EUROPEAN JOURNAL OF PSYCHOTRAUMATOLOGY
2021, VOL. 12, 1859821
https://doi.org/10.1080/20008198.2020.1859821

EUROPEAN JOURNAL OF PSYCHO-TRAUMATOLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY FOR TRAUMATIC STRESS STUDIES

Taylor & Francis
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CLINICAL RESEARCH ARTICLE

The efficacy of memantine in the treatment of civilian posttraumatic stress disorder: an open-label trial

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ABSTRACT

Background: Currently, there is a paucity of pharmacological treatment options for posttraumatic stress disorder (PTSD), and the development of a novel pharmacotherapeutic approach has become a matter of great interest.

Objective: We conducted a 12-week open-label clinical trial to examine the efficacy and safety of memantine, an *N*-methyl-D-aspartate receptor antagonist, in the treatment of civilian PTSD.

Method: Thirteen adult patients with DSM-IV PTSD, all civilian women, were enrolled. They were monitored at an ambulatory care facility every week until 4 weeks and then every 4 weeks until 12 weeks. Memantine was added to each patient's current medication, with the initial dosage of 5 mg/day and then titrated. Concomitant medications were essentially kept unchanged during the trial. The primary outcome was PTSD diagnosis and severity assessed with the Posttraumatic Diagnostic Scale (PDS).

Results: Of the 13 cases, one dropped out and two were discarded due to the protocol deviation, and the analysis was done for the remaining 10. Mean PDS total scores decreased from 32.3 ± 9.7 at baseline to 12.2 ± 7.9 at endpoint, which was statistically significant with a large effect (paired *t*-test: $p = .002$, $d = 1.35$); intrusion, avoidance, hyperarousal symptoms were all significantly improved from baseline to endpoint. Six patients no longer fulfilled the diagnostic criteria of PTSD at endpoint. Some adverse, but not serious, effects possibly related to memantine were observed, including sleep problems, sleepiness, sedation, weight change and hypotension.

Conclusions: Memantine significantly reduced PTSD symptoms in civilian female PTSD patients and the drug was well tolerated. Future randomized controlled trials are necessary to verify the efficacy and safety of memantine in the treatment of PTSD.

ARTICLE HISTORY

Received 12 June 2020
Revised 16 November 2020
Accepted 21 November 2020

KEYWORDS

Posttraumatic stress disorder (PTSD); memantine; memory; clinical trial; re-experiencing; efficacy; safety

PALABRAS CLAVES

Trastorno de Estrés Postraumático (TEPT); Memantina; memoria; Ensayo Clínico; Reexperimentación; Eficacia; Seguridad

关键词

创伤后应激障碍 (PTSD); 美金刚; 记忆; 临床试验; 再体验; 有效性; 安全性

HIGHLIGHTS

- Memantine significantly reduced PTSD symptoms in civilian female PTSD patients and the drug was well tolerated.
- Its pre-post effect size is 1.35, almost comparable to that of trauma-focused CBT.
- The finding accords with the results of recent studies of fear memory in rodents.

La eficacia de Memantina en el tratamiento del Trastorno de Estrés Postraumático en civiles: un ensayo abierto

Antecedentes: Actualmente, hay escasez de opciones de tratamiento farmacológico para el trastorno de estrés postraumático (TEPT), y el desarrollo de un enfoque farmacoterapéutico nuevo se ha transformado en materia de gran interés.

Objetivo: Llevamos a cabo un ensayo clínico abierto de 12 semanas para examinar la eficacia y seguridad de memantina, un antagonista del receptor de N-metil-d-aspartato, en el tratamiento del TEPT en civiles.

Método: Se inscribieron trece pacientes adultas con TEPT según DSM-IV, todas mujeres civiles. Fueron monitoreadas en un centro de atención ambulatoria semanalmente por 4 semanas, y luego cada 4 semanas hasta las 12 semanas. Se agregó memantina al tratamiento farmacológico actual de cada paciente, con dosis inicial de 5 mg/día y titulación posterior. Los fármacos concomitantes fueron mantenidos esencialmente sin cambios durante el estudio. El objetivo primario fue el diagnóstico de TEPT y su severidad, evaluada con la Escala de Diagóstico Postraumático (PDS, por su sigla en inglés).

Resultados: De los 13 casos, uno abandonó y 2 fueron descartados debido a desvío del protocolo, y el análisis fue realizado con los 10 restantes. El puntaje total promedio de PDS disminuyó de 32.3 ± 9.7 en el basal a 12.2 ± 7.9 al término, lo que fue estadísticamente significativo con un tamaño de efecto grande (prueba t pareada: p=.002, d=1.35); los síntomas de intrusión, evitación e hiperactivación mejoraron todos en forma al término respecto a la basal. Seis pacientes dejaron de cumplir los criterios de TEPT al término. Se observaron algunos efectos adversos, pero no serios, posiblemente relacionados

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This trial is registered in the UMIN Clinical Trials Registry (UMIN000022467) and the Japan Registry of Clinical Trials (jRCTs031180200).

a memantina, que incluyeron problemas del sueño, somnolencia, sedación, cambios en el peso e hipotensión.
Conclusiones: La memantina redujo significativamente los síntomas de TEPT en pacientes mujeres civiles con TEPT y el fármaco fue bien tolerado. Se requieren ensayos controlados aleatorizados en el futuro para verificar la eficacia y seguridad de la memantina en el tratamiento del TEPT.

美金刚(memantine)治疗平民创伤后应激障碍的功效:一项开放性试验

背景: 目前, 创伤后应激障碍 (PTSD) 的药物治疗选择不足, 开发新的药物治疗方法已成为大家非常关心的问题。
目的: 我们进行了为期12周的开放性临床试验, 以考查一种N-甲基-d-天冬氨酸受体拮抗剂——美金刚, 治疗平民PTSD的有效性和安全性。
方法: 招募了13名DSM-IV PTSD成年患者, 均为平民女性。前4周每周在流动护理站对其进行监测, 然后到12周为止每4周监测一次。美金刚以5毫克/天的初始剂量添加到每位患者当前的药物中, 然后滴定。在试验期间, 伴随药物本质上保持不变。主要结果为使用创伤后诊断量表 (PDS) 评估的PTSD诊断情况和严重程度。
结果: 在13例病例中, 1例中途退出, 2例因操作规程有偏差被弃用, 对其余10例进行了分析。平均PDS总评分从基线的32.3±9.7降低至最终的12.2±7.9, 达到有大效应量的统计显著 (配对t检验:p= .002, d= 1.35) ;从基线到最终, 闯入, 回避, 高唤醒症状都有了显著改善。6名患者最终不再符合PTSD诊断标准。观察到一些可能与美金刚有关的不良但不严重的作用, 包括睡眠问题, 嗜睡, 镇静, 体重改变和低血压。
结论: 美金刚可以显著减轻平民女性PTSD患者的PTSD症状, 并且该药物具有良好的耐受性。未来有必要进行随机对照试验以验证美金刚在PTSD治疗中的有效性和安全性。
本试验已在 UMIN临床试验注册中心 (UMIN000022467) 和日本临床试验注册中心 (jRCTs031180200) 中注册。

1. Introduction

Posttraumatic stress disorder (PTSD) is a serious psychiatric condition that can develop after a major traumatic event, often leading to a chronic course and severe functional impairment. Lifetime prevalence of PTSD is estimated at approximately 3.9% worldwide (Koenen et al., 2017). Patients with this disorder exhibit a variety of psychological and behavioural symptoms, including re-experiencing, avoidance and hyperarousal. Of these, re-experiencing symptoms, namely involuntary retrieval of traumatic memories such as intrusive thoughts, flashbacks and nightmares, are largely unique to PTSD and as such are recognized as a central feature of this disorder (Ehlers & Clark, 2000). An important aspect of the re-experiencing phenomenon is that it can be observed not only in humans but also in animals in the form of conditioned fear responses (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Maren, 2001), implying the neurobiological mechanism underlying clinical symptoms.

The contemporary guidelines recommend trauma-focused psychotherapy as the first line treatment of PTSD based on evidence of its efficacy. However, there are some patients who do not benefit from these psychotherapies; it has been suggested among veterans that non-response rates are high, many patients continue to have symptoms, and these therapies show marginally superior results compared with active control conditions (Goetter et al., 2015; Steenkamp, Litz, Hoge, & Marmar, 2015). Furthermore, this psychotherapy is difficult to disseminate because of the burden of training of therapists, time and costs. Thus, there is a great need for pharmacotherapy, but its option is quite limited; only two selective serotonin reuptake inhibitors (SSRIs), paroxetine and sertraline, are approved by the United Stattes Food and Drug Administration. Moreover, a substantial proportion of patients with PTSD do not adequately respond to these SSRIs (Hoskins et al., 2015). A meta-analysis (Lee et al., 2016) shows that the efficacy of these SSRIs is considerably lower than that of trauma-focused psychotherapies. Therefore, the development of a novel pharmacotherapeutic approach for PTSD has become a matter of great interest and, accordingly, clinical trials have been conducted for various agents prescribed alone or in combination with psychotherapy, but mostly failed to show positive results (de Kleine, Rothbaum, & van Minnen, 2013; Hoskins et al., 2015; Merz, Schwarzer, & Gerger, 2019).

Memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is approved and widely used for the treatment of Alzheimer's disease (AD). The fact that NMDA receptor plays a pivotal role in learning and memory (Collingridge, 1987) suggests that this mechanism may be involved in the pathophysiology of PTSD (Krystal et al., 2017; Lijffijt et al., 2019). In rodent studies, memantine dramatically increased adult hippocampal neurogenesis (Ishikawa et al., 2014: Maekawa et al., 2009). Furthermore, forgetting of contextual fear memory was promoted through increased hippocampal neurogenesis when adult mice were treated with memantine once a week for 4 weeks following the formation of contextual fear memory (Akers et al., 2014; Ishikawa, Fukushima, Frankland, & Kida, 2016). In addition, this effect of memantine was observed without requiring additional interventions such as a fear memory retrieval

session (Ishikawa et al., 2016). These findings from animal models suggest that memantine can be efficacious for patients with PTSD as a simple stand-alone pharmacological treatment (Kida, 2019). In fact, the efficacy of memantine for human PTSD has been suggested by several case reports (Battista, Hierholzer, Khouzam, Barlow, & O'Toole, 2007; Chopra, Trevino, & Kowall, 2011) and one open-label trial (Ramaswamy, Madabushi, Hunziker, Bhatia, & Petty, 2015); the latter, however, failed to demonstrate the reduction of re-experiencing symptoms, a core phenomenon of PTSD, leaving some ambiguity about its true effects on the pathology of this disorder. These previous studies have targeted predominantly male veterans, and no memantine trials have been conducted among civilians with PTSD. Given a previous suggestion of the differential pharmacological treatment responses between civilians and veterans (Institute of Medicine, 2007), it would be of importance to examine its efficacy in civilians.

In the present study, we aimed to examine the efficacy and safety of memantine for civilian PTSD by conducting an open-label clinical trial. We particularly focused on the effect of memantine on PTSD symptomatology including re-experiencing symptoms, which did not improve in previous study. Possible effects on cognitive function were also examined, considering that memantine is an antidementia drug (Battista et al., 2007; Ramaswamy et al., 2015) and that PTSD is associated with cognitive impairment (Narita-Ohtaki et al., 2018; Scott et al., 2015).

2. Methods

2.1. Study design and participants

From August 2016 to present, we have conducted a 12-week open trial of memantine for PTSD patients; this trial is ongoing as of June 2020 for more detailed analyses with an expanded sample. This study was approved by both the National Centre of Neurology and Psychiatry (NCNP) Clinical Research Review Board and Ethical Committee, and was conducted in accordance with the Declaration of Helsinki. After description of the study, written informed consent was obtained from every participant.

Thirteen patients diagnosed as having DSM-IV PTSD were recruited from the outpatient clinic of the NCNP Hospital or from community through announcements on websites and at nearby clinics. All the patients were women, although this trial was open to both men and women. This participation of women alone was considered related to the fact that this trial targeted civilian PTSD. Indeed, the potentially eligible PTSD patients who had been visiting the collaborative hospitals/clinics for this study were mostly women; thus, we did not exclude any eligible male patients with PTSD.

During the trial participation, patients visited either the NCNP Hospital or a collaborative institute, Ai Clinic Kanda, both located in Tokyo. All patients had already been diagnosed as having PTSD by their attending clinicians. The experience of traumatic events and diagnosis of PTSD were confirmed by the validated Japanese version (Nagae et al., 2007) of the Posttraumatic Diagnostic Scale (PDS; Foa, 1995). Additionally, the Japanese version (Otsubo et al., 2005) of the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) was administered to identify any other Axis-I disorders as well as PTSD.

The inclusion criteria were: (1) patients diagnosed with PTSD; (2) patients attending NCNP Hospital or the collaborative institute; (3) individuals who were able to understand the nature of this study and provide informed consent; and (4) age between 20 and 59 years.

The exclusion criteria were: (1) patients with duration of illness less than 6 months; (2) individuals who received specific psychotherapy (e.g. prolonged exposure therapy, cognitive processing therapy, eye movement desensitization and reprocessing therapy) within 3 months prior to the study entry; (3) patients with comorbid schizophrenia, severe manic phase of bipolar disorder or intellectual disability; (4) individuals with serious suicidal ideation; (5) individuals with severe physical illnesses that can interfere with the study participation; (6) pregnant women; (7) individuals with the following physical conditions that are described in manufacturer's package insert of Memary (i.e. brand name of memantine) as 'careful administration', including history of epilepsy or convulsion, renal dysfunction, factors increasing urine pH and severe liver dysfunction; and (8) patients considered unqualified for the study by their attending physicians.

2.2. Treatment

This open-label clinical trial consisted of 12 weeks of memantine intake period, followed by 4-week (or more) post-trial observation period during which only adverse events associated with memantine were monitored. During the 12-week trial, patients were required to visit the hospital/clinic seven times: at baseline and after 1, 2, 3, 4, 8 and 12 weeks of treatment initiation. Memantine was added to each patient's current medication, with the initial dosage of 5 mg/day. The dosage was then increased by 5 mg/day weekly to the maintenance dosage of 20 mg/day. In the case of intolerance to this increase, the dosage was flexibly adjusted according to the condition of the patient. Other medications were

kept unchanged during the 12-week trial period except that minimum change in benzodiazepine sleep medications was allowed. Participants were compensated with 2000 JPY (approximately US$20) at each visit to defray travel expenses and inconvenience costs.

2.3. Outcomes

2.3.1. The primary outcome

The primary outcome was diagnosis and severity of PTSD assessed with the PDS.

The PDS was created in accordance with the diagnostic criteria of DSM-IV PTSD (Foa, 1995). It comprises four parts that evaluate traumatic experiences (Parts 1 and 2), PTSD symptoms during the past month (Part 3) and the associated functional impairments (Part 4). In the present study, we administered Parts 1 and 2 at baseline for the assessment of presence/absence of traumatic experiences, and Parts 3 and 4 at baseline and at 4, 8 and 12 weeks for the evaluation of PTSD diagnosis and severity. We have previously reported a sufficiently high concordance rate between the PDS and the Clinician-Administered PTSD Scale (Blake et al., 1995), a structured interview for the diagnosis of PTSD (i.e. 95.1%, $\kappa = 0.90$; Itoh et al., 2017).

2.3.2. Secondary outcomes

Secondary outcomes included: (1) PTSD severity assessed by the Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 2004), (2) cognitive function assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998), (3) depressive symptoms assessed with the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), (4) anxiety symptoms assessed with the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970), (5) posttraumatic cognitive styles assessed with the Posttraumatic Cognitions Inventory (PTCI; Foa, Ehlers, Clark, Tolin, & Orsillo, 1999), (6) overall symptom severity/improvement assessed with the Clinical Global Impression (CGI; Guy, 1976) and (7) adverse events assessed with the UKU Side Effect Rating Scale (Lingjaerde, Ahlfors, Bech, Dencker, & The, 1987).

The validated Japanese version (Asukai et al., 2002) of IES-R was administered at every visit. The IES-R is a 22-item self-report questionnaire measuring the severity of three core PTSD symptom clusters, i.e. intrusion, avoidance and hyperarousal, as well as the total score during the past week. Each item is scored on a 5-point scale of symptom intensity, with higher scores indicating greater symptom severity.

The validated Japanese version (Matsui, Kasai, & Nagasaki, 2010) of RBANS, a well-established neuropsychological test battery, was administered at baseline and at 12 weeks. With 12 subtests, the RBANS can assess immediate memory, visuospatial construction, language, attention and delayed memory, as well as the total score. Age-corrected standardized scores, with a population mean of 100 and standard deviation (*SD*) of 15, are calculated for each cognitive domain (Matsui et al., 2010; Randolph et al., 1998). The RBANS has demonstrated good psychometric properties among clinical and nonclinical populations (Duff et al., 2005; Matsui et al., 2010; McKay, Casey, Wertheimer, & Fichtenberg, 2007; Weber, 2003). Scoring was done in accordance with the manual guidelines (Matsui et al., 2010; Randolph et al., 1998).

The validated Japanese version (Kojima et al., 2002) of BDI-II was administered at baseline and at 12 weeks. It is a 21-item self-report questionnaire widely used to measure depression severity during the past 2 weeks. Each item is scored on a 4-point scale from 0 to 3, with higher scores indicating more severe depressive symptoms.

The validated Japanese version (Nakazato & Mizuguchi, 1982) of STAI was administered at baseline and at 12 weeks. This widely-used self-report questionnaire consists of two subscales for trait (STAI-T) and state (STAI-S) anxiety, each comprising 20 items scored on a 4-point scale from 1 to 4; higher scores indicate greater anxiety.

The validated Japanese version (Nagae et al., 2004) of PTCI was administered at baseline and at 4, 8 and 12 weeks. It is a 36-item self-report questionnaire for assessing trauma-related thoughts and beliefs classified into three subscales, including negative cognitions about self, self-blame and negative cognitions about the world, as well as the total score.

Clinical status was assessed at baseline and at 4, 8 and 12 weeks, by using CGI Severity (CGI-S) and Improvement (CGI-I) scales; for CGI-I, baseline assessment is not conducted.

Adverse events were assessed at each visit by using the Japanese version (Chiba & Takahashi, 2005) of UKU Side Effect Rating Scale and by checking blood pressure. Additionally, blood tests were performed at baseline and at 4 and 12 weeks in order to monitor hepatic and renal functions, blood glucose levels and creatine phosphokinase levels.

We also examined dissociation, childhood maltreatment history and intelligence, whose results will be published elsewhere.

2.4. Statistical analysis

Averages are reported as mean ± standard deviation (*SD*). All analyses for treatment responses were performed on an intention-to-treat basis, with the last observation carried forward (LOCF), in patients with

at least one follow-up assessment available. The paired *t*-test was used to compare baseline and LOCF results. Additionally, the Wilcoxon signed-rank test was performed to confirm the *t*-test results on the primary outcome.

Statistical significance was set at 2-tailed $p < .05$. All analyses were performed using the Statistical Package for the Social Sciences version 25.0 (IBM, Tokyo, Japan).

3. Results

3.1. Baseline characteristics

Baseline characteristics of each participant are listed in Table 1. Thirteen patients with PTSD, all women, with mean age of 32.9 ± 6.4 years (range: 23–46 years) were enrolled. Of the 13 patients, two were smokers and 11 were non-smokers. Most of the patients (11/13: 84.6%) developed the disorder after experiencing childhood maltreatment or adulthood interpersonal violence such as domestic and/or sexual violence. All the patients had suffered from PTSD for 3 years or more at the time of study entry. Three patients had received trauma-focused psychotherapy prior to participating in this study; of these, two patients had received prolonged exposure therapy but dropped out, and one had received prolonged exposure therapy but the efficacy was insufficient. Most of them had multiple psychiatric comorbidities such as mood and anxiety disorders and were taking psychotropic medications such as antidepressants and sleep medications. There were no patients who had a history of traumatic brain injury prior to participating in this study. The mean PDS total score at baseline was 32.3 ± 9.8, which indicated that our patients were on average moderately to severely ill. The mean RBANS total score at baseline was 83.2 ± 21.5, indicating that their global cognitive function was approximately 1 *SD* below the population average.

Within the first 4 weeks, of the 13 cases, one dropped out due to unpredictable change in life situation, and two were discarded due to change of the concomitant medication. For them no follow-up assessment of PDS was conducted, and therefore the pre-post analyses were performed for the remaining 10 patients who participated in the follow-up PDS assessment. Mean age of the 10 completers and that of the three non-completers were 34.3 ± 6.2 and 28.3 ± 5.5 (respectively), and mean baseline PDS total scores of the two groups were 32.3 ± 9.7 and 32.3 ± 12.1 (respectively), indicating that these baseline characteristics were comparable between groups. Of the 10 completers, one patient failed to complete the assessment of RBANS memory (immediate and delayed memory) index at endpoint because of heightened anxiety during the testing; for this patient, valid RBANS data were obtained for the other three indices (i.e. visuospatial construction, language and attention), and therefore only these data were included in the analyses.

There were two patients in whom benzodiazepine sleep medications were changed during the trial period; brotizolam 0.25 mg/day was added at 2 weeks in one patient and estazolam 2 mg/day was discontinued at 1 week in another patient (Table 1).

3.2. Efficacy

Changes in the PDS total score from baseline to endpoint are illustrated in Figure 1. As shown in Figure 1(a) and Table 1, this score decreased over time in most patients. For the 10 completers, mean PDS total scores at week 4, week 8 and endpoint were 21.3 ± 10.4, 17.0 ± 10.1 and 12.2 ± 7.9, respectively. The decrease from baseline was at a trend level at week 4 ($t = 2.2$, $df = 9$, $p = .056$, $d = 0.69$) and subsequently became significant at week 8 ($t = 3.1$, $df = 9$, $p = .013$, $d = 0.97$) and at endpoint ($t = 4.3$, $df = 9$, $p = .002$, $d = 1.35$); these results were generally confirmed by the Wilcoxon signed-rank test ($p = .047$ at week 4; $p = .028$ at week 8; and $p = .012$ at endpoint). For the three subscales of PDS, intrusion, avoidance and hyperarousal scores were all significantly decreased from baseline to endpoint ($t = 3.9$, $df = 9$, $p = .004$, $d = 1.23$; $t = 3.5$, $df = 9$, $p = .007$, $d = 1.10$; and $t = 4.2$, $df = 9$, $p = .002$, $d = 1.32$, respectively) (Figure 1(b)). Based on the consensus that Cohen's *d* of 0.2, 0.5 and 0.8 represent small, moderate and large effects, respectively (Cohen, 1988), the size of symptom reduction at endpoint was considered large. Six of the 10 completers no longer fulfilled the diagnostic criteria of PTSD at endpoint (Figure 1(c)).

Table 2 shows changes in secondary outcomes from baseline to endpoint. In line with the PDS results, PTSD severity assessed with the IES-R was significantly decreased for all the three symptom clusters as well as the total score. For cognitive function, no significant change was observed in any of the RBANS indices. Of the nine patients who completed the RBANS assessment both at baseline and endpoint, the number of patients whose RBANS total score was lower than 85 (i.e. 1 *SD* below the population mean) was four (44.4%) at baseline, and this number remained unchanged at endpoint; same patients showed compromised cognitive function both before and after the memantine treatment. Depression and trait anxiety, but not state anxiety, were significantly decreased after treatment. Regarding the posttraumatic cognitive style, negative cognitions about self and those about the world, but not self-blame, were significantly reduced. Clinical global impression was significantly improved.

Table 1. Baseline characteristics and outcomes of each participant.

ID	Sex	Age (years)	Type of index trauma	Illness duration[#] (years)	Previous trauma-focused psychotherapy	Comorbid psychiatric disorder	Concomitant psychotropic medication (dosage: mg/day)	Duration of trial participation (weeks)	Memantine dosage at endpoint (mg/day)	Decrease in PDS total score at endpoint (%)	Change in concomitant medication during the trial[†]	Adverse events*	Results of blood test for checking possible side effects (only values outside normal range are listed along with baseline values)	Reason for discontinuation
1	F	34	Interpersonal violence	20	Prolonged exposure therapy (dropout)	BD (currently euthymic)	Aripiprazole (3)	12	0	86.96	Brotizolam (0.25) was added at 2 weeks	Fatiguability; Failing memory; Reduced duration of sleep; Increased dream activity; Palpitations; Fear; Nausea; Headache	(none)	Increased fear[e]
2	F	27	Abortion	4	Prolonged exposure therapy (insufficient efficacy)	Bulimia nervosa; BD (currently euthymic)	Sertraline (25), Etizolam (0.5), Flunitrazepam (2), Zolpidem (10)	8	5	84.38	(none)	Reduced duration of sleep; Elevated blood pressure; Constipation; Weight loss; Weight gain; Anxiety; Tension; Binge-eating	ALT (U/L): (54 at baseline); 35 at 4 weeks; 47 at 8 weeks Glu (mg/dL): (109 at baseline); 120 at 4 weeks; 148 at 8 weeks	Increased blood sugar[e]
3	F	35	Childhood maltreatment	23	(none)	MDD	Venlafaxine (112.5), Imipramine (10), Chlorpromazine (12.5), Tandospirone (20), Clonazepam (0.5), Zopiclone (10), Promethazine (25)	16	10	−10.00	(none)	Anxiety; Fear; Tension	CK (U/L): (170 at baseline); 361 at 4 weeks Cre (mg/dL): (0.66 at baseline); 0.77 at 4 weeks	(N.A.)
4	F	37	Childhood maltreatment	29	Prolonged exposure therapy (dropout)	MDD; Social anxiety disorder	Clomipramine (75), Amitriptyline (25), Bromazepam (6), Brotizolam (0.25), Pentobarbital (100), Phenobarbital (30)	16	7.5	42.50	(none)	Dizziness; Sleepiness; Sedation; Increased duration of sleep	(none)	(N.A.)

(*Continued*)

Table 1. (Continued).

ID	Sex	Age (years)	Type of index trauma	Illness duration[#] (years)	Previous trauma-focused psychotherapy	Comorbid psychiatric disorder	Concomitant psychotropic medication (dosage: mg/day)	Duration of trial participation (weeks)	Memantine dosage at endpoint (mg/day)	Decrease in PDS total score at endpoint (%)	Change in concomitant medication during the trial[†]	Adverse events*	Results of blood test for checking possible side effects (only values outside normal range are listed along with baseline values)	Reason for discontinuation
5	F	46	Interpersonal violence	33	(none)	MDD; Panic disorder	Duloxetine (60), Paroxetine (37.5), Chlorpromazine (12.5), Estazolam (2), Triazolam (0.125)	16	20	−5.00	Estazolam (2) was discontinued at 1 week	Sleepiness; Sedation	AST (U/L): (40 at baseline); 38 at 4 weeks; 33 at 12 weeks ALT (U/L): (31 at baseline); 33 at 4 weeks; 37 at 12 weeks	(N.A.)
6	F	27	Childhood maltreatment	13	(none)	Agoraphobia; Social anxiety disorder	Duloxetine (40), Zolpidem (10)	16	10	90.48	(none)	(none)	(none)	(N.A.)
7	F	37	Interpersonal violence	5	(none)	(none)	(none)	16	5	72.41	(none)	(none)	Cre (mg/dL): (0.41 at baseline); 0.42 at 4 weeks Glu (mg/dL): (90 at 4 weeks)[c]; 121 at 12 weeks	(N.A.)
8	F	39	Natural disaster	7	(none)	MDD	Venlafaxine (37.5)	16	10	88.89	(none)	Sleepiness; Sedation; Constipation; Weight gain	(none)	(N.A.)
9	F	34	Childhood maltreatment	> 20	(none)	MDD; OCD	Brexpiprazole (2), Quetiapine (25), Lorazepam (0.5), Prazosin (0.5)	2	10	(N.A.)	Brexpiprazole (2) was discontinued at 1 week[a]	Hypotension	(N.A.)	Change in concomitant medication[f]

(*Continued*)

Table 1. (Continued).

ID	Sex	Age (years)	Type of index trauma	Illness duration[#] (years)	Previous trauma-focused psychotherapy	Comorbid psychiatric disorder	Concomitant psychotropic medication (dosage: mg/day)	Duration of trial participation (weeks)	Memantine dosage at endpoint (mg/day)	Decrease in PDS total score at endpoint (%)	Change in concomitant medication during the trial[†]	Adverse events*	Results of blood test for checking possible side effects (only values outside normal range are listed along with baseline values)	Reason for discontinuation
10	F	35	Interpersonal violence	23	(none)	Social anxiety disorder	(none)	16	10	40.00	(none)	(none)	CK (U/L): (88 at baseline); 40 at 12 weeks	(N.A.)
11	F	28	Childhood maltreatment	> 15	(none)	BD (currently depressed); Agoraphobia; GAD; OCD	Valproate (600), Flunitrazepam (1), Prazosin (3)	2	10	(N.A.)	Mirtazapine (15) and brexpiprazole (1) were prescribed at 1 week[b]	Hypotension	(N.A.)	Change in concomitant medication[f]
12	F	23	Interpersonal violence	3	(none)	(none)	Aripiprazole (1)	2	5	(N.A.)	(none)	Increased tendency to sweating	(N.A.)	Difficulty in visiting the clinic regularly[f]
13	F	26	Interpersonal violence	11	(none)	MDD; Social anxiety disorder	Mirtazapine (7.5), Lorazepam (0.5), Ramelteon (8), Eszopiclone (3), Atomoxetine (120)	16	15	55.26	(none)	Sleepiness; Sedation; Increased duration of sleep; Increased dream activity; Hypotension	(none)[d]	(N.A.)

Abbreviations: N.A., not applicable; PDS, Posttraumatic Diagnostic Scale; BD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; GAD, generalized anxiety disorder.
[#]Estimated based on age of index trauma.
[†]Only minimum change in benzodiazepine sleep medications was allowed.
*Events that were mild or unlikely to be due to memantine were not included here.
[a]This patient thought that that anxiety and fear that lasted from before the initiation of memantine might be due to concomitant brexpiprazole, and therefore stopped taking it.
[b]This patient was found to physically abuse her child when she got depressed, and so we prescribed 15 mg of mirtazapine, 1 mg of brexpiprazole and offered a psychotherapy for emotional regulation; the abuse had existed before the trial, and was not related to memantine.
[c]Measurement of glucose level at baseline was missing.
[d]Measurement at 4 week and measurement of glucose level at 12 week were missing.
[e]Included in the LOCF analysis.
[f]Excluded from the LOCF analysis because of no follow-up PDS data.

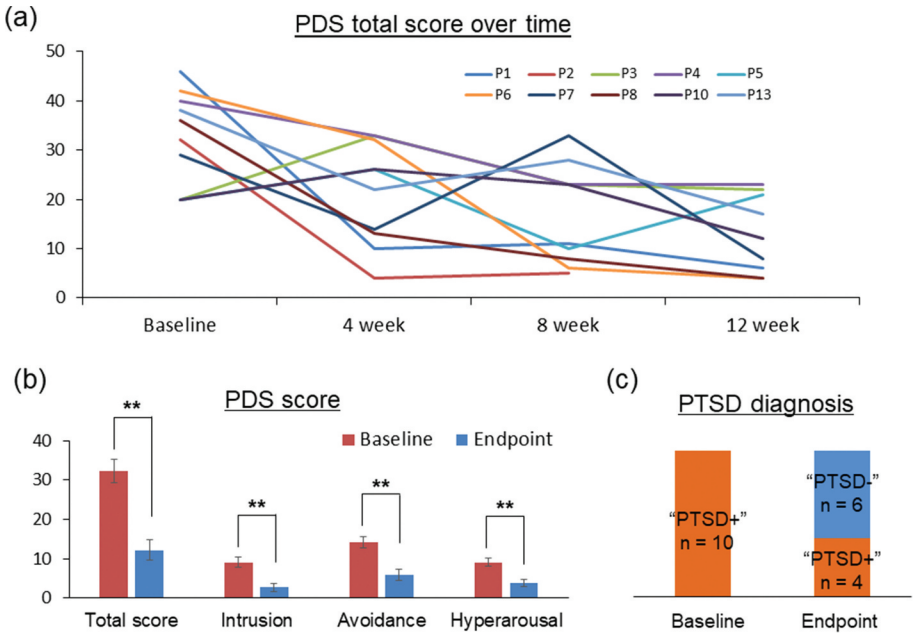

Figure 1. Primary outcome assessed with the Posttraumatic Diagnostic Scale (PDS). (a) PDS total scores over time for each participant. There was a significant decrease from baseline to endpoint according to paired *t*-test ($t = 4.3$, $df = 9$, $p = .002$). (b) Mean PDS total and subscale scores at baseline and at endpoint. Comparisons were made by paired *t*-test. $^{**}p < .01$. (c) PTSD diagnosis status at baseline and at endpoint.

Table 2. Changes in secondary outcomes from baseline to endpoint (mean ± *SD*).

			Paired *t*-test ($df = 9$)	
Variable	Baseline	Endpoint	*t*	*p*
IES-R, total score	51.0 ± 15.0	19.1 ± 15.1	5.0	**< .001**
Intrusion	18.5 ± 7.9	5.7 ± 4.3	4.6	**.001**
Avoidance	18.5 ± 9.4	9.3 ± 8.7	3.1	**.012**
Hyperarousal	14.0 ± 3.5	4.1 ± 3.8	5.3	**< .001**
RBANS, total score[a]	83.2 ± 21.5	87.0 ± 20.7	−1.2[b]	.27
Immediate memory[a]	80.4 ± 23.1	83.6 ± 11.7	−0.5[b]	.60
Visuospatial construction	91.8 ± 10.6	91.7 ± 19.5	0.0	.98
Language	96.2 ± 13.2	101.5 ± 11.8	−2.2	.06
Attention	89.1 ± 12.5	98.4 ± 12.9	−2.0	.07
Delayed memory[a]	93.2 ± 19.7	85.3 ± 19.8	2.0[b]	.09
BDI-II, total score	28.3 ± 17.4	15.0 ± 14.0	2.6	**.027**
STAI				
State	44.1 ± 12.0	44.2 ± 10.8	0.0	.98
Trait	62.9 ± 10.1	49.8 ± 13.1	4.5	**.001**
PTCI, total score	145.0 ± 57.0	109.7 ± 51.6	2.6	**.030**
Negative cognitions about self	96.9 ± 35.3	72.0 ± 33.8	2.8	**.019**
Self-blame	15.4 ± 10.0	12.2 ± 9.4	1.2	.25
Negative cognitions about the world	32.7 ± 14.1	25.5 ± 10.5	2.3	**.046**
Clinical Global Impression (CGI)				
CGI-S	4.7 ± 0.9	2.9 ± 0.8	4.9	**.001**
CGI-I	N.A.	1.8 ± 1.1	N.A.	N.A.

Abbreviations: *SD*, standard deviation; *df*, degree of freedom; N.A., not applicable; IES-R, Impact of Event Scale-Revised; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; BDI-II, Beck Depression Inventory-II; STAI, State-Trait Anxiety Inventory; PTCI, Posttraumatic Cognitions Inventory.
[a]$n = 9$.
[b]$df = 8$.

3.3. Safety

As listed in Table 1, various adverse events possibly related to memantine were observed, including sleep problems, sleepiness, sedation, weight change and hypotension, although not serious. While our study protocol indicated that the memantine dosage could be increased up to 20 mg/day, the dosage at endpoint was within the range of 5–10 mg in most patients (Table 1); one patient was taking 20 mg and another was on 15 mg at endpoint (Table 1). This was primarily because the higher dosages were paradoxically associated with increased anxiety symptoms in those patients.

4. Discussion

This 12-week open-label trial was the first, to our knowledge, to examine the efficacy of (adjunctive) memantine in the treatment of civilian women with PTSD. Memantine significantly improved PTSD symptoms over the trial period, with the pre-post effect size of 1.35, and led to remission in

a majority of patients at endpoint. Depression and trait anxiety were also reduced, and posttraumatic cognitive styles became less negative.

Although preliminary, this finding fills the paucity of effective pharmacological treatment for PTSD and suggests a highly effective treatment option with memantine, whose effect size was comparable to that of trauma-focused pharmacotherapy. Given that our patients had been ill for more than several years despite receiving ordinary mental health services (be they pharmacological interventions or psychotherapeutic ones), and that memantine can be prescribed as treatment as usual, the observed efficacy would urge us to further investigate its effect in a controlled clinical trial.

Our finding accords with that of the previous open-label memantine trial for PTSD veterans in terms of the overall symptom improvement (Ramaswamy et al., 2015). Concerning the core intrusion (or re-experiencing) symptoms, however, the study of Ramaswamy et al. (2015) did not observe a significant effect on this symptom dimension whereas the present study found a marked effect. It might be that the effect of memantine on this symptom is greater in civilian than in veterans, being in line with the general tendency towards better treatment responses in civilians vs. veterans with PTSD (Institute of Medicine, 2007), but more data are needed to draw any conclusion.

Our results also indicated that depression, trait anxiety and clinical global impression significantly improved after memantine treatment while state anxiety did not. The reason for this absence of change in state anxiety is not fully clear, but it could be speculated that memantine has a tendency to increase anxiety, as was reported by three participants (see Table 1), and it undermined the anxiolytic effects of the drug. Or, memantine does not improve the psychological vulnerability to daily stressors, so that state-distress remained. A further investigation is necessary to clarify these points with increased sample size and various psychobiological factors.

Memantine, an antidementia drug, is shown to slow the progression of memory/cognitive symptoms of AD. In the present trial, however, the compromised cognitive function in PTSD patients was not ameliorated by memantine. This result was not in agreement with that of Ramaswamy et al. (2015), in which impaired cognitive function as assessed with the RBANS was significantly alleviated. These conflicting results might again be attributable to the differential sample characteristics between studies such as trauma type, sex and ethnicity. The baseline severity and profile of cognitive impairment should be also adjusted to explain the discrepant findings, because such greater cognitive dysfunction associated with a reversible condition (like PTSD) could mean that there is more room to be improved by treatment.

With respect to the safety, no severe adverse events occurred, although a variety of mild to moderate adverse events possibly caused by memantine were observed. Our results also suggest that the maximum possible memantine dosage of 20 mg/day may not be well tolerated in relatively young female patients with PTSD. Since memantine is approved only for the treatment of elderly patients with AD, its safety in younger populations is largely unclear. The optimal amount of memantine in the treatment of PTSD will therefore need to be investigated in future studies.

The mechanism by which memantine mitigates PTSD symptoms is not clear. It may be useful to note, however, that memantine is an NMDA receptor antagonist and the involvement of NMDA receptors in cognition and mood is well documented (Lakhan, Caro, & Hadzimichalis, 2013). Given this, together with the evidence for roles of NMDA receptors in multiple psychiatric disorders (Amidfar et al., 2019; Lijffijt et al., 2019), it would be plausible to assume that the memantine's antagonistic effect on NMDA receptors is involved in its efficacy for PTSD. This assumption implies that the effect of memantine on PTSD can be exerted via its general effects on mood and cognitive symptoms. Another explanation comes from molecular researches of fear memory. Notably, mouse studies have shown that memantine facilitates the forgetting of fear memory and improves PTSD-like behaviours through its neurogenesis enhancing effect (Ishikawa, Uchida, Kitaoka, Furuyashiki, & Kida, 2019; Kida, 2019). This suggests that memantine can directly suppress conditioned fear responses, probably via its forgetting effects, and thus alleviate the core symptomatology of PTSD. Indeed, our findings indicated that while PTSD symptoms (assessed with PDS and IES-R) and depression (BDI-II) were both significantly reduced by memantine the former reduction was more remarkable. Still, further biological studies are necessary to understand mechanism(s) underlying the efficacy of memantine in PTSD.

There were several limitations to this study. First, this is an open trial that did not have placebo or active control groups, which may have introduced some potential biases. Second, the small sample size prevented us from performing post-hoc multivariate analyses to control for or stratify by potentially confounding demographic/clinical variables. Third, our sample was relatively homogeneous in terms of sex, trauma type and ethnicity, but heterogeneous regarding age, baseline symptom severity and comorbid psychiatric disorders. On the other hand, the results obtained in this female-only sample may not be readily extrapolated to male patients with PTSD. Fourth, most of the patients were not on current standard pharmacological treatments for PTSD at the entry of this study. For example, seven of the total 13 patients were receiving

benzodiazepines or barbiturates (Table 1), which are not recommended in evidence-based practice for PTSD. This might reflect the long duration of illness in our patients; standard pharmacotherapy would have been done at the initial stage of treatment, but its efficacy was likely not sufficient, and then more complicated treatment attempts may have been made as a desperate measure. In addition, most of the patients had comorbid psychiatric disorders such as mood and anxiety disorders, which would have required additional medications. Fifth, as our patients were receiving a broad range of pharmacological treatments at baseline and we were not able to standardize these concomitant medications, interpretation of the results should be made with caution; for example, there may have been interactions between memantine and other drugs for both efficacy and side effects. Finally, this 12-week trial obviously precludes the ability to study the long-term effects of memantine for PTSD, particularly in this population of chronically ill patients. Although we can only speculate on this issue of long-term effects, it may be possible that the favourable effects observed here do not persist after the trial and symptoms become worse again, as is often the case with pharmacological trials for PTSD (Merz et al., 2019). Still, there is another possibility that the effect of memantine, unlike that of other medications, can last longer, given that memantine is shown to improve PTSD-like behaviours in mice by facilitating the 'forgetting' of fear memory (Ishikawa et al., 2019; Kida, 2019).

In summary, findings from this open-label trial suggest that memantine can be effective and relatively well tolerated in civilian female patients with PTSD. Our findings, along with those of recent animal studies, further raise the possibility that this effect of memantine can be at least in part exerted by a PTSD-specific mechanism. Future randomized controlled trials are needed to verify the efficacy and safety of memantine in the treatment of PTSD.

Acknowledgments

We would like to thank all individuals who participated in this study.

Disclosure statement

No potential conflict of interest was reported by the authors.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [YK], upon reasonable request. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Funding

This study was supported in part by Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 19H01047 (to YK) and grant from the Japan Research Foundation for Clinical Pharmacology (to HH).

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