

Efficacy of memantine augmentation in moderate to severe obsessive-compulsive symptoms

First author : Dr.Zahra Sepehrmanesh,
second and corresponding author: Atefeh Sattarinezhad,
3 Fatemeh Sadat Ghoreishi, 4Habibollah Rahimi

Abstract

Background: Obsessive-compulsive disorder (OCD) is one of the most common neuropsychiatric disorders with a 60% treatment response. This trial was designed to assess the efficacy of memantine augmentation in moderate to severe OCD.

Methods: This double-blinded trial was performed on 30 outpatients aged 18-60 years randomly assigned into two groups. One group received memantine with a daily dose of 5-10 mg plus 50-200mg of sertraline for eight weeks. The other group received sertraline plus a placebo for the same duration. A psychiatrist assessed patients at week 0,2,4,8 with Yale-Brown Obsessive Compulsive Scale (Y-BOCS). One-way repeated measure ANOVA was performed using IBM SPSS software.

Results: Participants included 30 outpatients aged (38.30 ± 10.66) years, 80% women. There was no significant difference between the two groups in terms of demographic data. During follow-up, the total Y-BOCS score decreased in both groups ($P < 0.05$) without a significant between-group difference. Friedman test indicated a decrease in obsession subscale scores with no significant between-group difference ($P < 0.05$). In the case of the compulsion subscale, there was a significant decrease in groups ($P < 0.05$), more considerably in the memantine than in the placebo group ($P < 0.05$).

Conclusions: Memantine augmentation of sertraline has no superiority over standard treatment except for the compulsion subscale.

Keywords: Obsessive-Compulsive Disorder, Memantine, Selective Serotonin Reuptake Inhibitor, Glutamate

Background

Obsessive-compulsive disorder (OCD) is a common disorder of the new Obsessive and Compulsive Related Disorders (OCRD) category of the Diagnostic and Statistical Manual of mental disorders fifth edition (DSM-5) known to be a leading cause of morbidity and caregiver burden [1, 2] with a worldwide prevalence of 1-3% [3, 4] and 1.8% in Iran [5]. Only 60 percent of patients who receive standard treatment with serotonin reuptake inhibitors (SRIs) or cognitive behavioral psychotherapy (CBT) respond to the treatment [6]. Administration of CBT is limited due to the unavailability of trained psychotherapists and its dependence on patient cooperation and higher price of services [3, 7- 9]. Transcranial direct current stimulation (t.DCS), repeated transcranial magnetic stimulation (r.TMS), and deep brain stimulation (DBS) techniques are neither available nor applicable to all patients [8, 10]. Therefore; several pharmacological augmentation strategies have been proposed based on the neurotransmitters implicated in the etiology of OCD which is mostly located in the cortico-striato-thalamo-cortical circuit (CSTC), a key circuit involved in OCD. CSTC direct pathway hyperactivity and/or its indirect pathway hypo activity result in glutamate excitotoxic concentrations [11, 12]. Serotonin and dopamine systems dysregulation underlie OCD development [2, 13, 14]. Polymorphism of N-methyl D-aspartate (NMDA) receptor and glutamate hyperactivity is related to OCD [2, 14, 15, 16]. Serotonin reuptake inhibitors serve as first-line treatments for OCD [17- 19]. Several augmentation strategies have been suggested based on the neurotransmitters involved in the pathophysiology of OCD. Dopamine antagonists such as antipsychotics have been utilized to augment the treatment of OCD in treatment-resistant patients, but due to the adverse effects of antipsychotics, glutamate inhibitors appear to be a safer option [19, 20, 21, 22]. Memantine, a partial non-competitive glutamate antagonist, has been tried in several clinical trials. It is an approved

treatment for Alzheimer's disease with minimal side effects [11, 19, 23, 24]. Following several case series, and open-label studies, Ghaleiha et al explored memantine efficacy in a randomized double-blind placebo-controlled study on patients with moderate to severe OCD [11, 25- 30]. Haghghi et al and Modarresi et al conducted further placebo-controlled trials on serotonin reuptake inhibitors refractory patients and found memantine beneficial in alleviating symptoms of OCD; however, Farnia et al [4] contended that memantine efficacy as an adjuvant was more than placebo. Kishi et al organized a meta-analysis on the efficacy of memantine as an augmentation strategy. They underlined that adding memantine to standard SRI therapy was superior to a placebo [31]. Modarresi et al performed a systematic review and meta-analysis about memantine efficacy in moderate to severe OCD and claimed that memantine is effective in the augmentation of SRIs [19]. Andrade rebutted their systematic review and meta-analysis and suggested that the routine use of memantine as an augmentation strategy in guidelines needs to be further justified [32, 33]. Askari et al challenged Modarresi et al with the results of their clinical trial [34]. We performed this study in an attempt to contribute to the literature.

Materials and methods:

This study is registered in the Iranian Registry of Clinical Trials under the code IRCT2020227049851N1. It is approved by the ethical committee of Kashan University of Medical Sciences with the ethical code: IR.KAUMS.MEDNT.REC.1399.238 and complies with the ethical considerations of the Declaration of Helsinki. Participants signed informed consent after the nature of the project had been thoroughly explained.

This investigation was designed as an 8-week randomized, double-blinded clinical trial. 100 outpatients were clinically screened by a psychiatrist and those who fulfilled the DSM-5 criteria of OCD and met the inclusion and exclusion criteria were enrolled until a sample size of thirty patients was reached. They were randomly allocated into two categories using permuted block randomization with a ratio of 1:1 and blocks of four. Participants, randomizers, psychiatrists, and data analyzers were blinded to allocation. Placebo tablets were prepared exactly as memantine in terms of form, size, and color (Figure 1 depicts the survey process).

The study sample included patients aged 18 to 60 with a clinical diagnosis of OCD based on DSM-5 criteria and a Y-BOCS score of ≥ 16 . The exclusion criteria were: 1- pregnancy and breast-feeding or not taking contraception in women of childbearing age, 2- diagnosis of other psychiatric disorders or any other medical condition, 3- taking other medications, 4- a history of using serotonin reuptake inhibitors from six weeks before screening time, 5- receiving psychotherapies simultaneously, and 6- a previous history of memantine use.

A group of 15 patients received a daily dose of 50-200 mg sertraline tablets (Sobhan-Darou Company, Tehran, Iran) plus memantine tablets (Daroupakhsh Company, Tehran, Iran) with a dose of 5-10 mg per day. The other group received 50-200 mg per day of sertraline tablets plus a placebo. Memantine was started at a dose of 5 mg and increased to 10 mg per day after one week and continued for eight weeks. Sertraline was started with a daily dose of 50 mg and its dosage was titrated in 50 mg increments weekly. Both groups were visited four times at weeks 0, 2, 4, and 8 by a psychiatrist. Follow-up visits and Y-BOCS scorings were performed similarly for all participants.

The major outcome of the study was the total Y-BOCS score and its subscale scores. Persian version of the Y-BOCS questionnaire validated by Esfahani et al was used for assessment. It includes 10 questions categorized into two 5-question obsession and compulsion subscales [35].

Assuming a dropout rate of 20%, the sample size was calculated at 30, including 15 cases in the memantine and 15 in the placebo group [11]. 28 patients fulfilled the study. Independent t and Fisher exact tests were performed to ensure that demographic data were comparable and homogenous in the two arms of the study. Total Y-BOCS and subscale score changes in and between groups during the 8-week course of study were compared using one-way repeated measure ANOVA, and its assumptions were verified using Box M and Mauchly's tests. In cases where the sphericity was not met the Greenhouse-Geisser

correction was used. The Friedman and Man-Whitney U non-parametric tests were used for obsession Y-BOCS scores. The software used for data analysis was SPSS V. 21 (IBM, New York, NY, USA).

Results

A total of 30 outpatients were approached. Twenty-eight subjects completed the study and two patients withdrew at week two. One patient from the memantine group left the project due to diarrhea and one patient from the control group withdrew consent to attend CBT sessions. Twenty-four participants (80%) were females, with mean age $M=38.30$, $SD=10.66$, and 24 patients (80%) were married. No substantial differences were found in terms of age, sex, education, and marital status between study groups, using independent t-test, Chi-square, and Fisher exact tests (Table 1).

The results of the one-way repeated measure ANOVA revealed a significant reduction of the total Y-BOCS scores over time ($P > 0.001$ and $F = 434.20$) without any significant between-group differences ($P = 0.08$ and $F = 3.15$). Mauchly's test of sphericity was performed and in case of deviation from sphericity, the Greenhouse-Geisser coefficient was administered. Table 3 demonstrates changes in total Y-BOCS score in memantine vs placebo groups over time.

The results of the Friedman test confirmed that obsession subscale scores decreased significantly over time in both groups ($P < 0.05$); however, no significant difference was detected between groups in the Mann-Whitney U test ($P = 0.062$).

In the case of the compulsion subscale, the results of one-way repeated measure ANOVA revealed a significant decrease in both groups over time ($P > 0.001$ and $F = 264.14$) and the decrease in the memantine plus sertraline group was significantly more considerable than the placebo plus sertraline group ($P = 0.03$ and $F = 5.12$). (Figures 2 and 3)

Discussion

The present clinical trial highlights that memantine augmentation of sertraline does not result in a further reduction of OCD symptoms' severity. To date, five diverse double-blinded clinical trials have been conducted to evaluate the efficacy of memantine augmentation of serotonin reuptake inhibitors in the treatment of OCD. Ghaleiha et al administered a daily dose of 20 mg of memantine vs. placebo in combination with fluvoxamine 200 mg per day in outpatients with total Y-BOCS ≥ 21 and reported a 100% treatment response in the memantine group compared to a 32% response in the placebo group. In comparison with our study, they applied a higher dose of memantine and a different standard first-line SSRI which can justify the difference in our findings [11]. Haghghiet al tried a dose of 5-10 mg per day of memantine and substantiated the significant role of memantine in the augmentation of OCD treatment. They had recruited inpatients whereas we conducted our trial on outpatients [36]. Modarresi et al also reported a significant reduction in Y-BOCS score at the end of weeks 8 and 12 [2]. They had recruited SRI refractory patients and concluded that an 8-week time to effect was essential to detect the efficacy of add-on memantine which contradicts the results of our trial. We initiated sertraline at the same time as memantine initiation and did not recruit patients previously stabilized on sertraline; therefore, prior exposure and stabilization on SRIs might have affected the results. Farina et al conducted their study for eight weeks on outpatients with a total Y-BOCS of ≥ 15 and disputed further improvement of symptoms with memantine augmentation of SRIs. Their three-arm study employed patients with similar Y-BOCS scores as ours and agrees with our results. Askari et al recruited 70 outpatients with a total Y-BOCS of ≥ 21 and excluded refractory OCD patients. Although they used a 20 mg dose of memantine for 12 consecutive weeks their results did not attest to the role of memantine as an augmentation of the standard treatment of OCD. Our study corroborates the results of Farnia et al and Askari et al, contributing to the current literature.

The results of our analysis imply that obsessions and compulsions may respond differently to memantine augmentation of sertraline. It is hypothesized that the effect of memantine on the compulsion subscale might reflect its role in the executive function of OCD patients. This theory needs further exploration by future studies.

The present study's main limitation was the short trial duration and the exclusion of OCD patients with comorbidities and the female predominance of cases. We did not include inpatients and the possibility of non-compliance and patients' self-treatments cannot be ruled out. In addition, previous experiences of taking SRIs or CBT were not considered.

Conclusion:

Memantine is not effective in the augmentation of the standard treatment of moderate to severe OCD patients, although it might slightly affect compulsion improvement.

Declarations:

Ethics approval and consent to participate: This study complies with ethical considerations of the Declaration of Helsinki and is approved by the Ethics Committee of Kashan University of Medical Sciences under the code of IR.KAUMS.MEDNT.REC.1399.238

Consent for publication: Not applicable

Availability of data and material:The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality concerns although are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

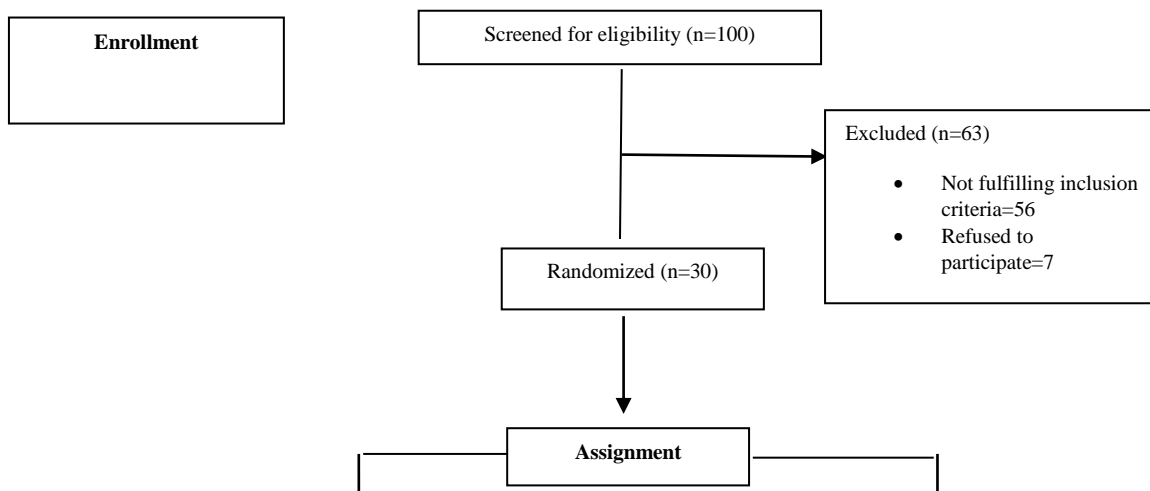
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Authors' Contribution:

A. S: Conceptualization, Investigation, Writing-original draft, Writing Reviewing and Editing, Funding acquisition. H.R: Methodology, Data curation, Formal analysis, Software, Writing-Reviewing and Editing. F.G: Visualization, Investigation.

Z.S: Supervision, Investigation.

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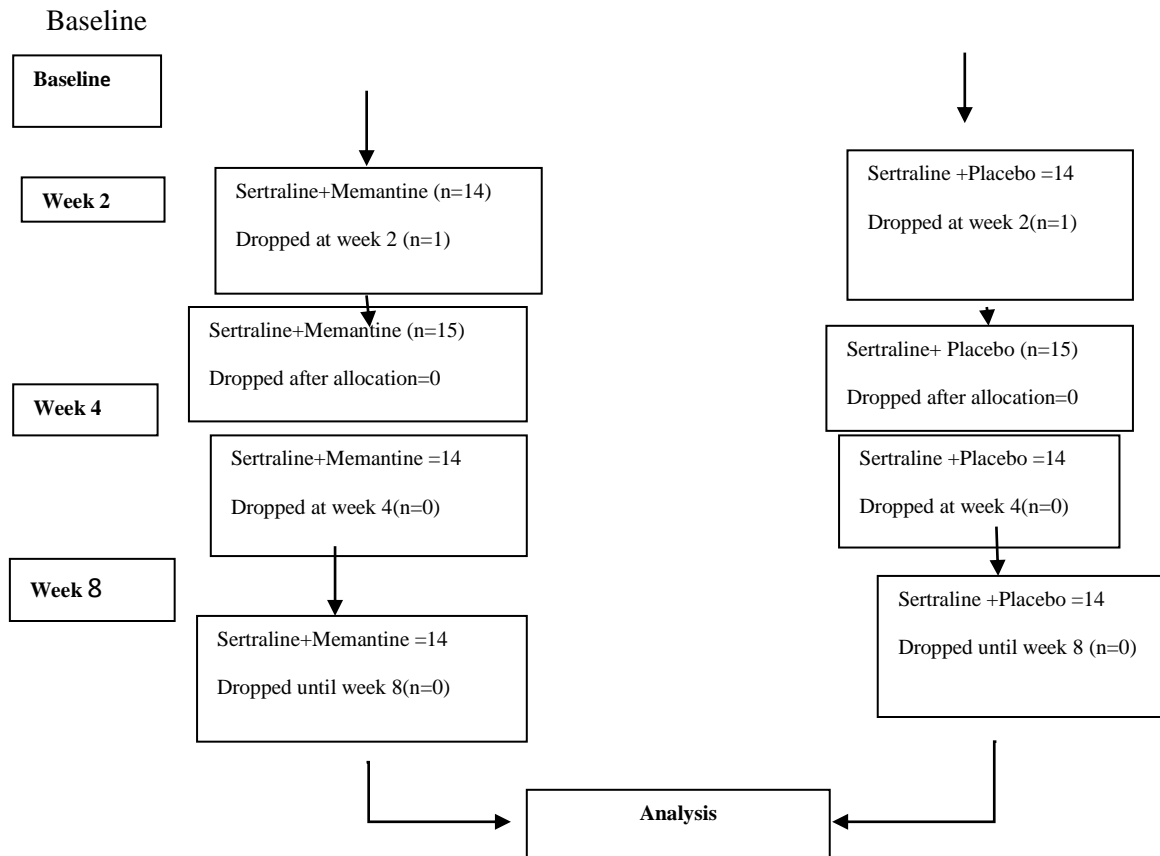


Figure1-Enrollment, randomization, treatment, and follow-up flow diagram of the trial

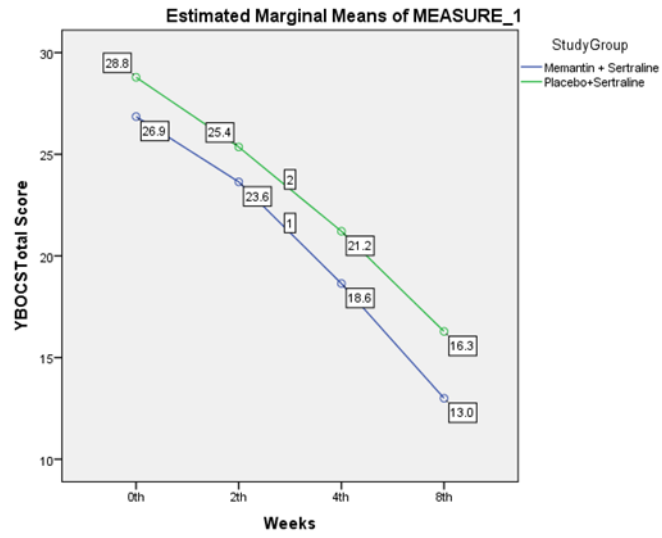


Figure 2-Total Y-BOCS score changes over time across groups of trial

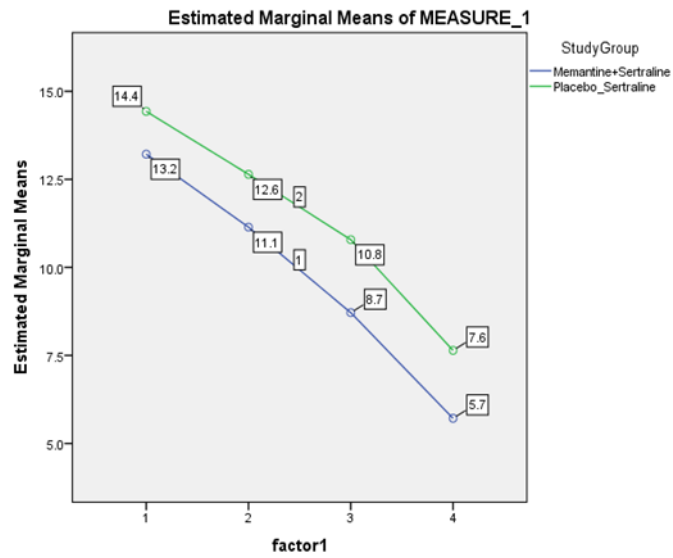


Figure 3-Changes of compulsion Y-BOCS scores across groups over trial time

Table 1- Values of demographic variables across groups

	Groups		P-value	
	SER+MEM ¹	SER+PLA ²		
N	15	15		
Age(years) ³	37.1±(10.12)	39.4±(11.42)	0.58	
Marital status ⁴	Single	4(66.7)	2(33.3)	0.65
	Married	11(45.8)	13(54.2)	0.65
Gender ⁵	Female	13(54.2)	11(45.8)	0.65
	Male	2(33.3)	4(66.7)	0.65
Education ⁶	Lower than a high school diploma	6(33.3)	12(66.7)	0.05
	High school diploma	8(80)	2(20)	0.05
	Higher degrees	1(50)	1(50)	0.05

¹SER+MEM=sertraline+memantine

²PLA+SER=placebo+sertraline

³Values are expressed as mean±SD

⁴Values are expressed as No. (%)

⁵Values are expressed as No. (%)

⁶Values are expressed as No. (%)

Table 2-Descriptive and statistical values of total and subscale Y-BOCS score across groups at baseline

	Study Group	N	Mean	Std. deviation ⁷	Std. Error Mean	P-value
Total Y-BOCS before treatment	MEM+SER ⁸	15	27.13	4.033	1.041	0.20
	PLA+SER ⁹	15	29.00	3.891	1.005	0.20
Obsession Y-BOCS before treatment	MEM+SER	15	13.87	2.134	0.551	0.39
	PLA+SER	15	14.47	1.642	0.424	0.39
Compulsion Y-BOCS before treatment	MEM+SER	15	13.27	2.187	0.565	0.13
	PLA+SER	15	14.53	2.356	0.608	0.13

⁷Std.deviation=standard deviation

⁸MEM+SER=memantine+sertraline

⁹PLA+SER=placebo+sertraline

Table 3-Descriptive and statistical values of total Y-BOCS score across trial groups at different intervals

	Study Group	Mean	Std. Deviation	N
Total Y-BOCS before treatment	MEM ¹⁰ +SER ¹¹	26.86	4.036	14
	PLA ¹² +SER	28.79	3.945	14
	Total	27.82	4.037	28
Total Y-BOCS 2 weeks after treatment	MEM+SER	23.64	3.586	14
	PLA+SER	25.36	4.517	14
	Total	24.50	4.096	28
Total Y-BOCS 4 weeks after treatment	MEM+SER	18.64	3.411	14
	PLA+SER	21.21	4.246	14
	Total	19.93	3.999	28
Total Y-BOCS 8 weeks after treatment	MEM+SER	13.00	2.774	14
	PLA+SER	16.29	3.197	14
	Total	14.64	3.380	28

¹⁰MEM=memantine

¹¹SER=sertraline

¹²PLA=placebo

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