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Original Article

The Effect of Add-on Memantine in New Onset Combat-Related Posttraumatic Stress Disorder Core Symptoms: A Pilot Study

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Abstract

Objective: Studies using standard neuropsychological instrumentation have shown memory deficits in posttraumatic stress disorder (PTSD) patients. We examined the efficacy and safety of memantine in new cases of combat-related PTSD in the military by conducting a 16-week prospective double-blind randomized controlled trial.
Method: Twenty-six new combat-related PTSD cases were recruited from among the military personnel based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Patients were assigned to memantine and Placebo groups. They were monitored at baseline, week eight, and week 16. Memantine was added to each patient's current medication with an initial dosage of 5 mg/day, raised by 5 mg/day every week until it reached the maintenance level of 20 mg/day. The concurrent drugs were essentially kept unchanged during the trial. The primary outcome was PTSD severity as assessed by the Clinician-administered PTSD Scale (CAPS). The CAPS is a valid and reliable tool for the diagnosis of PTSD and measurement of its severity according to the DSM–4.
Results: CAPS mean score in baseline (P = 0.811) and weeks eight (P = 0.389) and 16 (P = 0.066) did not show any significant differences between the two groups. The mean CAPS score in the memantine group significantly (P = 0.006) decreased (Mean differences = -8.79) compared to the placebo group, showing that intervention with memantine was effective. The mean total CAPS in weeks eight (Mean differences = -14.21) and 16 (Mean differences = -27) were less than the baseline, which was significantly meaningful (P < 0.001).
Conclusion: Findings of this study suggest that add-on memantine can be effective in veteran patients with PTSD. So our data provide useful insight into the management of new cases of combat-related PTSD.

Key words: *Glutamate; Memantin; N-Methyl-D-Aspartate Receptor; Posttraumatic Stress Disorder*

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Posttraumatic stress disorder (PTSD) is a significant psychiatric disorder that can occur after a major traumatic incident and has a long-term course with substantial functional impairment (1). Re-experiencing, avoidance, and hyperarousal are some of the psychological and behavioral symptoms that patients with this illness experience. Re-experiencing symptoms, which include involuntary retrieval of traumatic memories such as intrusive thoughts, flashbacks, and nightmares, are primarily specific to PTSD and are thus considered a core component of this disease (2). The global prevalence of PTSD is estimated to be around 3.9 percent throughout a lifetime (1). PTSD is a widespread issue among military members who have been exposed to battle (3, 4). Traumatic events have a distinct incidence and distribution over the world. Specific communities are commonly subjected to traumatic experiences such as combats, organized violence, terrorism, and natural catastrophes in many geographical regions (5). In Iran, the lifetime prevalence of combat-related PTSD was reported at 46% in war veterans and 30% in civilians (4, 5).

Corticotropin-releasing hormone (CRH) and hypothalamic–pituitary–adrenal (HPA) axis anomalies and noradrenergic, serotonergic, and glutamatergic system dysfunctions may be affected by biological pathways. According to preclinical evidence, stress/trauma-activated glutamate circuits are thought to cause glutamate spillover, which triggers pro-inflammatory processes and excitotoxicity. There is a relatively limited window between the brain's adaptive neuroplastic response to stress and glutamate's potentially excitotoxic effects. When this safe threshold is breached, a cascade of neuronal events occurs, affecting the brain's anatomical and functional aspects (6-8). This stress-induced glutamate spillover and excitotoxicity are thought to have three basic outcomes: (1) reduced glutamatergic neural activity due to presynaptic metabotropic glutamate receptor activation; (2) paradoxical elevation of extrasynaptic glutamate levels due to reduced astrocyte function and astrocyte loss; and (3) reductions in synaptic connectivity in corticolimbic circuits (e.g. hippocampus and medial prefrontal cortex which are regions known to regulate stress responsivity and emotion) related to HPA dysfunction and extrasynaptic NR2B-containing NMDA (N-methyl-D-aspartate) receptor overstimulation (6, 9). Though there is scant data from human subjects, there is growing evidence that anomalies in the glutamatergic system are linked to stress response and PTSD (7, 10). Glutamate has been postulated to have a role in the pathophysiology of PTSD, in part through its activities on the HPA axis, where data from animal research supports its function in stress-induced CRH release regulation (11, 12). Experiments showing that pre-treatment with a glutamatergic NMDA-receptor antagonist reduced stress response as assessed by the adrenocorticotropic hormone (ACTH) release add to the evidence supporting this notion (13, 14). Changes in glutamate levels appear to be important in the start and maintenance of the HPA response. Furthermore, the generation of dissociative-like symptoms (common in PTSD) when ketamine, an NMDA-receptor antagonist that transiently promotes glutamate release, was given to humans shows that a hyperglutamatergic state might be involved in PTSD (14, 15). For chronic PTSD symptoms, ketamine proved to be a rapid, safe, and very effective pharmacological intervention (15). In addition, D-cycloserine, a D-alanine analog and partial agonist at the N-methyl-D-aspartate (NMDA) receptor, has been recommended as adjuvant therapy for combat-related persistent PTSD numbness and avoidance (16).

Memantine is an uncompetitive NMDA receptor blocker. As a neuroprotective agent, memantine offers a wide variety of potential applications, which might be expanded even further. Memantine's potential usage in schizophrenia and depression is now the most promising (17-19). In addition, memantine as an adjuvant treatment to sertraline was found to have beneficial effects on improving executive function in individuals with Obsessive-compulsive disorder (OCD) and the safety and tolerability of memantine in these patients (20). Also, a systematic review and meta-analysis provided evidence that glutamate-modulating medications may be beneficial as an alternate or supplemental treatment to treat moderate to severe OCD (21). Depression and trait anxiety were also decreased, as were negative posttraumatic cognitive patterns, following the use of these medications (22). Furthermore, memantine was thought to have a lot of promise at first; since, although inhibiting NMDA, it did not have any NMDA antagonist adverse effects. This feature has been linked to ligand's significant voltage dependence (23). It must be noted that the rate of PTSD increased after the onset of the coronavirus disease 2019 (COVID-19) (24). Since outbreaks of acute infectious illnesses might have long-term psychological health consequences in the broader population, it is even more important to manage PTSD (25).

Recently in a 12-week open-label trial study, memantine (adjunctive) considerably alleviated civilian PTSD symptoms throughout the course of the study, with a pre-post effect size of 1.35, and resulted in remission in the majority of patients at the endpoint (22). But there is some gap in knowing whether the same effect could be expected in combat-related PTSD patients. Also, it is not known whether a longer duration of follow-up is beneficial in symptom reduction or not. In the present study, we aimed to examine the efficacy and safety of memantine in new cases of combat-related PTSD in the military by conducting a 16-week prospective double-blind trial of memantine specifically designed to assess its impact on PTSD core symptom clusters. We particularly focused on the effect of memantine on

combat-related PTSD symptomatology using the Clinician-Administered PTSD Scale (CAPS).

Materials and Methods

Ethical statement

This pilot study drew participants from Isfahan University's outpatient psychiatric clinic and community referrals from 2019 to 2020. During a full screening exam for PTSD program entrance, a diagnosis of combat-related PTSD was made. The research was authorized by the Isfahan University of Medical Sciences Research Ethics Committee and the Iranian Registry of Clinical Trials (IRCT), and it followed the Helsinki Declaration's ethical guidelines (IR.MUI.MED.REC.1399.527 and IRCT20200923048816N1). Before participating in the study, all individuals gave their informed consent after learning about the procedures in detail.

Participants

Patients had to meet the following criteria to be included: (1) male or female patients aged 19–65 years; (2) military new cases (with less than 12 months' duration of disease) who met DSM-5 combat-related PTSD criteria; (3) competent to provide informed consent; (4) able to attend clinic appointments; and (5) if female, using an approved contraceptive if of childbearing potential. Patients were not allowed to participate in the trial if they had any of the following conditions: (1) past memantine medication; (2) a medical condition that might make memantine administration unsafe, such as clinically significant/severe hepatic, cardiac, renal, or pulmonary illness, or seizure disorders, except for pediatric seizure disorders; (3) Patients with a history of alcohol and psychotropic drug use in the last month or with a history of addiction; (4) a major psychotic illness based on DSM-5 (schizophrenia, schizoaffective disorder, or bipolar disorder); (5) suicide or homicidal ideas or other clinically substantial dangerousness; (6) change in psychotropic medication within 90 days of study admission.

Study procedures

Patients who matched the eligibility requirements were randomly assigned to one of two groups: memantine or placebo. Patients who referred to a psychiatric clinic and met the inclusion criteria were selected as double random blocks in this study. The epidemiologist set up a random number table. To prevent bias and maintain blindness of the drugs in the intervention and placebo groups, the patient being prescribed the drug, the evaluator, and the statistical consultant did not know the type of drug. The psychiatrist who visited the patient and gave the packaged and coded drugs to the patient, the researcher who filled out the questionnaire, the researcher who entered the data into the software, and the epidemiologist who performed statical analyses were blinded.

This study included a 16-week memantine intake phase. Patients were required to attend the clinic three times throughout the 16-week trial: baseline, eight, and 16 weeks after the therapy began. In the memantine group, memantine (Sobhan Darou Co, Tehran, Iran) was added to each patient's existing PTSD prescription at a dose of 5 mg per day at first. The dose was subsequently raised by 5 mg/day every week until it reached the maintenance level of 20 mg/day. In the placebo group, the placebo was prescribed along with the patient's current PTSD treatment and was similar to a memantine tablet in color, odor, and shape. The concurrent drugs were essentially maintained unchanged during the trial.

In the event of intolerance to the increase, the dosage was adjusted flexibly based on the patient's condition.

Assessment of effectiveness

The CAPS, completed at study visits at baseline and at weeks eight and 16, was the main outcome measure. The CAPS is a structured interview in which the frequency and severity of the 17 DSM-IV PTSD symptoms are scored on a 5-point (0-4) scale (26). Symptoms that are endorsed with a frequency of one or more and intensity of two or more are regarded to fulfill the minimal criterion to be labeled a PTSD symptom. The CAPS may be used to determine whether or not a person satisfies the DSM-IV criteria for a PTSD diagnosis, and the frequency and intensity items can be added together to give a symptom severity rating that ranges from 0 to 136, with a severity score of 45 or higher required for a PTSD diagnosis (27). Higher CAPS ratings suggest that PTSD symptoms are more severe. Therefore, a clinically meaningful reduction in the CAPS scores from baseline to endpoint was defined as at least a 50% reduction (26). It has three main symptom clusters, including re-experiencing (five symptoms), avoidance (two symptoms), and hyperarousal (five symptoms). For the re-experiencing, arousal, and avoidance subscales, Cicchetti *et al.* (2009) observed high interrater reliability for frequency and severity ($r > 0.92$ for each subscale) as well as good internal consistency ($\alpha > 0.87$ for each subscale) (28).

Assessment of safety and tolerability

At each visit, adverse events and vital signs were assessed. In addition, each patient was given a phone number to call the research coordinator 24 hours a day to report adverse events.

Statistical analyses

The data were analyzed using SPSS.18 statistical software. Chi^2 and independent t-test were used for comparing categorical data and continuous parameters, respectively. The normality distribution of outcomes was assessed using the Shaprio-Wilk test. Analyses of variance, following a General Linear Model procedure (GLM), were used to analyze mean CAPS scores during the study period. Repeated measure analysis was used for time×group interaction. The confidence interval and significance level were set at %95 and 0.05, respectively.

Results

Patients randomly assigned to the memantine group (n = 13) included 11 males and two females (Mean age = 30.62, SD = 8.016), while the placebo group (n = 13) included 12 males and one female patient (Mean age = 33.15, SD = 5.914) (Figure 1, Table 1). Of the patients in both groups, six (n = 3 in either group) were smokers, and 20 were non-smokers (n = 10 in either group). In addition, the usage of selective serotonin reuptake inhibitors (SSRI), benzodiazepines, trazodone, and antipsychotics was the same in both groups, but 23% of patients in the memantine group used prazosin, while it was 76.9% in the placebo group. The mean age (P = 0.319), education (P = 0.507), and disease duration days (P = 0.721) did not show significant differences between memantine and placebo groups in the baseline (Table 1).

Based on the Shapiro-Wilk test, the mean CAPS score had a normal distribution at baseline and weeks eight and 16. In addition, the CAPS mean score at baseline (P = 0.811), week eight (P = 0.389), and week 16 (P = 0.066) did not show any significant differences between the memantine and placebo groups (Table 2). The time effect on mean CAPS scores in all assessment times in both groups was significant (P < 0.001). The mean CAPS score significantly (P = 0.006) decreased (Mean differences = -8.79) within the memantine group during the study, which shows that intervention with memantine was effective. In addition, within the memantine group, the mean total CAPS in weeks eight (Mean differences = -14.21) and 16 (Mean differences = -27) were less than the baseline, which was significantly meaningful (P < 0.001). The social, familial, and job functions of the two groups were significantly affected by memantine. (P < 0.001).

Comparing each adverse effect, there were no significant differences between the two groups (P > 0.05) (Table 3).

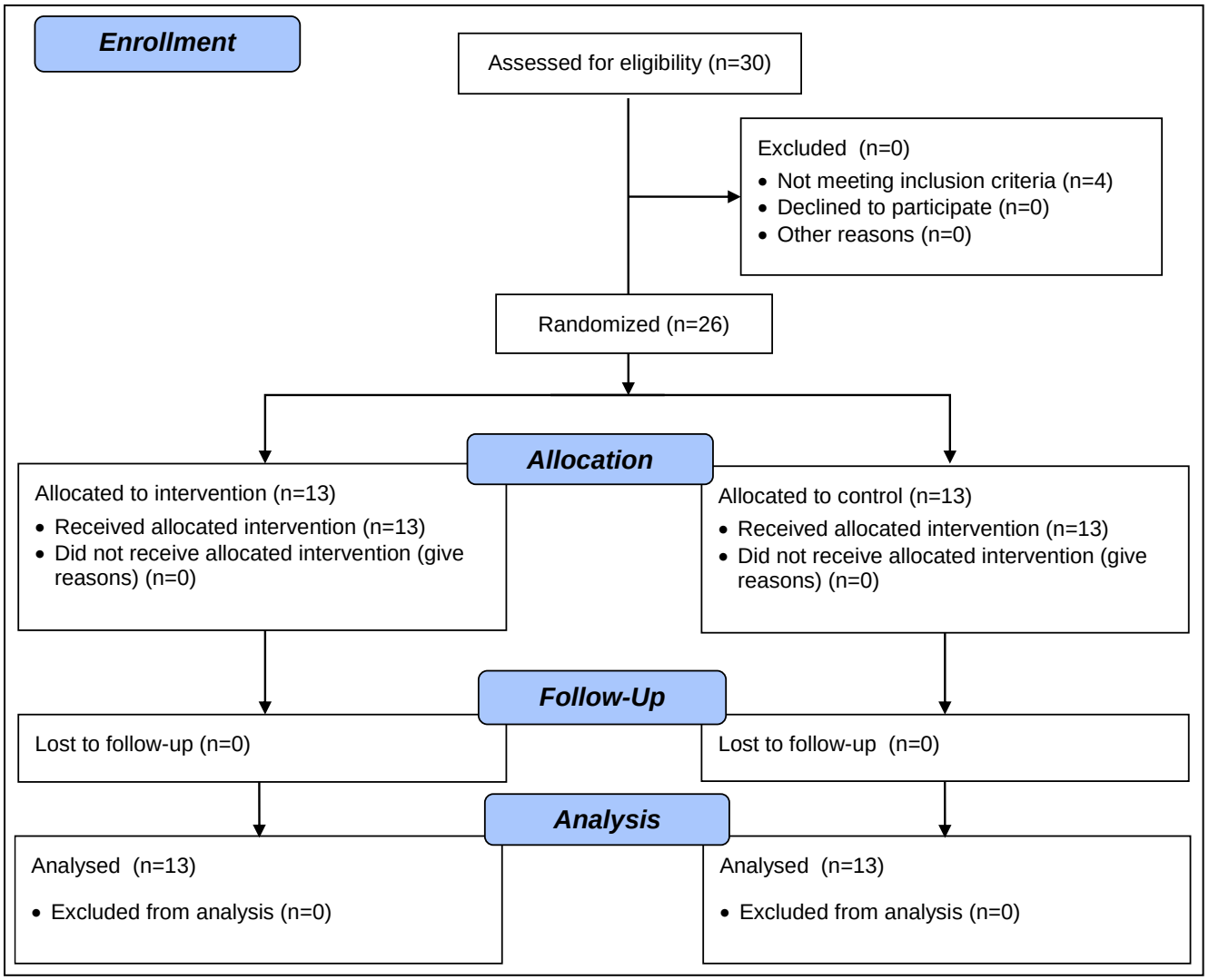

Figure 1. Flow Diagram of the Trial Process

Table 1. Baseline Characteristics of Study Participants

Variable	Memantine (n = 13)	Placebo (n = 13)	P-value
Age, years	30.6 ± 8.0	33.1 ± 5.9	0.319
Education, years	13.6 ± 2.7	13.9 ± 3.5	0.507
Disease duration, days	55.3 ± 13.7	57.3 ± 13.2	0.721
Gender, n (%)			
Male	11 (84.6)	2 (15.4)	0.235
Female	12 (92.3)	1 (7.7)	
Smoking, n (%)			
Yes	3 (23.1)	3 (23.1)	0.094
No	10 (76.9)	10 (76.9)	
Marital, n (%)			
Single	5 (38.5)	3 (23.1)	0.118
Married	8 (61.5)	10 (76.9)	
Substance user, n (%)	0 (0)	0 (0)	
Physical injury, n (%)			
Yes	6 (46.2)	6 (46.2)	0.98
No	7 (53.8)	7 (53.8)	
Medication history, n (%)			
Selective serotonin reuptake inhibitors (SSRIs)			
Yes			
Benzodiazepines	13 (100)	13 (100)	
Yes			
No	8 (61.5)	8 (61.5)	
Trazodone	5 (38.5)	5 (38.5)	
Yes			0.09
No	4 (30.8)	5 (38.5)	
Antipsychotics	9 (69.2)	8 (61.5)	
Yes			
No	5 (38.5)	6 (46.2)	
Prazosin	8 (61.5)	7 (53.8)	
Yes			
No	3 (23.1)	10 (76.9)	
	10 (76.9)	3 (23.1)	

Table 2. Frequency and Severity of Clinician-Administered PTSD Scale (CAPS) Scores in Treatment Groups and Different Assessment (n = 26)

Group	Assessment time	Mean ± SD	P-value between two groups	t	95% Confidence Interval
CAPS total score Memantine	Baseline	112.8 ± 13.3	Baseline: 0.811	Baseline: - 0.242	Baseline: (-11.727 to 9.265)
	Week 8	96.8 ± 13.0			
	Week 16	80.0 ± 13.6	Week 8: 0.389	Week 8: - 0.880	Week 8: (-16.765 to 6.795)
Placebo	Baseline	114.1 ± 12.5			
	Week 8	101.8 ± 14.1	Week 16: 0.066	Week 16: -1.947	Week 16: (-24.859 to 0.859)
	Week 16	92.0 ± 15.2			
Frequency of CAPS B (Intrusion) Memantine		15.00 ± 3.606			
	Baseline	13.33 ± 3.798	Baseline: 0.90	Baseline: -0.117	Baseline: (-2.878 to 2.570)
	Week 8	11.27 ± 3.797			
	Week 16		Week 8: 0.968		

Placebo	Baseline Week 8 Week 16	15.15 ± 3.105 13.27 ± 3.349 11.91 ± 3.477	Week 16: 0.686	Week 8: 0.040 Week 16: -0.410	Week 8: (-3.057 to 3.178) Week 16: (-3.876 to 2.603)
Severity of CAPS B (Intrusion) Memantine	Baseline Week 8 Week 16	14.8 ± 3.602 12.17 ± 3.040 9.91 ± 3.360	Baseline: 0.463 Week 8: 0.952	Baseline: -0.747	Baseline: (-3.498 to 1.649)
Placebo	Baseline Week 8 Week 16	14.9 ± 2.753 13.09 ± 2.879 11.45 ± 3.267	Week 16: 0.287	Week 8: -0.061 Week 16: -1.094	Week 8: (-2.672 to 2.518) Week 16: (-4.493 to 1.402)
Frequency of CAPS C (Avoidance) Memantine	Baseline Week 8 Week 16	19.6 ± 4.1 17.2 ± 3.6 13.8 ± 2.9	Baseline: 0.271 Week 8: 0.024	Baseline: -1.131 Week 8: -2.443	Baseline: (-5.461 to 1.612) Week 8: (-7.584 to -0.597)
Placebo	Baseline Week 8 Week 16	20.0 ± 4.3 19.1 ± 4.5 17.8 ± 4.7	Week 16: 0.817	Week 16: -0.234	Week 16: (-3.783 to 3.014)
Severity of CAPS C (Avoidance) Memantine	Baseline Week 8 Week 16	19.5 ± 3.5 16.1 ± 3.2 13.0 ± 3.3	Baseline: 0.709 Week 8: 0.764	Baseline: 0.378 Week 8: 0.304	Baseline: (-2.405 to 3.482) Week 8: (-1.684 to 2.260)
Placebo	Baseline Week 8 Week 16	19.0 ± 3.8 17.7 ± 4.1 17.0 ± 4.2	Week 16: 0.742	Week 16: 0.334	Week 16: (-1.907 to 2.634)
Frequency of CAPS D (Hyperarousal) Memantine	Baseline Week 8 Week 16	17.5 ± 1.8 15.8 ± 1.8 13.9 ± 1.7	Baseline: 0.323 Week 8: 0.423	Baseline: 1.012 Week 8: 0.819	Baseline: (-0.976 to 2.824) Week 8: (-1.296 to 2.933)
Placebo	Baseline Week 8 Week 16	17.8 ± 2.2 14.9 ± 2.5 13.1 ± 2.8	Week 16: 0.630	Week 16: -0.488	Week 16: (-2.015 to 1.245)
Severity of CAPS D (Hyperarousal) Memantine	Baseline Week 8 Week 16	16.3 ± 1.8 14.8 ± 1.7 12.8 ± 1.6	Baseline: 0.122 Week 8: 0.764	Baseline: -1.603 Week 8: 0.304	Baseline: (-2.992 to 0.376) Week 8: (-1.684 to 2.260)
Placebo	Baseline Week 8 Week 16	17.7 ± 2.3 14.5 ± 2.7 12.4 ± 3.2	Week 16: 0.742	Week 16: 0.334	Week 16: (-1.907 to 2.634)

*Controlling for age, education, marital status, cigarette smoking, gender, disease duration days and substance-use

Table 3. Frequency of Adverse Effects after 16 Weeks

Complication	Memantine	Placebo	P-value	95% Confidence Interval
Allergy, n (%) Yes No	1 (7.7) 12 (92.3)	1 (7.7) 12 (92.3)	1.00	(-0.225 to 0.225)
Agitation, n (%) Yes No	3 (23.1) 10 (76.9)	4 (30.8) 9 (69.2)	0.674	(-0.449 to 0.295)

Headache, n (%)				
Yes	2 (15.4)	3 (23.1)	0.635	(-0.523 to 0.144)
No	11 (84.6)	10 (76.9)		
Insomnia, n (%)				
Yes	2 (15.4)	2 (15.4)	0.307	(-0.272 to 0.09)
No	11 (84.6)	11 (84.6)		
Gastrointestinal distress, n (%)				
Yes	2 (15.4)	3 (23.1)	0.251	(-0.523 to 0.144)
No	11 (84.6)	10 (76.9)		

Discussion

The main findings of this study revealed that the mean CAPS score in the memantine group significantly decreased from baseline to week 16 during the study, which shows that intervention with memantine was effective. Moreover, the average total CAPS score between the two study groups showed no significant differences. This finding fills the gap in effective pharmacologic treatment for PTSD and suggests a highly effective treatment option with memantine. Similar to our study, an open trial assessing the effectiveness of memantine in the treatment of 13 civilian PTSD patients found that memantine (5-20 mg) significantly improved the symptoms of PTSD during the 12-week trial period with a pre-post effect size of 1.35 and led to remission in a majority of patients at the endpoint (22). Another open trial study demonstrated an improvement in cognitive symptoms in chronic PTSD patients following the therapy with memantine (5-20 mg) for 16 weeks (29). In addition, in a 12-week pilot trial of memantine (5-20 mg) on four cases with combat PTSD, treatment with memantine produced a steady improvement in delayed memory recall, a variable reduction in depressive symptoms, and a variable reduction in hyperexcitation symptoms (30).

Improvement in CAPS scores reflects improvement in PTSD symptoms, including intrusion, avoidance, and hyperarousal. In this study, memantine in week 8 significantly reduced the frequency of avoidance symptom compared to baseline but had no significant effect on other symptoms (Intrusion and Hyperarousal). A preferential reduction in the excitatory impulse to inhibitory neurons in the cortical circuits and subsequent changes in the balance between excitation and inhibition are two mechanisms suggested to explain the therapeutic benefits of memantine (31).

In an open trial on the effect of memantine on cognitive impairment in veterans with PTSD, it was shown that memantine had no significant effect on these symptoms (Intrusion, Hyperarousal, and avoidance) (29). Contrarily, the previous open-label study on the effects of memantine on 13 civilians with PTSD reported that memantine (5-20 mg) has a significant effect on these symptoms (Intrusion, Hyperarousal, and avoidance) (22). The effect of memantine on these symptoms may be more significant among civilians than veterans, which is in line with the general trend of treatment responses in civilians relative to PTSD-affected veterans (22). Moreover, it is plausible that a true effect of memantine on this subset of PTSD symptoms may have been omitted in the background of its effect on overall reporting of memory improvement (29).

Limitation

The small sample size, selection of participants from outpatient clinics, and using other medications by participants were our study limitations. Although our research had a longer follow-up time than previous comparable studies on combat-related PTSD, multi-center trials with larger sample size, various methods to measure cognition and executive function, and longer follow-up periods are recommended.

Conclusion

Findings of this study suggest that add-on memantine can be effective in veteran patients with PTSD. So, our data provides useful insight into the management of new cases of combat-related PTSD.

Acknowledgment

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Conflict of Interest

None.

References

1. Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, et al. Posttraumatic stress disorder in the World Mental Health Surveys. Psychol Med. 2017;47(13):2260-74.
2. Ehlers A, Clark DM. A cognitive model of posttraumatic stress disorder. Behav Res Ther. 2000;38(4):319-45.
3. Smith TC, Ryan MA, Wingard DL, Slymen DJ, Sallis JF, Kritz-Silverstein D. New onset and persistent symptoms of post-traumatic stress disorder self reported after deployment and combat exposures: prospective population based

US military cohort study. Brit Med Jour. 2008;336(7640):366-71.
4. Zargar F, Foruzandeh E, Omidi A, Mohammadi A. Psychological health and marital adjustment in Iranian employed veterans and veterans receiving disability pension. Iran Red Crescent Med J. 2014;16(7):e10219.
5. Sepahvand H, Mokhtari Hashtjini M, Salesi M, Sahraei H, Pirzad Jahromi G. Prevalence of Post-Traumatic Stress Disorder (PTSD) in Iranian Population Following Disasters and Wars: A Systematic Review and Meta-Analysis. Iran J Psychiat Behav Sci. 2019;13(1):e66124.
6. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of post-traumatic stress disorder. Nat Rev Neurosci. 2012;13(11):769-87.
7. Popoli M, Yan Z, McEwen BS, Sanacora G. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. Nat Rev Neurosci. 2011;13(1):22-37.
8. Reul JM, Nutt DJ. Glutamate and cortisol--a critical confluence in PTSD? J Psychopharmacol. 2008;22(5):469-72.
9. Abdallah CG, Averill LA, Krystal JH. Ketamine as a promising prototype for a new generation of rapid-acting antidepressants. Ann N Y Acad Sci. 2015;1344(1):66-77.
10. Averill LA, Purohit P, Averill CL, Boesl MA, Krystal JH, Abdallah CG. Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies. Neurosci Lett. 2017;649:147-55.
11. Gabr RW, Birkle DL, Azzaro AJ. Stimulation of the amygdala by glutamate facilitates corticotropin-releasing factor release from the median eminence and activation of the hypothalamic-pituitary-adrenal axis in stressed rats. Neuroendocrinology. 1995;62(4):333-9.
12. Zelena D, Mergl Z, Makara GB. Glutamate agonists activate the hypothalamic-pituitary-adrenal axis through hypothalamic paraventricular nucleus but not through vasopressinerg neurons. Brain Res. 2005;1031(2):185-93.
13. Tokarev D, Jezová D. Effect of central administration of the non-NMDA receptor antagonist DNQX on ACTH and corticosterone release before and during immobilization stress. Methods Find Exp Clin Pharmacol. 1997;19(5):323-8.
14. Chambers RA, Bremner JD, Moghaddam B, Southwick SM, Charney DS, Krystal JH. Glutamate and post-traumatic stress disorder: toward a psychobiology of dissociation. Semin Clin Neuropsychiatry. 1999;4(4):274-81.
15. Jumaili WA, Trivedi C, Chao T, Kubosumi A, Jain S. The safety and efficacy of ketamine NMDA receptor blocker as a therapeutic intervention for PTSD review of a randomized clinical trial. Behav Brain Res. 2022;424:113804.
16. Attari A, Rajabi F, Maracy MR. D-cycloserine for treatment of numbing and avoidance in chronic post traumatic stress disorder: A randomized, double blind, clinical trial. J Res Med Sci. 2014;19(7):592-8.
17. Czarnecka K, Chuchmacz J, Wójtowicz P, Szymański P. Memantine in neurological disorders - schizophrenia and depression. J Mol Med (Berl). 2021;99(3):327-34.
18. Omranifard V, Rajabi F, Mohammadian-Sichani M, Maracy M. The effect of add-on memantine on global function and quality of life in schizophrenia: A randomized, double-blind, controlled, clinical trial. Adv Biomed Res. 2015;4:211.
19. Omranifard V, Rajabi F, Mohammadian-Sichani M, Maracy MR. The effect of add-on memantine on positive, negative and depressive symptoms of schizophrenia: a doubleblind, randomized, controlled trial. Actas Esp Psiquiatr. 2017;45(3):108-15.
20. Askari S, Mokhtari S, Shariat SV, Shariati B, Yarahmadi M, Shalbafan M. Memantine augmentation of sertraline in the treatment of symptoms and executive function among patients with obsessive-compulsive disorder: A double-blind placebo-controlled, randomized clinical trial. BMC Psychiatry. 2022;22(1):34.
21. Hadi F, Kashefinejad S, Kamalzadeh L, Hoobehfekr S, Shalbafan M. Glutamatergic medications as adjunctive therapy for moderate to severe obsessive-compulsive disorder in adults: a systematic review and meta-analysis. BMC Pharmacol Toxicol. 2021;22(1):69.
22. Hori H, Itoh M, Matsui M, Kamo T, Saito T, Nishimatsu Y, et al. The efficacy of memantine in the treatment of civilian posttraumatic stress disorder: an open-label trial. Eur J Psychotraumatol. 2021;12(1):1859821.
23. Di Iorio G, Baroni G, Lorusso M, Montemitro C, Spano MC, di Giannantonio M. Efficacy of Memantine in Schizophrenic Patients: A Systematic Review. J Amino Acids. 2017;2017:7021071.
24. Cénat JM, Blais-Rochette C, Kokou-Kpolou CK, Noorishad PG, Mukunzi JN, McIntee SE, et al. Prevalence of symptoms of depression, anxiety, insomnia, posttraumatic stress disorder, and psychological distress among populations affected by the COVID-19 pandemic: A systematic review and meta-analysis. Psychiatry Res. 2021;295:113599.
25. Shen X, Yan S, Jiang H, Cao H, Dowling R, Feng J, et al. Post-traumatic Stress Disorder and Associated Factors 1 Year After the Beginning of the COVID-19 Pandemic Among Chinese Residents. Front Psychiatry. 2021;12:766127.
26. Weathers FW, Keane TM, Davidson JR. Clinician-administered PTSD scale: a review of the first ten years of research. Depress Anxiety. 2001;13(3):132-56.
27. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al. The development of a Clinician-Administered PTSD Scale. J Trauma Stress. 1995;8(1):75-90.
28. Cicchetti D, Fontana A, Showalter D. Evaluating the reliability of multiple assessments of PTSD

symptomatology: multiple examiners, one patient. Psychiatry Res. 2009;166(2-3):269-80.
29. Ramaswamy S, Madabushi J, Hunziker J, Bhatia SC, Petty F. An Open-Label Trial of Memantine for Cognitive Impairment in Patients with Posttraumatic Stress Disorder. J Aging Res. 2015;2015:934162.
30. Battista MA, Hierholzer R, Khouzam HR, Barlow A, O'Toole S. Pilot trial of memantine in the treatment of posttraumatic stress disorder. Psychiatry. 2007;70(2):167-74.
31. Gorbachenko VA, Lukyanetz EA. Effects of memantine on the passive avoidance test in young rats. Fiziolohichnyĭ Zhurnal. 2020; 66(5):3-10.