Effect of Rivastigmine Augmentation in Treatment of Male Patients With Combat-Related Chronic Posttraumatic Stress Disorder

A Randomized Controlled Trial

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Abstract:

Background: Posttraumatic stress disorder (PTSD) is one of the chronic and disabling psychiatric disorders, particularly in combat veterans. In a case series, rivastigmine was suggested to be an effective augmentation in treatment of PTSD. The aim of the present study was to evaluate this finding in a randomized controlled trial.

Method: A 12-week, double-blind, placebo-controlled clinical trial was performed on 36 male patients (aged 42–60 years) diagnosed with chronic, combat-related PTSD. Subjects were screened for apparent cognitive deficits by means of Mini-Mental State Examination. All patients received selective serotonin reuptake inhibitors plus sodium valproate for 4 weeks and then reevaluated. Subjects who did not show adequate response were randomly assigned into 3 groups receiving rivastigmine (up to 6 mg/d), placebo, or the prior treatment regimen. Efficacy of medication was measured by administering PTSD Check List–Military Version at baseline and weeks 2, 4, 8, and 12. Collected data were analyzed by analysis of variance and repeated measurement. Reported differences were considered significant at the level of 0.05 or less.

Results: The 3 groups showed statistically significant reductions in the total PTSD Check List–Military Version, avoidance subscale, and the reexperience subscale but not in the hyperarousal subscale. No significant differences were found between the 3 groups.

Conclusions: In contrast to the previous case series, findings of the current study did not support the efficacy of adjunctive rivastigmine in treatment of PTSD. This hypothetically could be due to the fact that all the study's subjects scored higher than 25 on Mini-Mental State Examination.

Key Words: posttraumatic stress disorder, rivastigmine, cognitive disorders, clinical trial

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Posttraumatic stress disorder (PTSD) is one of the most disabling trauma-related disorders that can occur after exposure to harmful events that are outside the range of usual experience.[1,2] Patients might demonstrate a range of psychological, behavioral, and cognitive symptoms. The core symptoms are reexperiencing, avoidance, numbing, and hyperarousal.[3] The duration of symptoms must be at least 1 month.[4] Posttraumatic stress disorder is associated with significant impairments in patient's social, professional, and personal life functions.[5–7] First-line treatments for PTSD are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors.[8,9] Various types of medications, such as benzodiazepines and mood stabilizers, have been studied in treatment of chronic PTSD. However, findings regarding these options are controversial, and they are not considered as part of the standard routine treatment.[10–12]

Iran has a huge number of patients diagnosed with PTSD after the Iran-Iraq war (1980-1988); unfortunately, a considerable number of these patients are treatment-resistant cases.[13] Therefore, finding new treatment options to help these patients is one of the major concerns of the local researchers and psychiatrists.[4] A previously published case series suggested that rivastigmine could be an effective add-on to the standard treatment of PTSD.[14]

Rivastigmine is an acetylcholinesterase inhibitor (AchEI).[15,16] Acetylcholinesterase inhibitors (such as rivastigmine, donepezil, tacrine, galantamine, and memantine) produce enhancement of cholinergic neurotransmission by increasing the availability of synaptic acetylcholine.[17] Therefore, these medications are the first-line treatment in diseases in which cholinergic synapses are damaged but functional.[17] Rivastigmine is a slowly reversible noncompetitive inhibitor of both acetylcholinesterase (AChE) and butylcholinesterase (BuChE).[18] It elevates the concentration of extracellular acetylcholine.[18,19] Ahnaou et al[15] found that rivastigmine improve the plasticity and cognitive processes by enhancing the coherent slow theta and gamma activity in the scopolamine-induced cognitive deficit rat model.

Rivastigmine has been used to treat mild to moderate dementia in Alzheimer disease,[18] cognitive impairments of patients diagnosed with Parkinson disease,[20] and behavioral symptoms and cognitive deficiencies of patients diagnosed with Huntington disease.[21] Shimizu et al[22] found that AchEI treatment can result in a significant increase in regional cerebral blood flow, mainly in the frontal lobe through which they can prevent the progression of cognitive impairment. Rivastigmine's mechanism of action does not involve cytochrome P-450; therefore, it causes less drug-drug interactions in the elderly. In addition, it has low plasma protein binding, which makes its half-life less than 5 hours.[8]

Fayyazi Bordbar and Talaei[14] in a case series conveyed that 3 treatment-resistant PTSD (TR-PTSD) patients showed improvement in hyperarousal symptoms after 1 month of receiving 6 mg/d rivastigmine. They explained that the underlying mechanism of rivastigmine effect in PTSD could be due to its effect on improving the imbalance of adrenergic-cholinergic systems. The purpose of the current study was to evaluate the effectiveness of rivastigmine in treatment of TR-PTSD patients in a randomized controlled setting.

METHODS

Study Design and Settings

This pilot, double-blind, placebo-controlled clinical trial was conducted at the Ibn-E-Sina Psychiatric University Hospital,

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Mashhad, Iran. The ethics committee of Mashhad University of Medical Sciences has approved the study protocol (The trial's registration number in Iranian Registry of Clinical Trials: IRCT201211195280N10).

Subjects

A total of 36 male patients (aged between 40 and 65 years) who have been diagnosed with chronic PTSD and were admitted to the combat veterans' ward of the Ibn-E-Sina Psychiatric Hospital were enrolled in the trial. The diagnosis of chronic PTSD was made based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) criteria by 2 national board-certified psychiatrists. The etiology of the PTSD in all cases was the 8-year Iran-Iraq war, which lasted from September 1980 to August 1988. At least 10 years had passed since the onset of the PTSD in all patients, and they all had experienced several prior hospital admissions. Subjects were screened for apparent cognitive deficit by means of Mini-Mental State Examination (MMSE). Subjects who had MMSE score of less than 25 were excluded from the study. No history of drug (except for nicotine), and alcohol abuse has been reported by the patients. As part of the baseline visits, patients provided their medical records. Their previous treatment trials have been reviewed based on their previous hospitalization charts and their psychiatrists' notes. Patients were asked whether any of the previous treatments have significantly improved their symptoms or if they have experienced at least 25% clinical improvement as a result of the received medication. The number of past failed medications was not an inclusion-exclusion criterion. However, not surprisingly, considering the chronicity of their disorder, all the enrolled patients had at least 2 past episodes of not responding to adequate dose and duration of pharmacotherapy (with SSRIs, serotonin-norepinephrine reuptake inhibitors, benzodiazepines, tricyclic antidepressants, and anticonvulsants). It should be noted that there are yet no universally accepted clinical criteria regarding the definition of TR-PTSD.

The purpose and voluntary nature of the study were explained to the participants and written informed consent was signed by all of them. Patients were informed that they could withdraw from the study at any point. Exclusion criteria included a history of sensitivity to rivastigmine, active medical disease, a primary diagnosis of other psychiatric disorders other than PTSD (eg, primary diagnosis of major depressive disorder), and presence of intellectual disability and personality disorders.

Protocol

Patients who enrolled in the study completed the PTSD Check List–Military Version (PCL-M) at the baseline screening visit. All patients received citalopram (40 mg/d) and sodium valproate (20 mg/kg per day). Sodium valproate was added to citalopram mainly due to the fact that all the patients had at least 1 history of failed monotherapy with SSRI. Therefore, it seemed rational to assume that a single SSRI trial would not be sufficient in the first phase of the trial. In addition, all the patients were diagnosed with chronic combat-related PTSD with irritability, mood swings, and several hyperarousal symptoms. Hence, valproic acid was added to their regimen as a mood stabilizer and an augmentation to SSRI.[23–25]

After 4 weeks, the PCL-M scale was measured again. Patients who showed more than 25% improvement in the second PCL-M were excluded. Subjects who exhibited less than 25% improvement were randomized into 3 groups using a computer-generated randomization list. Spitzer Quality of Life Index and Beck Depression Inventory were used to assess the base line quality of life index and baseline depression score of all the enrolled subjects. To keep the sample size fix at 36, each excluded subject was replaced with a new enrolled subject.

The case group (n = 12) received rivastigmine capsules (1.5 mg twice daily for 4 weeks followed by 3 mg twice daily for 8 weeks) in addition to their routine medications (citalopram and sodium valproate). The control group (n = 12) received placebo, which was in the same shape, color, and weight as rivastigmine capsules, plus the routine medications. The last group (n = 12) continued their routine medications and did not receive any other medications. There were no statistically significant differences between the 3 groups in regards to age, time from onset of the disease, and their routine medications' doses.

The 3 groups were followed up for 12 weeks. PTSD Check List–Military Version, Beck Depression Inventory (BDI-II), and Spitzer's Quality of Life Index were measured at weeks 2, 4, 8, and 12. All measurements were administered by a trained clinical psychologist who was blind to the patients' group and treatment protocol. Patients' adherence to rivastigmine treatment was monitored by a psychiatrist using the standard compliance checklist. The common adverse effects of rivastigmine include diarrhea, indigestion, loss of appetite, loss of strength, nausea, vomiting, and weight loss.[19] None of these adverse effects occurred severe enough to cause subjects to withdraw from the study. No other concomitant psychiatric medication, particularly, benzodiazepines, antipsychotics, and stimulants were allowed. Figure 1 presents the flow diagram of the study design.

Questionnaires and Scales

PTSD Checklist–Military Version

The PTSD checklist (PCL) was developed at National Center for PTSD in 1993 by Weathers et al as a means to assess the severity of PTSD symptoms. This questionnaire consists of 17 self-reporting questions based on the *DSM-IV-TR* symptoms of PTSD. Questions include 3 main categories: reexperience symptoms (questions 1–5), avoidance (questions 6–12), and arousal (questions 13–17). Subjects can rate the questions on a scale of 1 to 5 (1 = not at all, 2 = a little bit, 3 = moderately, 4 = quite a bit, and 5 = extremely). Sum of the scores ranges from 17 to 85. A higher score indicates more severity. The recommended minimum decreased score to determine whether a patient has responded to the treatment is 5; this threshold is suggested to be considered 10 points for a clinically meaningful improvement.[4] The PCL-M is a subtype of PCL, which is specifically designed for combat-related PTSD. The internal consistency of PCL and its subtypes is reported to be 0.97 and 0.92, respectively. In addition, PCL demonstrated a test-retest reliability of 0.96 and a validity of 0.77 to 0.93.[4]

Spitzer Quality of Life Index

Spitzer et al (1981) developed this measure to assess the quality of life of the patients diagnosed with chronic disorders. This scale consists of questions in 5 major areas including activity level, activities of daily living, health, support of the family and friends, and emotional state or outlook. Each question could be rated on a scale of 0 to 2, with total score ranging from 0 to 10. Higher scores represent better quality of life.[4] The internal consistency of this scale was reported as Cronbach alpha of 0.66 to 0.80, the Spearman rank correlation of 0.81, and a correlation of 0.61 when the test was done by 2 different clinicians.[4]

Beck Depression Inventory-II

The BDI-II (1996) is the revised version of BDI based on the diagnostic criteria of *DSM-IV-TR* for major depressive disorder. It

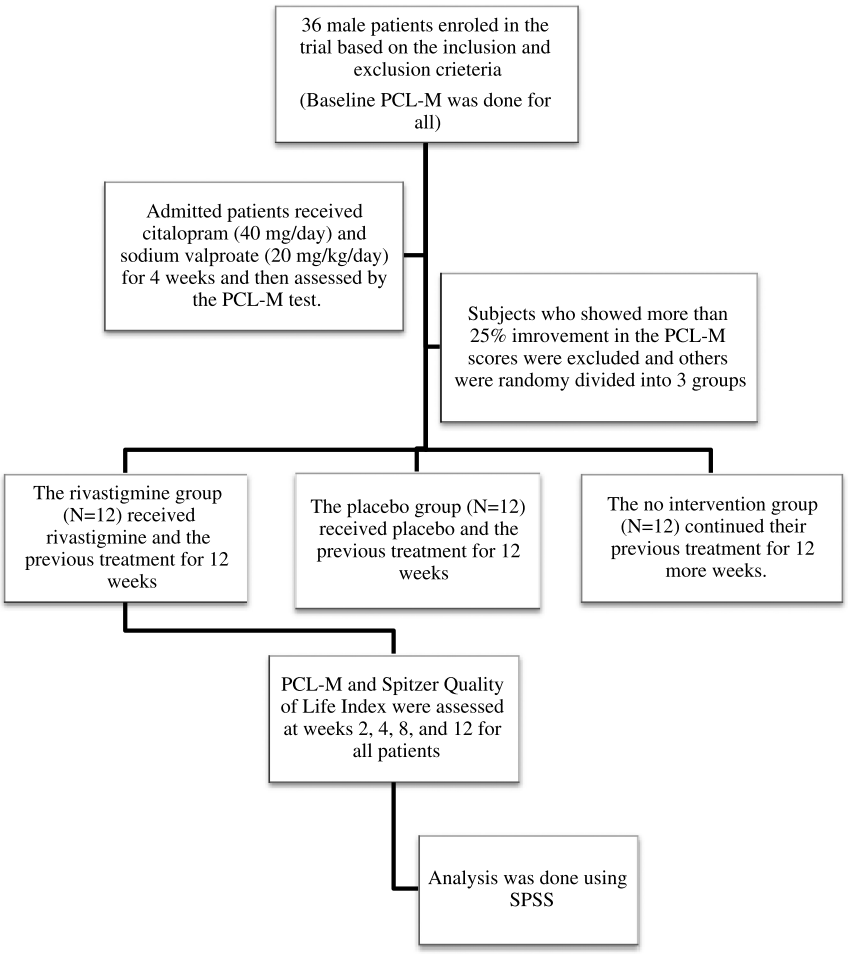

FIGURE 1. Flow diagram of the study based on Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (R43P).

consists of 21 questions regarding client's depressive symptoms in the past 2 weeks. Each question could be answered on a scale value of 0 to 3 and the total score ranges from 0 to 63. The higher scores indicate more severe depressive symptoms. Beck Depression Inventory-II showed a positive correlation of 0.71 with Hamilton Depression Rating Scale. It also has a high test-retest reliability ($r = 0.93$) and a high internal consistency ($r = 0.91$).[4]

Statistical Analysis

All the collected data were analyzed using the Statistical Package for the Social Sciences, 20th release (SPSS Science, Apache Software Foundation, Chicago, Ill). The normal distribution of data was confirmed by Kolmogorov-Smirnov *Z*. Student *t* test was used for the analysis of normally distributed data. Analysis of variance (ANOVA) with repeated measurement was used to compare the 3 groups. Nominal variables were compared by Pearson χ^2 test. A 2-sided *P* value less than 0.05 was considered significant.

RESULTS

The mean ± standard deviation (SD) of subjects' age was 50.22 ± 5.66 in total, 50.08 ± 4.50 for the rivastigmine group, 51.50 ± 6.40 for the placebo group, and 49.08 ± 6.13 for the group with no intervention. No statistically significant differences were observed between the mean ages of the 3 groups. All subjects were married; 55.9% of the subjects did not have a permanent job at the time of the study.

Table 1 depicts the mean scores of the PCL-M and its subcategories for the 3 groups at different time points of the study. Table 2 depicts the results of the repeated ANOVA that compared the PCL-M scores of the 3 groups at different time points of the study. No significant difference was observed between the 3 groups' reexperiencing symptoms in various time points. Hotelling trace of Tukey test did not reveal any significant difference between the 3 groups as well ($P = 0.36$). However, the overall score of all the subjects showed a significant improvement at the end of the 12th week in comparison with the baseline scores ($P = 0.02$) (Fig. 2).

Considering the scores of avoidance symptoms, no significant difference was observed between the 3 groups at each time checkpoint. In addition, comparison of the 3 groups showed no significant difference in their scores ($P = 0.94$). However, the overall score of the 3 groups showed a significant improvement at the end of the week 12 when compared with the baseline scores ($P < 0.0001$) (Fig. 2). No significant difference was observed between the arousal scores of the 3 groups at each time point and on overall between-group comparison ($P = 0.72$). In contrast to the previous scores, no significant overall improvement was observed in the arousal scores after the 12 weeks of the study ($P = 0.28$) (Fig. 2).

As far as the total scores of the PCL-M, the only significant difference between groups was observed in week 4 ($P = 0.04$). Therefore, the results of the week 4 were followed up with the

TABLE 1. PCL-M Scores on 3 Main Subcategories (Mean ± Standard Deviation)

Scale	Group	Week 0	Week 2	Week 4	Week 8	Week 12	*P*
Reexperience	Rivastigmine (n = 12)	14.08 ± 2.968	13.83 ± 2.48	13.66 ± 2.14	13.63 ± 2.11	13.54 ± 2.504	All groups = 0.02*; within groups = 0.36
	Placebo (n = 12)	15.08 ± 1.78	14.66 ± 2.05	14.18 ± 0.87	14.25 ± 2.09	14.00 ± 2.41	
	None (n = 12)	15.41 ± 1.16	15.16 ± 2.58	14.91 ± 2.062	14.09 ± 1.70	14.58 ± 1.88	
Avoidant numbing	Rivastigmine	18.25 ± 3.79	17.91 ± 3.11	17.16 ± 3.77	16.63 ± 3.17	16.63 ± 3.88	All = 0.0001*; within groups = 0.85
	Placebo	20.00 ± 1.80	19.33 ± 1.37	18.63 ± 1.12	18.66 ± 1.49	17.91 ± 1.83	
	None	19.75 ± 1.76	19.41 ± 2.42	18.91 ± 2.64	18.36 ± 2.54	17.66 ± 2.49	
Hyper arousal	Rivastigmine	15.66 ± 2.933	15.00 ± 2.59	14.50 ± 2.90	14.27 ± 2.41	14.45 ± 2.91	All = 0.13; within groups = 0.69
	Placebo	15.91 ± 2.15	15.58 ± 2.87	15.45 ± 2.29	15.91 ± 2.42	15.41 ± 2.77	
	None	17.33 ± 2.01	16.08 ± 2.06	16.83 ± 2.16	16.36 ± 2.110	16.58 ± 2.39	
Total PCL-M score	Rivastigmine	48.00 ± 7.03	46.58 ± 6.28	45.33 ± 5.29	44.63 ± 5.76	44.63 ± 7.67	All = 0.0001*; within groups = 0.56
	Placebo	51.00 ± 4.15	49.66 ± 4.79	48.18 ± 3.34	48.91 ± 4.35	47.25 ± 6.35	
	None	52.50 ± 2.46	50.66 ± 5.94	50.58 ± 5.71	48.72 ± 5.51	48.83 ± 6.04	

Values are expressed as mean ± SD. Group comparisons were done using the ANOVA with repeated measurement.
*$P < 0.05$ is considered significant.

Tukey HSD. Interestingly, this difference was not between the rivastigmine and the placebo group (Table 3). When the results were analyzed considering the time passage, no difference was observed between the 3 groups ($P = 0.57$). However, the overall patients' score showed a significant improvement after the week 12 ($P < 0.0001$) (Fig. 2).

DISCUSSION

Patients who have been randomized to receive rivastigmine, placebo, or no augmentation were the ones who did not show more than 25% improvements after receiving 4 weeks of citalopram plus sodium valproate. After the 12 weeks of the randomized phase of the study, the 3 groups showed statistically significant improvements in the total PCL-M score, avoidant score, and reexperience scores. However, none of these scales showed more than 5 points improvement. Therefore, while the statistical analysis of scores revealed a significant improvement, it is hard to consider it a clinical improvement. The arousal score did not show statistical significant improvement in any of the 3 groups. These findings suggest that arousal could be the hardest responding symptoms among the symptoms of the PTSD, and it might need the adjunctive treatments more than the other symptom categories. In addition, these findings highlight the importance of follow-up and multiple visits in treatment of PTSD, as suggested by previous studies. The following discussion will be focused on evaluating whether adding rivastigmine to the routine regimen had resulted in any additional therapeutic benefits.

Results of the current study demonstrated that there was no statistically significant difference between the PCL-M, arousal, reexperience, and avoidant scores of the 3 groups at different time points, except for the PCL-M score at week 4. Patients who received rivastigmine had a significant lower PCL-M score in week 4 when compared with patients who received no augmentation. However, this difference was not significant between the rivastigmine and placebo group.

The post hoc power analysis of the results showed a low and inadequate power, as expected due to the small sample size and insignificant outcomes. Because this study reports negative findings and the post hoc power analysis has been criticized as being misinterpreted when the outcomes had failed to reject the null hypothesis, analyses of the confidence intervals (CIs) were done as an alternative to test the power of the study. The mean post treatment PCL-M scores of the 3 groups with 90% certainty would fall within the range of 40.99 to 48.27 for the rivastigmine group, 44.23 to 50.26 for the placebo group, and 45.96 to 51.69 for the no-intervention group. The 90% CI of difference between the posttreatment PCL-M scores of the rivastigmine and placebo group was −7.35 to 2.1. In addition, the 90% CI of difference between the posttreatment PCL-M scores of the rivastigmine and no-intervention group was −8.83 to 0.43. Both of these CI ranges contain zero, which gives us enough precision to conclude that the current data does not provide sufficient evidence to reject the

TABLE 2. Between-Groups Comparisons at Each Time Point for the Subcategories and Total PCL-M

	Between-Groups Comparison *P*			
	Reexperience Score (*P*)	Avoidance Score (*P*)	Arousal Score (*P*)	Total PCL-M Score (*P*)
Week 0	0.286	0.227	0.202	0.090
Week 2	0.395	0.246	0.582	0.251
Week 4	0.252	0.213	0.084	0.040*
Week 8	0.749	0.127	0.100	0.098
Week 12	0.533	0.528	0.181	0.331

Between-groups comparisons were done using the ANOVA with repeated measurement.
*$P < 0.05$ is considered significant.

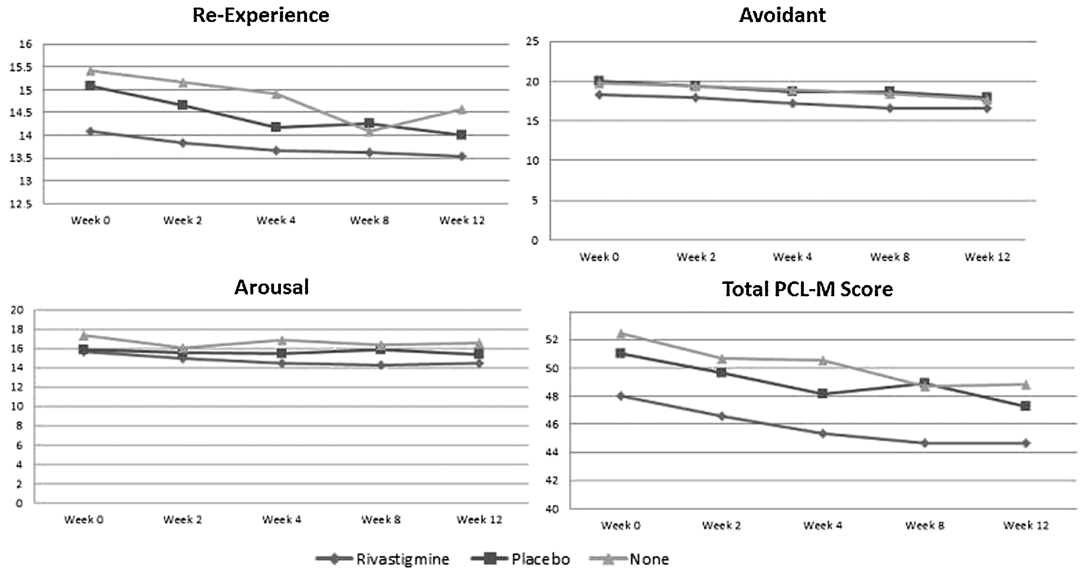

FIGURE 2. Change of mean reexperience, avoidant, arousal, and total PCL-M scores at different time points for the 3 groups. The reexperience, avoidant, and total PCL-M scores of the 3 groups showed statistically significant improvement from week 0 to week 12, but no significant differences was found between the rivastigmine and placebo groups. In addition, the improvement was not clinically significant. None of the 3 groups' hyperarousal scores showed a significant improvement from week 0 to week 12.

null hypothesis. However, these intervals are relatively wide, which is mainly due to the small sample size of the study. This further emphasizes that this study provides little knowledge about the potential effect of rivastigmine and further information is needed in this regard.

As noted before, this pilot study was designed to examine the findings of a case series that suggested rivastigmine could be an effective add-on in treatment of PTSD.[14] The mentioned case series suggested that rivastigmine 3 mg twice a day improved the PCL-M scores (67 to 37 after 1 month and to 30 after 6 months) of the PTSD patients.[14] In contrast, findings of the current study did not demonstrate any statistical significant differences between rivastigmine (same dose as the case series) and placebo. To explain the findings, it would be helpful to review the possible mechanisms through which rivastigmine might benefit PTSD patients.

It has been suggested that veterans diagnosed with PTSD experience increased adrenergic activity, which results in symptoms such as increased blood pressure, palpitation, and hot flushes. In addition, an increased serum level of norepinephrine and urine level of epinephrine have been shown in blood and urine samples of PTSD patients, respectively. In summary, there is an elevated sympathetic tone and decreased parasympathetic activity in chronic PTSD.[26] Moreover, acetylcholine is suggested to be the responsible neurotransmitter in the inhibitory avoidance mechanism of anxiety disorders. Excess levels of acetylcholine could result in creating nonforgettable memories in conjunction with the effect of norepinephrine, cortisol, and corticotropin-releasing hormone.[27] By the same token, Tochigi et al[28] found that serum cholinesterase level was significantly reduced in the victims of the Tokyo subway sarin attack who developed PTSD after the attack, compared with the matched controls. It has been shown that cholinesterase mediates effects of stress on fear conditioning and neuronal plasticity in hippocampus. Therefore, it could be hypothesized that cholinergic-adrenergic imbalance might be the underlying mechanism of some of the PTSD symptoms.[29–32]

It has been shown that structural changes in the hippocampus area of the brain are responsible for some of the PTSD symptoms. These changes are similar to the changes that have been found in aging and Alzheimer disease.[15,18,33] The other area of brain that has been found to undergo some changes in the course of PTSD is the frontal lobe. These changes are associated with deficits in cognitive performances.[33]

Some studies reported that veterans with PTSD have some degrees of cognitive impairments such as deficient initial learning of auditory-verbal and visual-spatial information, heightened sensitivity to interference, more frequent intrusions on free recall, and more false-positives on recognition tasks. In addition, orientation, logical memory, and letter-number sequencing have been suggested to be impaired among PTSD patients.[2,7,34] Schoeman et al[2] reported that PTSD was associated with cognitive deficiencies in attention, visual memory, and nonverbal concept formation in adolescents.

Vasterling et al studied the Persian Gulf War veterans and found relative performance deficiencies on tasks of sustained attention, mental manipulation, initial acquisition of information, and retroactive interference among the veterans diagnosed with PTSD. These cognitive impairments have also been reported in the prisoner-of-war survivors and civilian refugees.[35] Interestingly, they found that cognitive intrusion was correlated positively with reexperiencing symptoms and negatively with avoidance-numbing

TABLE 3. Post Hoc Test for Week 4 Total PCL-M Scores to Find the Level of Significant Difference

Groups		Mean Differences	Error	*P*
Rivastigmine	None	−5.2500	2.01456	0.03*
	Placebo	−2.8485	2.05983	0.36
Placebo	Rivastigmine	2.8485	2.05983	0.36
	None	−2.4015	2.05983	0.48
None	Rivastigmine	5.2500	2.01456	0.03*
	Placebo	2.4015	2.05983	0.48

Tukey HSD was done to determine the point of significant difference between the 3 groups.

*$P < 0.05$ is considered significant.

symptoms. They did not find any significant relationship between the cognitive intrusion and arousal symptoms.[35] This might explain the absence of response in the hyperarousal symptoms in the present study.

Considering the cognitive deficits found in PTSD, findings of the brain studies, and biochemical studies, it seems reasonable to hypothesize that rivastigmine can improve the cognitive symptoms of PTSD patients by its AchE-inhibiting function. By the same token, the target of the Parkinson disease treatment is the imbalance of the dopaminergic-cholinergic system. Therefore, rivastigmine could hypothetically improve the cholinergic-adrenergic balance by decreasing AchE. However, patient enrolled in the current study had normal MMSE scores (>25) that rules out any apparent cognitive deficit.

In conclusion, it is too early to discuss the potential outcomes of the AchEIs in treatment of PTSD. A case report that has been published by Wolff[36] described an 87-year-old naval veteran of World War II who did not meet criteria for PTSD under normal circumstances. The mentioned patient had received 5 mg donepezil daily for his memory impairments. Upon increasing the dose of donepezil to 10 mg, his memories of a kamikaze strike were considerably intensified to the point that resulted in emotional distress.[36] Therefore, more research is needed to clarify these reported controversies to give us a better understanding regarding the potential role that AchEIs can play in treatment of PTSD.

Further studies regarding the role of AchEIs might be of added value to the field of PTSD treatment. Finally, although MMSE is widely used as an estimate of cognitive functioning, the battery of neuropsychological assessments such as tests of attention, tests of executive functioning, and tests of learning and memory are more sensitive to cognitive impairment. In addition, Sešok et al[21] suggested that MMSE is less sensitive in discriminating mild cognitive deficits. Therefore, using both measures in future studies could provide more reliable results.

LIMITATIONS

The most important limitation to mention is that patients with MMSE scores less than 25 were excluded. Therefore, it could be assumed that the enrolled patient did not have an apparent cognitive deficit. Another noticeable limitation of this study is its small sample size, which was mainly because of the limited resources and ethical considerations. This small sample size could not provide a high statistical power. The other factor that potentially limited the power of the study was enrollment of 2 control groups (one received placebo and one did not receive any intervention). Although, this strategy could have helped us to differentiate whether the potential beneficial effects were due to the placebo effect or due to the SSRI + valproate treatment, also to differentiate how much of the potential significant difference was due to the attentive, regular care that the subjects have received throughout the study, it more prominently reduced the power of the analysis.

Another potential limitation of the study was the 4-week pretreatment period. This phase of the study could potentially confuse the outcome of the study because it is possible that patients start to respond after 4 to 6 weeks. To reduce this error, all the patients were reassessed after 4 weeks to find out if any of the patients started to show any response to this treatment regimen. Although all the enrolled patients had a history of not responding to at least 2 pharmacotherapies of adequate dose and duration, one of the subjects did show more than 25% improvement at the 4-week assessment and was replaced. Therefore, we cannot make the assumption that the sample consisted of 100% nonresponders. However, the improvement was very small and basically, clinically nonmeaningful. Moreover, the remaining subjects did not show a clinically significant improvement. Hence, it is assumed that this potential limitation did not meaningfully affect the results.

It should be also noted that patient were discharged from the hospital after week 2 to 4. This may have potentially decreased the compliance of the patients with their medication. All the enrolled patients were males because combat-related female PTSD patients are less frequent. The enrolled patients were all diagnosed with combat-related PTSD with history of multiple admissions and failed past medication trials; therefore, these results might not be generalizable to other PTSD populations. As far as the double-blindness of the study, the psychiatrists did not prescribe the placebo/rivastigmine. They were provided with packs of medication (rivastigmine/placebo), which had the same shape and color, each with a barcode. The decision to match the barcodes with patients was made based on the computerized randomization, and the psychiatrists were blind whether the patient is receiving the placebo or rivastigmine. However, the patients in the no-augmentation group were the only ones who did not have regular compliance/adverse effect visits with the psychiatrists. Therefore, the psychiatrists were not blind to this group. The psychiatrists were not involved in the care/regular visits of patients in the no-augmentation group and a rater who was blind to the study performed the measurements. Finally, follow-up was not continued after week 12 of the study.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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