-2.22-6.48), p-value=0.33 in placebo group) and general linear model repeated measures revealed no significant difference between two groups (p value= 0.40) (Figure 7).

Adverse effects

Adverse events were recorded during the study. Side effects were mild and did not result in withdrawal. Frequency of side effects was not different between the two groups (Table 3).

Table 3

Frequency of adverse events in the two groups

Adverse events	Trearment group				
	memantine+sertraline		placebo+sertraline		p-value
	N	%	N	%	
Muscle pain	2	5.7	2	6.7	0.87
Headache	2	5.7	2	6.7	0.87
Diarhea	1	2.9	0	0	0.35
Constipation	0	0	0	0	1
Decreased libido	5	14.3	3	10	0.60
Decreased appetite	5	14.3	3	10	0.60
Lightheadness	1	2.9	0	0	0.35
Palpitation	0	0	1	3.3	0.28
Insomnia	3	8.6	0	0	0.10
Vomiting	3	8.6	1	3.3	0.38

Discussion

Results of the current clinical trial don`t show a significant difference in the improvement of severity of symptoms of patients with moderate to severe OCD with augmentation of memantine (10mg/ twice per day) to sertraline through 12 weeks of the study. Although, the findings indicate a significant improvement of executive function of the patients of memantine arm in Categories, one of the items of WSCT, in comparison with the placebo group. Interestingly, observed adverse effects were not suffering nor life-threatening in both groups and none of the adverse effects was, significantly, higher in the memantine group than the placebo group.

To the best of our knowledge, four previous randomized-placebo controlled clinical trial have investigated the efficacy of memantine as an adjunctive agent to standard serotonergic medications for the treatment of OCD and reported complex findings of its efficacy, whereas this is the first 12-week double-blind, placebo-controlled clinical trial to evaluate the efficacy of memantine on the severity of symptoms as well as the cognitive function of patients with moderate to severe OCD, as an augmentation to sertraline.

Our results are in agreement with Farnia et al. report that investigated the efficacy of memantine plus fluoxetine in an 8-week, three arms trial with gabapentin plus fluoxetine and placebo plus fluoxetine in outpatients with OCD. Similar to our report, they didn`t show a significant difference between arms based on neither YBOCS total score nor response rate (33). We report the same finding in our 12-week trial about the augmentation of memantine to another approved SSRI, sertraline. Nevertheless, Ghaleiha et al. reported memantine (10 mg/ twice per day) plus fluvoxamine more efficient than placebo plus fluvoxamine in an 8-week double-blinded, randomized, controlled trial among thirty-eight patient in the treatment of severity of symptoms and response rate of patients with moderate to severe OCD patients. In agreement with our trial, they observed no significant adverse effect in the memantine group in comparison with the placebo group(42). Our trial provided longer follow-up as well as, to some extent, a larger sample size. The inconsistency of these two trials might be on account of augmenting memantine to different medications.

Modarresi et al. investigated the efficacy of memantine (10 mg/ twice per day) as an augmented agent for the treatment of patients with Serotonin Reuptake Inhibitors (SRIs) treatment-refractory OCD among thirty-two participants in a 12-week trial. Moreover, they indicated a significant reduction of severity of symptoms based on YBCS as well as more response rate in the memantine group than the placebo group. In addition, similar to our findings, they reported memantine as a well-tolerated and safe agent(34). The results of their study are hardly comparable to ours due to substantial differences between recruited participants. Their trial was performed among SRIs treatment-refractory patients, while we recruited patients with moderate to severe symptoms with non-refractory OCD. Standard medications were mixed among both groups, whereas we used sertraline with the same dose among both groups to elaborate more comparable results between each group.

In the same vein, Haghighi and his colleagues performed a 12-week placebo-controlled trial on 29 inpatients with OCD to evaluate the efficacy of memantine (5–10 mg/ day) as an adjunctive agent to an

SSRI or clomipramine. They reported YBOCS decreased, significantly, in the memantine group in comparison with the placebo group(35).

Two trials of Bakhla et al., and Aboujaoude et al., are not easily comparable with our study due to their different designs as open-label trials(31, 43). Moreover, study of Stewart et al., is a single-blinded case-control study that cannot be compared with our study as double-blinded controlled trial. Same as previously mentioned trial findings of the study is not easily comparable with our findings due to difference of patient setting, the dosage of memantine as well as standard medications.

Although some of the evidence presented supports the efficacy and safety of glutamatergic medications like memantine in the treatment of OCD patients, a recent review article suggested more well-conducted in vivo and basic experimental studies(20).

Additionally, we evaluated the effect of memantine as an augmentation to sertraline for improvement of cognitive impairment of patients with moderate to severe OCD that is one of the most disabling manifestations of this neuropsychiatric disorder(8, 9, 12). To the best of our knowledge, our study is the first double-blind, placebo-controlled, clinical trial for this purpose. Despite the efficacy of the agent on cognitive impairment of other neuropsychiatric conditions, more specifically Alzheimer is well- known(44), our finding showed a probable efficacy of augmentation of memantine to sertraline in this manner, however, more well-designed with a larger sample size as well as long follow-up are necessary.

Limitations

Despite numerous strengths of the current study, there are some important limitations for our trial that should be considered by further studies. Although the sample size of our study was larger than previous studies, this is a clinical trial with small sample size. In addition, as we know, based on delayed response in OCD patients in comparison with some other neurotic psychiatric disorders like depression, a 12-week follow-up seems to be a short time to observe the efficacy of the treatment on the severity of symptoms and cognitive functioning of the patients. Moreover, we only used WCST to examine the executive function and cognition of our participants. Using multiple tests to examine different aspects of cognition and using functional brain imaging and electroencephalography can show the purpose of this study, even more clear. Therefore, designing multi-center trials with a large sample size, with multiple tools to examine cognition and executive function, and longer follow-up is suggested. The effect of improved cognition on quality of life of patients was not the purpose of our study and was not examined by us. Additional studies on this concept is suggested. Finally, we recruited patients with non-refractory OCD in the study, and generalization of the findings to this group of patients is not reasonable.

Conclusion

Our findings suggest a probable effect of memantine as adjuvant therapy to sertraline on cognitive function of patients with OCD as well as its safety and tolerability in comparison with placebo.

Nevertheless, the current results don`t support the efficacy of memantine as an adjunctive agent to sertraline for improving the severity of symptoms among patients with OCD. Based on mixed results about the efficacy of memantine on OCD symptoms, further trials are necessary.

Abbreviations

Obsessive-Compulsive Disorder: OCD; N-Methyl-D-aspartate: NMDA; selective serotonin reuptake inhibitor: SSRI; Diagnostic and Statistical Manual of Mental Disorders: DSM–5; Yale-Brown obsessive compulsive scale: Y-BOCS; Wisconsin Card Sorting Test: WCST; Cognitive Behavioral Therapy: CBT; Cortico-striato-thalamo-cortical (CSTC); Cerebrospinal fluid: CSF; Temporal lobe: TL; Randomized controlled trial: RCT; Mean difference: MD; confidence interval: CI; standard deviation: SD

Declarations

Ethics approval and consent to participate

The trial was approved by the ethics committee of Iran University of Medical Sciences institutional review board (IR.IUMS.REC.1398.640) and conducted according to the Declaration of Helsinki and subsequent revisions. Written informed consent was obtained from all participants. Patients were informed that their participation was a voluntary activity and that they had the right to leave the study at any time with no negative effect on their treatment. The trial was registered at the Iranian Registry of Clinical Trials (www.irct.ir; IRCT ID: IRCT20170123032145N4).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to report.

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Authors' contributions

SA, SVS, BS and MS made substantial contributions to the conception and design of the work. SA, BS, MY and MS have substantial contribution in data gathering. SVS analyzed and interpreted the data. SA, SM, and MS have major contribution in writing the manuscript. All authors read and approved the final manuscript.

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Figures

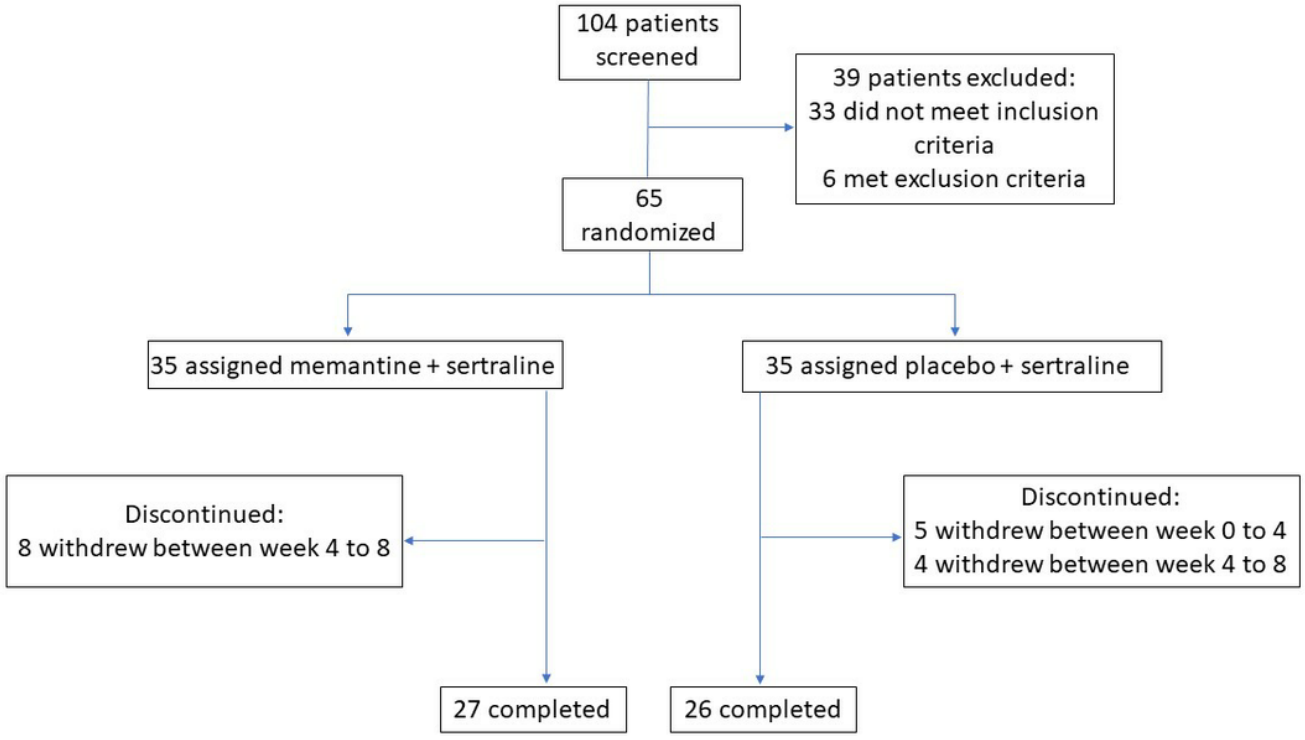
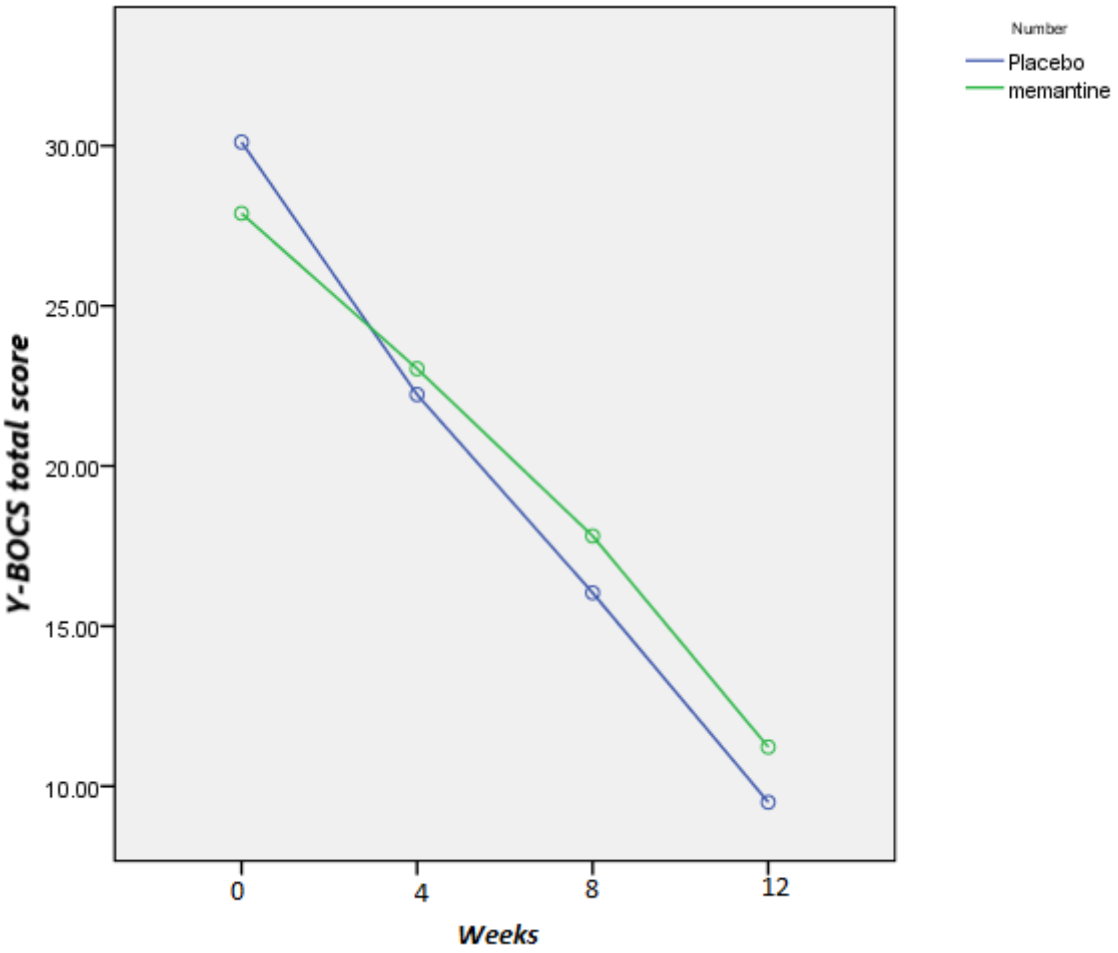


Figure 1

Trial participants' flow-diagram.

Figure 2



Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score trend for each group during the trial course

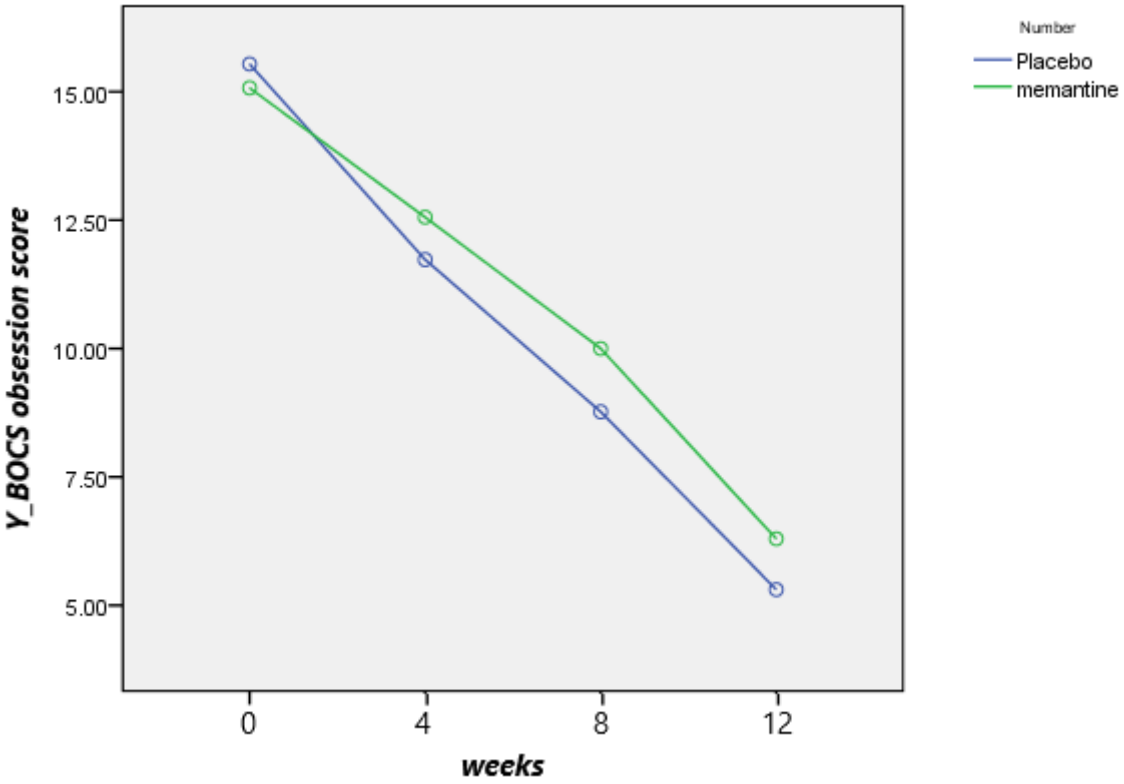


Figure 3

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) obsession subscale score trend for each group during the trial course

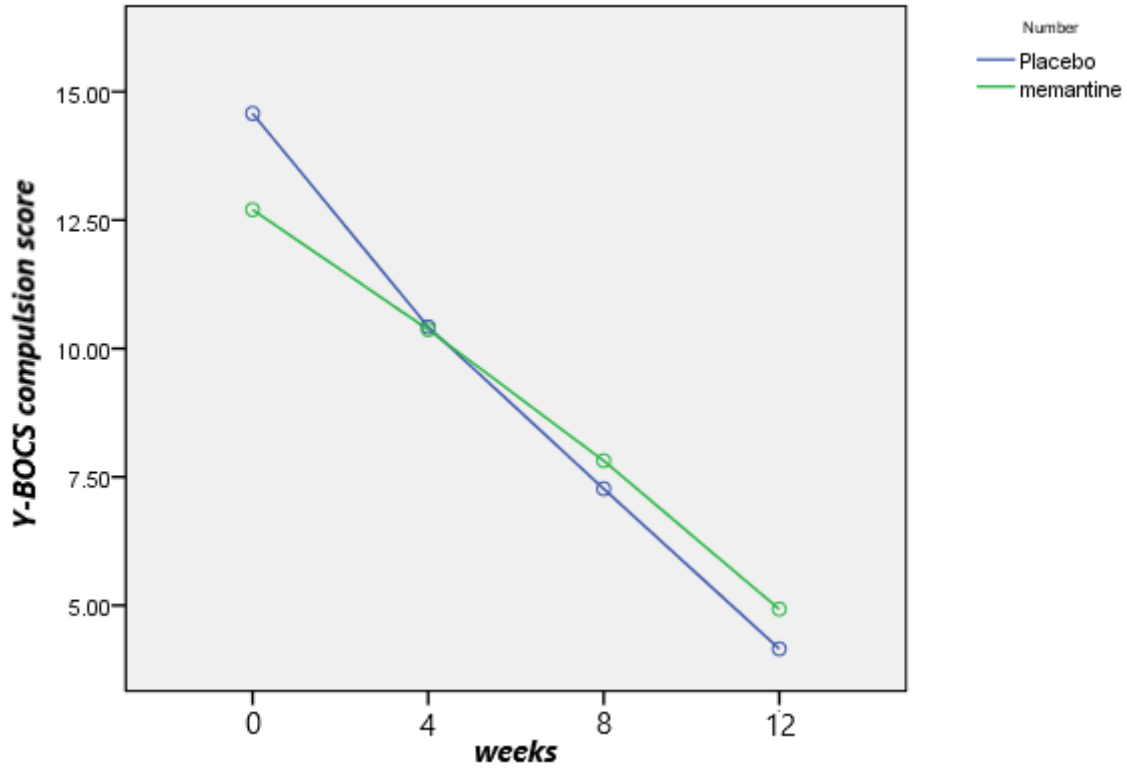


Figure 4

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) compulsion subscale score trend for each group during the trial course

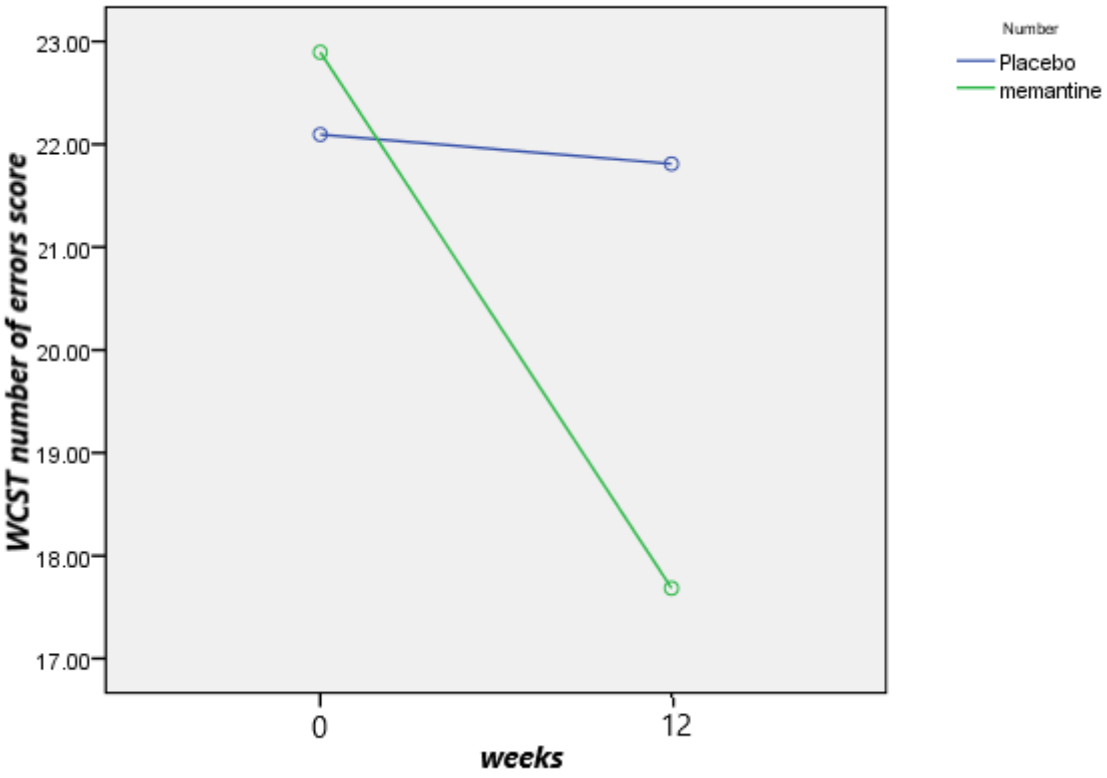


Figure 5

WCST number of set-loss errors subscale score trend for each group during the trial course

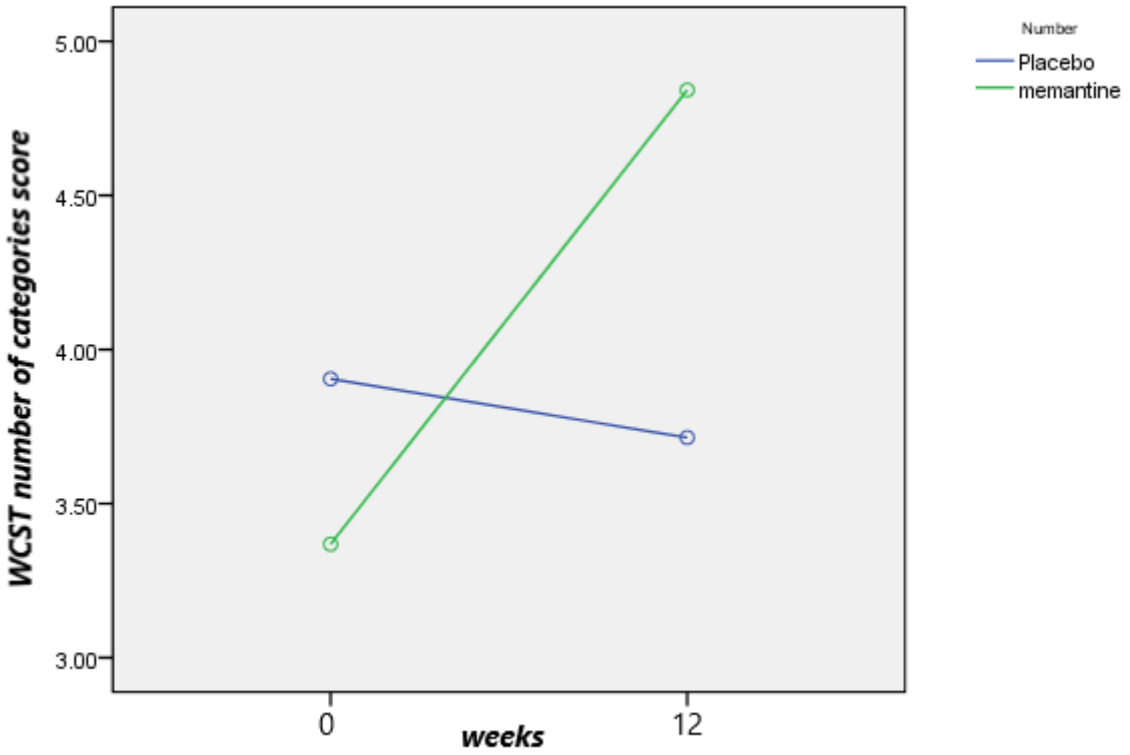


Figure 6

WCST number of categories subscale score trend for each group during the trial course

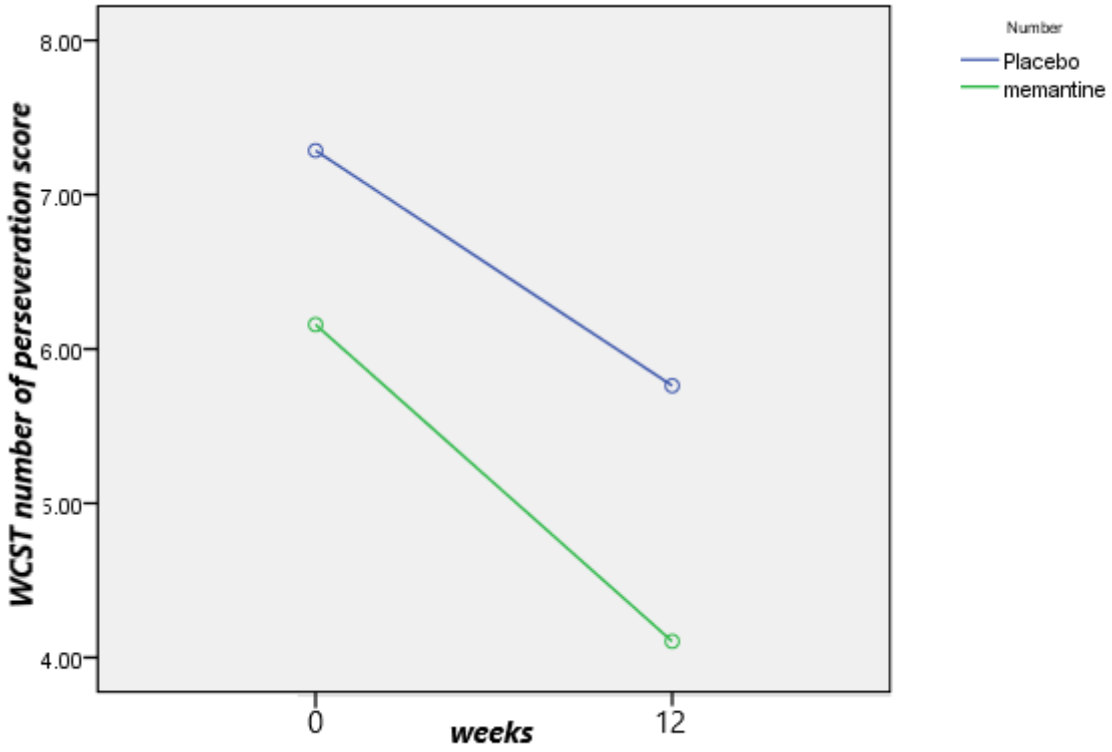


Figure 7

WCST number of perseverative errors subscale score trend for each group during the trial course

Supplementary Files

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