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Pharmacological treatment of Post-Traumatic Stress Disorder: a treatment guide based on a systematic literature review

Tratamento farmacológico do Transtorno de Estresse Pós-Traumático: um guia de tratamento baseado em uma revisão sistemática

Tratamiento farmacológico del Trastorno de Estrés Postraumático: una guía de tratamiento basada en una revisión sistemática

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ABSTRACT:
Objective: To review the literature from the last twenty years on pharmacological treatments for post-traumatic stress disorder to clarify questions about the efficacy and tolerability of pharmacotherapy and the superiority of one specific agent over another for creating a treatment guideline based on levels of evidence. **Methods:** Randomized clinical trials and systematic reviews were searched in Medline-PubMed, PsycINFO, Web of Science, Scielo, and Lilacs. The screening of the criteria established by the Transparent Reporting of Systematic Reviews and Meta-Analyses was used, followed by the analysis of risk of bias of the Critical Appraisal Skills Programme. Lastly, the level of evidence and grade of recommendation was acquired, following the Oxford Center for Evidence-based Medicine 2009 Levels of Evidence. **Results:** The search retrieved double-blind, randomized and placebo-controlled clinical trials. Comparative clinical trials between different drugs were also evaluated and systematic reviews on drug efficacy and meta-analyses. A total of 1.458 studies were found; 58

of these studies were pre-selected and the final sample was composed of 20 studies. **Conclusions:** Of the 17 drugs included, the following is the order of recommendation based on the levels of evidence established in this study - 1st sertraline; 2nd venlafaxine and paroxetine; 3rd atypical antipsychotics.

Keywords: stress disorders post-traumatic, drug therapy, stress disorders, post-traumatic, psychopharmacology.

RESUMO:

Objetivo: Revisar a literatura dos últimos vinte anos sobre o tratamento farmacológico do transtorno de estresse pós-traumático para elucidar dúvidas sobre a eficácia e tolerabilidade da farmacologia e a superioridade de um fármaco específico sobre outro para criar um guia de tratamento baseado em níveis de evidências. **Métodos:** Ensaios clínicos randomizados e revisões sistemáticas foram buscadas no Medline-PubMed, PsycINFO, Web of Science, Scielo e Lilacs. O critério de triagem utilizado foi o estabelecido pelo Transparent Reporting of Systematic Reviews and Meta-Analyses, seguido pela análise de *risk of bias* do Critical Appraisal Skills Programme. Por último, o nível de evidência e o grau de recomendação foram obtidos seguindo o Oxford Center for Evidence-based Medicine 2009 Levels of Evidence. **Resultados:** Foram selecionados ensaios clínicos duplo-cegos, randomizados, placebo controlados. Ensaios clínicos comparativos entre duas drogas e revisões sistemáticas, sobre eficácia e tolerabilidade, e metanálises também foram selecionadas. Um total de 1.458 estudos foram encontrados; 58 destes estudos foram pré-selecionados e a amostra final foi composta por 20 estudos. **Conclusão:** Das 17 drogas incluídas, a ordem de recomendação baseada nos níveis de evidências estabelecidos neste estudo foi: 1º sertralina; 2º venlafaxina e paroxetina; 3º antipsicóticos atípicos.

Palavras-chave: transtornos de estresses pós-traumáticos, tratamento farmacológico, transtornos de estresse, pós-trauma, farmacoterapia, psicofarmacologia.

RESUMEN:

Objetivo: Revisar la literatura de los últimos veinte años sobre tratamientos farmacológicos para el trastorno de estrés postraumático para aclarar preguntas sobre la eficacia y tolerabilidad de la farmacoterapia y la superioridad de un agente específico sobre otro, así creando una guía

de tratamiento basada en los niveles de evidencia. **Métodos:** Se realizaron búsquedas en ensayos clínicos aleatorios y revisiones sistemáticas en Medline-PubMed, PsycINFO, Web of Science, Scielo y Lilacs. Se utilizó el cribado de los criterios establecidos por el Transparent Reporting of Systematic Reviews and Meta-Analyses, seguido del análisis del riesgo de sesgo del Critical Appraisal Skills Programme. Por último, se adquirió el nivel de evidencia y el grado de recomendación, siguiendo los Oxford Center for Evidence-based Medicine 2009 Levels of Evidence. **Resultados:** La búsqueda recuperó ensayos clínicos doble ciego aleatorizados y controlados con placebo. Ensayos clínicos comparativos entre diferentes fármacos también fueron evaluados y se realizaron revisiones sistemáticas sobre fármacos, eficacia y metaanálisis. Se encontró un total de 1.458 estudios; 58 de estos estudios fueron preseleccionados y la muestra final estuvo compuesta por veinte estudios. **Conclusiones:** De los diecisiete fármacos incluidos, el siguiente es el orden de recomendación basada en los niveles de evidencia establecidos en este estudio - 1ª sertralina; 2ª venlafaxina y paroxetina; 3º antipsicóticos atípicos.

Palabras clave: trastornos por estrés postraumático, trastornos de estrés, post-trauma, farmacologia, psicofarmacología.

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Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric disorder characterized by symptoms that occur after a traumatic event that threatens the physical integrity or life of a person or significant other [1]. Not only can the victim of this event develop PTSD, but also can witnesses to the incident, for example, in cases of rescuers or family members. Evidence from scientific studies indicates that the lifetime occurrence of PTSD in the United States of America is around 7-8%, while in Brazil, it stands at approximately 11% [2]. Regarding assessments of comorbidity, nearly 80% of individuals with PTSD reported experiencing other concurrent psychiatric conditions [3]. Because PTSD is a common mental disorder that is difficult to treat and carries a high risk of chronicity, comorbidity, and functional impairment, debate about therapeutic approaches is essential. Several therapeutic guidelines recommend different types of trauma-focused psychotherapies as the first-line treatment [4]. For pharmacological approaches, recommendations are inconsistent and no consensus is on them. Some guidelines recommend selective serotonin reuptake inhibitors (SSRIs) as possible first-line treatment [4]. However, many guidelines consider antidepressants as a second-line treatment or adjunctive to psychotherapies [5]. To date, the United States Food and Drug Administration (FDA) has approved only two SSRIs (sertraline and paroxetine) for the treatment of PTSD. These drugs have been shown to be effective in reducing symptom severity and preventing relapse in patients with PTSD [6], although only about 60% of patients respond to pharmacological treatment and fewer than 30% achieve full remission through it [7]. Although many guidelines indicate trauma focus psychotherapy as first line treatment or at least psychotherapy plus medication as an adjuvant treatment, in developing countries and in the public health system trained psychotherapists are costly and rarely available a guide that provides evidence for pharmacological treatment seems necessary. Thus, the present review intends specifically to determine the efficacy of pharmacological treatments compared with placebos - without contrasting drugs with

psychotherapy- for evaluating whether antidepressants such as selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors (SNRIs) are effective in treating PTSD, and whether one of these drugs is better than the others based on the level of evidence from the studies evaluated. Therefore, a systematic review of the literature on the efficacy of pharmacological treatments for PTSD was conducted to clarify any doubts about the superiority of a particular agent over another. Hence, the need for this study is to determine a flow of drug escalation for treatment when the first trial does not have the expected effect. To this end, we set up the drug with the highest level of treatment evidence as the first option and other drugs as subsequent alternatives for circumstances in which the first option was unable to adequately treat the patient. This review included articles published over the past 20 years (2001–2021) on pharmacological treatments for PTSD to create a treatment guideline based on levels of evidence according to the quality of the studies reviewed. Although other systematic reviews were published before, the idea of designing a practice guideline for our population and the particularities of the Brazilian public system seem very important. This approach led to the development of a possible treatment guideline, achieved by integrating pre-existing clinical trials and systematic reviews within a unified study.

Methods

The transparent reporting of systematic reviews and meta-analyses (PRISMA) [8] criteria were used for study selection, and later the Critical Appraisal Skills Program (CASP) [9] was used to assess risk of bias [Annexes 1 and 2], and finally the Oxford center for evidence-based medicine 2009 levels of evidence (OCEBM) [10] [Annex 3] was used to classify the level of evidence and grade of recommendation. The study included double-blind, randomized, and placebo-controlled clinical trials, comparative clinical trials between different drugs, and systematic reviews with or without meta-analysis of the efficacy of published drugs. Through the amalgamation of various research designs, we were able to craft a systematic review that encompassed a significant quantity of top-notch articles available in the scientific literature.

The inclusion criteria were the following: **1)** double-blind, controlled, comparative clinical trial or systematic review with or without meta-analysis; **2)** study participants diagnosed with post-traumatic stress disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R, or DSM IV, or International Classification of Diseases (ICD)

criteria 10; and **3)** results based on validated scales for assessing the severity of the condition by a trained reviewer, referred to in each study analyzed.

The exclusion criteria were the following: **1)** presence of psychiatric disorders other than PTSD, excluding comorbidity with depression or anxiety; **2)** diagnosis of alcohol and/or drug abuse in the past 6 months; **3)** presence of severe comorbid clinical conditions; **4)** articles published in languages other than English or Portuguese; **5)** inclusion of participants younger than 18 years in the study sample; **6)** psychotherapy used as an adjunct or compared with a drug; **7)** open studies; **8)** unfinished studies, such as those still in progress with partial results not yet published; **9)** systematic reviews with or without meta-analysis including several open studies; and **10)** duplicates - clinical trial that is within an included systematic review.

The keywords used to search the databases were "posttraumatic stress disorder OR post-traumatic stress disorder OR PTSD OR stress disorder AND treatment OR pharmacological treatment OR pharmacotherapy." The search was restricted to articles in English or Portuguese between 2001 and 2020. Two reviewers filtered the database search based on titles and abstracts. A third reviewer discussed the inclusion and exclusion criteria in case of doubt.

Thus, after selection based on the PRISMA criteria [Figure 1], in the Pubmed-Medline, PsycINFO, Lilacs, Scielo, and Web of Science databases, the internal validity of the studies was assessed, with the risk of bias assessed by two independent reviewers based on the CASP questionnaire responses for later comparison and joint discussion for deciding the final classification in case of disagreement. Finally, the 2009 OCEBM Levels of Evidence was applied to classify the level of evidence and the grade of recommendation of the included articles.

In the identification phase, 1,458 articles were found, of which 1,400 were excluded because they were duplicates or did not match the filters used for the search. In the screening phase, the 58 articles from the previous phase were reanalyzed, of which 15 were excluded because of incompatible study designs. Still in the screening phase, the 43 articles from the previous step were reanalyzed, of which 18 were excluded because they did not meet the inclusion criteria or meet the exclusion criteria. Finally, the 25 articles from the previous step were analyzed, of which 5 articles

were excluded because they were included in a systematic review or meta-analysis that was included in this study. Notably, there was no exclusion within the systematic reviews when the same clinical trial was included in different systematic reviews because this could change the conclusions of the included systematic review. After the above exclusion, the total number of studies included reached 20.

Results

The main characteristics of the clinical trials can be found in Table 1, and those of the systematic reviews in Table 2. The analysis of bias identified by the CASP clinical trials questionnaire are Annex 4, and the analysis of bias identified by the CASP questionnaire for systematic reviews are in Annex 5. Finally, the grade of recommendation of all studies included in this review, according to the OCEBM are in Table 3. More details of the clinical trials are in Annex 6.

The drugs evaluated in this systematic review are as follows: atypical antipsychotics [11], bupropion [12], cannabinoids [13], divalproex [14], fluoxetine [15], ganaxolone [16], ketamine [17], paroxetine [18], prazosin [19], pregabalin [20], propranolol [21], quetiapine [22], rivastigmine [23], sertraline [24 – 26], tiagabine [27], topiramate [28] and venlafaxine [29, 30].

In the context of the investigated drugs, it is observed that sertraline is mentioned in 3 studies, representing approximately 15% of the studies. Paroxetine appears in 1 study, accounting for approximately 5% of the studies. Venlafaxine is featured in 2 studies, representing about 10% of the studies. Atypical antipsychotics are covered in a total of 2 studies, representing approximately 10% of the studies. Particularly quetiapine (an atypical antipsychotics) is mentioned in 1 study, accounting for approximately 5% of the studies. Propranolol, Ganaxolone, Rivastigmine, Ketamine, Pregabalin, Tiagabine, Fluoxetine, Bupropion, Divalproex, and Topiramate each feature in separate studies, each accounting for 5% of the individual studies.

The OCEBM 2009 levels of evidence classify studies into different levels based on their methodological rigor. Level 1a includes high-quality systematic reviews of randomized controlled trials, while Level 1b comprises individual randomized controlled trials with narrow confidence intervals. Level 2a consists of systematic reviews with homogeneity, and Level 2b encompasses low-quality randomized controlled trials. Level 2c

pertains to outcomes research, Level 3a involves systematic reviews of case-control studies, and Level 3b includes individual case-control studies. Level 4 comprises case-series and poor-quality cohort and case-control studies, while Level 5 encompasses expert opinions without explicit critical appraisal or based on physiology, bench research, or first principles. Recommendations are graded as Grade A if supported by consistent Level 1 evidence, Grade B if supported by Level 2 or 3 evidence or extrapolations from Level 1, and Grade C if supported by Level 4 evidence or extrapolations from Level 2 or 3 studies.

When comparing the most investigated drugs with a placebo, sertraline emerges as the most effective, safe, and tolerable option for treating PTSD resulting from trauma, particularly in military contexts.

Sertraline is the main recommendation, despite the level of evidence being 2b [24 - 26] which implies that this drug encompasses randomized controlled trials of low to moderate quality due to follow-up losses exceeding 80%, the level of recommendation is a grade B due the consistent level 2b, and the low risk of bias in RCR, low costs, and high safety.

Studies indicate that paroxetine is effective and well-tolerated in treating adults with PTSD, leading to a reduction in symptoms. Paroxetine, in turn, has a single study with level of evidence 2b [18], for the same reason as in 4 other studies [24 - 26, 30], and grade B recommendation according to the OCEBM criteria - due the consistent level 2 -, with a good description of the treatment of PTSD symptoms and a similar sample to the total sample of venlafaxine in this guideline. However, there are still minor sources of bias in venlafaxine, as the study of paroxetine has high bias in one of the criteria according to CASP, because comorbidity with depression is included. This may affect the transparent effect of the treatment of post-traumatic stress disorder, although the association with depression is quite common in this disorder and was accepted in the inclusion criteria of this guideline.

Venlafaxine has the most clinical trials with grade B recommendations, due the consistent level 2 in one study [29] and an extrapolation from level 1 in another [30]. A study was classified with 1b [29], which implies that this drug encompasses randomized controlled trials with a narrow confidence interval (e.g. effect size is known precisely), and another with 2b [30], for

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the same reason as in studies other 3 studies [24 – 26]. The tolerability is responsible for being a second option after sertraline.

Regarding atypical antipsychotics, studies suggest efficacy in some cases for olanzapine. Risperidone, some studies indicate efficacy, especially for symptoms related to psychosis. Quetiapine, one study suggests efficacy. Atypical antipsychotics can be effective in some cases, but tolerance may vary. Quetiapine is considered the most tolerable due to its relatively lower side effect profile compared to other atypical antipsychotics. It is associated with fewer extrapyramidal side effects, such as tremors or rigidity. Additionally, it has a lower potential to cause tardive dyskinesia and possesses sedative properties that can be beneficial for patients suffering from PTSD.

This group of drugs occupies the third place because it is covered in a systematic review with level of evidence 1b - given that it is a systematic review achieved level 1, albeit with some heterogeneity, and grade B recommendation [11]. Quetiapine was analyzed in a randomized clinical trial with level of evidence 2b and grade B recommendation [22], according to the OCEBM, although it had a high blinding bias.

Propranolol appears to be a promising and effective treatment option for PTSD, but further long-term studies are needed. Ganaxolone, Ketamine, Pregabalin, Tiagabine, Fluoxetine, Bupropion, Divalproex, and Topiramate, results vary from efficacy to a lack of significant effect compared to placebo.

According to the present review, the classification made by levels of evidence and grades of recommendation (according to OCEBM 2009 levels of evidence), and the analysis of the risk of bias of the studies (according to CASP), sertraline is in the first place, venlafaxine and paroxetine are secondary options. Lastly atypical antipsychotics can be beneficial.

Discussion

Despite recent studies of numerous drugs for the treatment of PTSD, few options have shown significant results. This study supports the use of sertraline as the main drug for the pharmacological treatment of PTSD, followed by paroxetine, venlafaxine, and atypical antipsychotics. The first option of pharmacological treatment is also available in the public health system and shows effectiveness. Sertraline is an antidepressant classified as a selective serotonin reuptake inhibitor (SSRI), it is absorbed in the

gastrointestinal tract, enhancing the availability of serotonin in the central nervous system, with peak plasma levels achieved between 1-8 hours post-ingestion. This drug undergoes metabolism and is primarily excreted by the liver (inhibiting cytochrome P450), with a half-life ranging from 22-36 hours. The main side effect, which may be more pronounced in some patients than others, is a reduction in dopamine levels, potentially contributing to emotional blunting, cognitive sluggishness, and apathy [31]. Considering sertraline as a potential treatment for PTSD, it is essential to weigh its advantages and disadvantages. On one hand, the effectiveness and widespread prescription of sertraline across various psychiatric disorders, as major depressive disorder, generalized anxiety disorder, premenstrual dysphoric disorder, obsessive-compulsive disorder, panic disorder, among others, demonstrate its potential to improve patients' well-being. For PTSD symptoms like anxiety triggered by repetitive memories of the traumatic event, hyperarousal and avoidance related to the fear circuitry can be attenuated by its effects. Besides negative humor related symptoms similar to depression are also treated by SSRI. Its well-tolerated nature and safety in cases of overdose also provide a level of reassurance. Additionally, its cost-effectiveness could potentially alleviate financial burdens for both patients and public health systems. However, it's imperative to acknowledge the potential side effects of sertraline, especially in PTSD patients. While the reduction in dopamine levels may contribute to emotional blunting, cognitive sluggishness, and apathy, that could maybe seem to alleviate acute symptoms, it's essential to closely monitor these effects and consider individual variations in response. Balancing the benefits and risks of sertraline in the context of PTSD treatment is crucial for making informed decisions that prioritize the overall well-being of patients.

Unfortunately, some patients will have unsatisfactory response to sertraline (due to lower effect or significant side effects), an alternative can be paroxetine, belonging to the same class as sertraline being another selective serotonin reuptake inhibitor. It functions by blocking the reuptake of serotonin in the brain, leading to increased levels of serotonin in the synaptic clefts between nerve cells. This is believed to improve mood and alleviate symptoms of depression and anxiety [31].

Venlafaxine, on the other hand, belongs to a different classification. It is a selective serotonin and norepinephrine reuptake inhibitor antidepressant, which operates by inhibiting the reuptake of both serotonin and norepinephrine in the brain resulting in increased levels of these

neurotransmitters in the synaptic clefts, thought to play a role in regulating mood, emotions, and anxiety. Venlafaxine's dual action on both serotonin and norepinephrine is believed to be particularly beneficial in addressing the complex symptoms often seen in conditions like PTSD, where disturbances in both neurotransmitter systems have been implicated [31]. Sometimes in the first days of its use venlafaxine can increase anxiety symptoms until receptors are downregulated and fear response decreases together with anxiety. For non-responsive patients it is an option, as well it is for depression.

Finally, the atypical antipsychotics, primarily indicated to treat conditions like schizophrenia and bipolar disorder, have also demonstrated some effectiveness in PTSD. Their exact mechanism of action is complex and not entirely understood. However, they generally act by blocking dopamine receptors in the brain, which helps to regulate the levels of neurotransmitters associated with mood and cognition [31]. Additionally, atypical antipsychotics, mainly quetiapine with some recent studies, may also affect serotonin receptors, providing an additional mechanism for their potential benefits in PTSD treatment.

Reviewing potential drugs to treat PTSD is crucial, the field needs further studies because none of the drugs used were developed for this specific pathology, the inclusion of a reflection on the risks and benefits of pharmacological treatment for PTSD is crucial for a comprehensive understanding of the topic.

Limitations of this study include the lack of analysis of the concurrent use of the evaluated drugs to analyze improvement and/or worsening of therapy, the lack of analysis of the association between pharmacological therapy and psychotherapeutic therapy, which is the established gold standard for the treatment of PTSD [4], and the fact that the patient may become refractory to a particular drug in the long term, as the longest follow-up period in the included studies was 12 weeks.

In this regard, it is important to emphasize that the efficacy of several drugs is still being studied in clinical trials. However, these drugs have not yet shown beneficial or better results than sertraline, venlafaxine, paroxetine, and atypical antipsychotics. Thus, there is an urgent need to constantly update the options for pharmacological treatment as the results of new studies investigating the use of drugs for the treatment of PTSD become available.

Conclusions

Based on the level of evidence from the studies included in the systematic review, this guideline to the pharmacological treatment of PTSD suggests that the drugs used in the treatment of post-traumatic stress disorder with the greatest chance of positive outcomes are from the most to the least effective: 1st sertraline; 2nd venlafaxine and paroxetine; 3rd atypical antipsychotics.

In the lack of psychotherapeutic based options practitioners should prescribe the drugs listed above as evidence based clinical practice.

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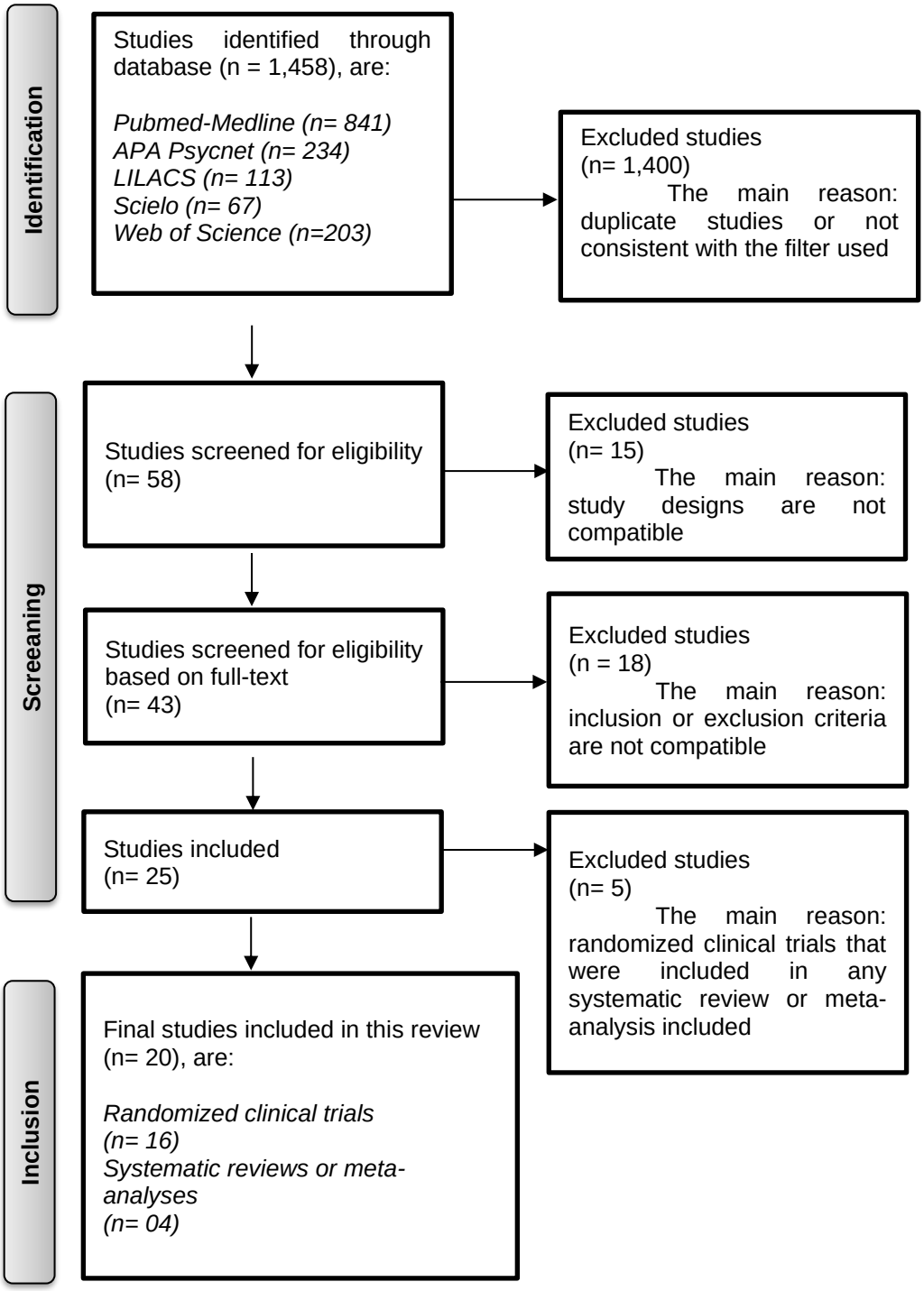

Figure 1. Flowchart of article selection according to the Transparent reporting of systematic reviews and meta-analyses (PRISMA) criteria

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Table 1. Included clinical trials

Clinical trial, year	Population	Intervention	Control	Outcome
Bupropion				
A Placebo-Controlled Trial of Bupropion SR in the Treatment of Chronic Posttraumatic Stress Disorder, 2007 [12].	N= 30, divided into: G1 (bupropion): 20 (not divided by sex) G2 (placebo): 10 (not divided by sex)	Bupropion	Placebo	Bupropion SR in the treatment of PTSD had no significant effect in the study sample.
Divalproex				
Divalproex in the Treatment of Posttraumatic Stress Disorder, 2008 [14].	N= 64, divided into: G1 (sodium valproate): 34 (34 men) G2 (placebo): 34 (34 men)	Sodium valproate	Placebo	Bupropion SR in the treatment of PTSD had no significant effect in the study sample.
Fluoxetine				
Failed Efficacy of Fluoxetine in the Treatment of Posttraumatic Stress Disorder, 2007 [15].	N= 411, divided into: G1 (Fluoxetine 20mg): 163 (116 women and 47 men)	Fluoxetine	Placebo	The response rate to placebo was significantly higher than

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	G2 (Fluoxetine 40mg): 160 (115 women and 45 men) G3 (Placebo): 88 (63 women and 25 men)			the response rate to fluoxetine treatment.
Ganaxolone				
A randomized controlled trial of ganaxolone in posttraumatic stress disorder, 2017 [16].	N= 112, divided into: G1 (Ganaloxone): 59 (44 men and 15 women) G2 (Placebo): 53 (44 men and 9 women)	Ganaxolone	Placebo	No significant differences were found between the effects of ganaxolone and placebo on physician-administered PTSD symptom scores, general well-being, negative mood, or sleep.
Ketamine				
Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder: A	N= 41, divided into: G1 (Ketamine): 22 (13 women and 9 men)	Ketamine	Placebo (Midazolam)	Associated with a reduction in comorbid depressive symptoms and improvement in

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Randomized Clinical Trial, 2014 [17].	G2 (Placebo): 19 (6 women and 13 men)			overall clinical presentation, with treatment generally well tolerated and no clinically significant persistent dissociative symptoms. However, there is a lack of further studies to confirm this, as it is the first to indicate rapid improvement in symptoms.
Paroxetine				
Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study, 2001 [18].	N= 551, divided into: G1 (Placebo): 186 (62 men and 142 women) G2 (Paroxetine 20mg): 183 (57 men and 126 women)	Paroxetine	Placebo	It suggests that sertraline is an effective, safe, and tolerable treatment for PTSD.

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	G3 (Paroxetine 40mg): 182 (55 men and 127 women)			
Pregabalin				
Effect of Pregabalin Augmentation in Treatment of Patients with Combat-Related Chronic Posttraumatic Stress Disorder, 2014 [20].	N= 37, divided into: G1 (Pregabalin): 18 (all men) G2 (Placebo): 19 (all men)	Pregabalin	Placebo	It effectively reduced the severity of PTSD symptoms but was not effective in improving depression severity, anxiety, and quality of life.
Propranolol				
Reduction of PTSD Symptoms with Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial, 2018 [21].	N= 60, divided into: G1 (Propranolol): 30 (19 women and 11 men) G2 (Placebo): 30 (16 women and 14 men)	Propranolol	Placebo	It appears to be a new and effective treatment for PTSD, but further studies are needed that include long-term follow-up for different trauma populations.
Quetiapine				

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Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial, 2016 [22].	N= 119, divided into: G0 (Initial screening placebo): 119 G1 (Quetiapine): 42 (38 men and 4 women) G2 (Placebo): 38 (37 men and 1 woman)	Quetiapine	Placebo	Results suggest that quetiapine is effective as a single agent in the treatment of PTSD due to military trauma.
Rivastigmine				
Effect of Rivastigmine Augmentation in Treatment of Male Patients with Combat-Related Chronic Posttraumatic Stress Disorder, 2017 [23].	N= 36, divided into: G1 (Rivastigmine): 12 (all men) G2 (Placebo): 12 (all men) G3 (Previous treatment): 12 (all men)	Rivastigmine	Placebo and drug used in the previous treatment (non-standard)	The results do not support the efficacy of rivastigmine as adjunctive therapy in the treatment of PTSD.
Sertraline				
Effect and safety of sertraline for treating posttraumatic stress	N=72, divided into:	Sertraline	Placebo	It demonstrated that a 12-week treatment with sertraline was effective

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disorder: a multicenter randomized controlled study, 2017 [24].	G1 (Sertraline): 36 (31 men and 5 women) G2 (Placebo): 36 (32 men and 4 women)			and well tolerated in patients with PTSD.
A randomized, double-blind, placebo-controlled trial on the efficacy and tolerability of sertraline in Iranian veterans with post-traumatic stress disorder, 2011 [25].	N= 62, divided into: G1 (Sertraline): 32 patients (all men) G2 (Placebo): 30 patients (all men)	Sertraline	Placebo	It suggests that sertraline is an effective, safe, and tolerable treatment for PTSD due to military trauma.
Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder, 2001 [26].	N= 208, divided into: G1 (Sertraline): 100 (84 women and 16 men) G2 (Placebo): 108 (78 women and 30 men)	Sertraline	Placebo	It suggests that sertraline is an effective, safe, and tolerable treatment for PTSD.
Tiagabine				

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The Efficacy and Tolerability of Tiagabine in Adult Patients with Post-Traumatic Stress Disorder, 2007 [27].	N= 232, divided into: G1 (Tiagabine): 116 (not divided by sex) G2 (Placebo): 116 (no breakdown by sex)	Tiagabine	Placebo	It was not significantly different from placebo in treating PTSD symptoms.
Venlafaxine				
Venlafaxine Extended Release in Posttraumatic Stress Disorder, 2006 [29].	N= 531, divided into: G1 (Venlafaxine): 179 (not divided by sex) G2 (Sertraline): 173 (not divided by sex) G3 (Placebo): 179 (not divided by sex)	Venlafaxine	Placebo and Sertraline	Study results suggest that venlafaxine ER is effective and well tolerated in the short-term treatment of PTSD.
Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial, 2006 [30].	N= 329, divided into: G1 (Venlafaxine): 161 (72 men and 89 women)	Venlafaxine	Placebo	Effective and well tolerated in both short-term and continuing treatment of patients with PTSD.

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	G2 (Placebo): 168 (79 men and 89 women			

PTSD: Post-traumatic stress disorder; **SR:** Sustained release; **PTSD:** Post-traumatic stress disorder.

Table 2. Included systematic reviews

Systematic review, year	Internal clinical trials	Comments
Atypical antipsychotics		
The potential role of atypical antipsychotics for the treatment of posttraumatic stress disorder, 2014 [11].	Butterfield MI, Becker ME, Connor KM, Sutherland S, Churchill LE, Davidson JR. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. Int Clin Psychopharmacol 2001;16:197e203. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry	Systematic review with few studies (a very small N). Moreover, topiramate did not help reduce symptoms according to the outcome measures.

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	2002;159:1777e9. Hamner MB, Faldowski RA, Ulmer HG, Frueh BC, Huber MG, Arana GW. Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. Int Clin Psychopharmacol 2003;18:1e8. Reich DB, Winternitz S, Hennen J, Watts T, Stanculescu C. A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to child abuse in women. J Clin Psychiatry 2004;65:1601e6. Bartzokis G, Lu PH, Turner J, Mintz J, Saunders CS. Adjunctive risperidone	

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	in the treatment of chronic combat-related posttraumatic stress disorder. Biol Psychiatry 2005;57:474e9. Padala PR, Madison J, Monnahan M, Marcil W, Price P, Ramaswamy S, et al. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. Int Clin Psychopharmacol 2006;21: 275e80. Rothbaum BO, Killeen TK, Davidson JR, Brady KT, Connor KM, Heekin MH. Placebo-controlled trial of risperidone augmentation for selective serotonin reuptake inhibitor-resistant civilian posttraumatic stress disorder. J Clin Psychiatry 2008;69:520e5.	

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	Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, Vertrees JE, et al. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. JAMA 2011;306: 493e502. Carey P, Suliman S, Ganesan K, Seedat S, Stein DJ. Olanzapine monotherapy in posttraumatic stress disorder: efficacy in a randomized, double-blind, placebo-controlled study. Hum Psychopharmacol 2012;27:386e91.	
Cannabinoids		
Use of Medicinal Cannabis and Synthetic Cannabinoids in Post-Traumatic Stress	El Solh, AA Management of nightmares in patients with posttraumatic stress disorder:	This systematic review is too weak because it includes many observational studies and does not assess clinical

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Disorder (PTSD): A Systematic Review, 2019 [13].	Current perspectives. Nat. Sci. Sleep 2018, 10, 409–420, doi:10.2147/NSS.S166089. Schifano, F.; Papanti, GD; Corkery, JM; Orsolini, L. Post-traumatic stress and substance misuse; neurobiological and clinical pharmacological correlates. RAP 2018, 5, 50–58. Liberati, A.; Altman, DG; Tetzlaff, J.; Mulrow, C.; Gotzsche, PC; Ioannidis, JPA; Clarke, M.; Devereaux, PJ; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009, 339, b2700, doi:10.1136/bmj.b2700.	improvement in symptoms of post-traumatic stress disorder with the appropriate scales to measure such outcomes.

	Ney, LJ; Matthews, A.; Bruno, R.; Felmingham, KL Cannabinoid Interventions for PTSD: Where to Next? Program Neuro-Psychopharmacol. Biol. Psychiatry 2019, 93, 124–140, doi:10.1016/j.pnpbp.2019.03.017. Bordieri, MJ; Tull, MT; McDermott, MJ; Gratz, KL The Moderating role of experiential avoidance in the relationship between post-traumatic stress disorder symptom severity and cannabis dependence. j. Contextual Behavior. Sci. 2014, 3, 273–278, doi:10.1016/j.jcbs.2014.08.005. Bonn-Miller, MO; Boden, MT; Bucossi, MM; Babson, KA Self-	

	reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. Am. j. Drug Alcohol Abuse 2014, 40, 23–30. Tull, MT; McDermott, MJ; Gratz, KL Marijuana dependence moderates the effect of posttraumatic stress disorder on trauma cue reactivity in substance dependent patients. Drug Alcohol Depend. 2016, 159, 219–226, doi:10.1016/j.drugalcdep.2015.12.014. Johnson, MJ; Pierce, JD; Mavandadi, S.; Klaus, J.; Defelice, D.; Ingram, E.; Oslin, DW Mental health symptom severity in cannabis using and non-using Veterans with probable PTSD.	

	j. Affect. Discord. 2016, 190, 439–442, doi:10.1016/j.jad.2015.10.048. Greer, GR; Grob, CS; Halberstadt, AL PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. j. Psychoact. Drugs 2014, 46, 73–77. Roitman, P.; Mechoulam, R.; Cooper-Kazaz, R.; Shalev, A. Preliminary, open-label, pilot study of add-on oral Delta9-tetrahydrocannabinol in chronic post-traumatic stress disorder. clinic Drug Investigation. 2014, 34, 587–591. Wilkinson, ST; Stefanovics, E.; Rosenheck, RA Marijuana use is	

	associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. j. clinic Psychiatry 2015, 76, 1174–1180, doi:10.4088/JCP.14m09475. Pisanti, S.; Malfitano, AM; Ciaglia, E.; Lamberti, A.; Ranieri, R.; Cuomo, G.; Slaughter, M.; Faggiana, G.; Proto, MC; Fiore, D.; et al. Cannabidiol: State of the art and new challenges for therapeutic applications. Pharmacol. The R. 2017, 175, 133–150, doi:10.1016/j.pharmthera.2017.02.041.	
Prazosin		
Efficacy of Prazosin in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis, 2016 [19].	Germain A, Richardson R, Moul DE, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral	A very well-conducted systematic review using appropriate measures of clinical improvement in post-traumatic

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	treatments for sleep disturbances in US military veterans. J Psychosom Res. 2012;72(2):89-96. Raskind MA, Peskind ER, Hoff DJ, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with posttraumatic stress disorder. Biol Psychiatry. 2007;61(8):928-934. PubMed doi:10.1016/j.biopsych.2006.06.032 Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by Prazosin: a placebo-controlled study. Am J Psychiatry. 2003;160(2):371-373. PubMed doi:10.1176/appi.ajp.160.2.371	stress disorder in the population. However, the final result that emerged from the compilation of included studies indicates that prazosin is only indicated for the treatment of acute post-traumatic stress disorder and not for post-traumatic stress disorder itself (chronic), which is the subject of this new search.

	Raskind MA, Peterson K, Williams T, et al. A trial of Prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry. 2013;170(9):1003-1010. PubMed doi:10.1176/appi.ajp.2013.12081133 Ahmadpanah M, Sabzeiee P, Hosseini SM, et al. Comparing the effect of Prazosin and hydroxyzine on sleep quality in patients suffering from posttraumatic stress disorder. Neuropsychobiology. 2014;69(4):235-242. PubMed doi:10.1159/000362243 Taylor FB, Martin P, Thompson C, et	

	al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008;63(6):629-632. PubMed doi:10.1016/j.biopsych.2007.07.001	
Topiramate		
Topiramate as Monotherapy or Adjunctive Treatment for Posttraumatic Stress Disorder: A Meta-Analysis, 2018 [28].	Akuchekian, S., & Amanat, S. (2004). The comparison of topiramate and placebo in the treatment of posttraumatic stress disorder: A randomized, double-blind study. *Journal of Research in Medical Sciences*, *9*, 240–244. Tucker P, Trautman R. P., Wyatt, D. B., Thompson, J., Wu, S. C., Capece, J. A., & Rosenthal, N. R. (2007). Efficacy and safety of topiramate monotherapy in civilian	Systematic review with few studies (a very small N). Moreover, topiramate did not help reduce symptoms according to the outcome measures.

	posttraumatic stress disorder: A randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*, *68*, 201–206. https://doi.org/10.4088/jcp.v68n0204 Yeh, M. S., Mari, J. J., Costa, M. C., Andreoli, S. B., Bressan, R. A., & Mello, M. F. (2011). A double-blind randomized controlled trial to study the efficacy of topiramate in a civilian sample of PTSD. *CNS Neuroscience and Therapeutics*, *17*, 305–310. https://doi.org/10.1111/j.1755-5949.2010.00188.x Lindley, S. E., Carlson, E. B., & Hill, K. (2007). A randomized, double-blind, placebo-controlled trial of top-iramate augmentation for chronic	

	combat-related posttraumatic stress disorder. Batky, S. L., Pennington, D. L., Lasher, B., Neylan, T. C., Metzler, T., Waldrop, A.,. Herbst, E. (2014). Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: A randomized controlled pilot trial. *Alcoholism: Clinical and Experimental Research*, *38*, 2169–2177. https://doi.org/10.1111/acer.12496 Davis, L. L., Bartolucci, A., & Petty, F. (2016). *A Placebo-Controlled Pilot Study of Topiramate for the Treatment of PTSD*.	

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Table 3. Oxford center for evidence-based medicine 2009 levels of evidence classification for clinical trials and systematic reviews

Study	OCEBM level	OCEBM grade of recommendation
Atypical antipsychotics		
The potential role of atypical antipsychotics for the treatment of posttraumatic stress disorder, 2014 [11].	1b	B
Bupropion		
A Placebo-Controlled Trial of Bupropion SR in the Treatment of Chronic Posttraumatic Stress Disorder, 2007 [12].	2b	C
Cannabinoids		
Use of Medicinal Cannabis and Synthetic Cannabinoids in Post-Traumatic Stress Disorder (PTSD): A Systematic Review, 2019 [13].	4	D
Divalproex		
Divalproex in the Treatment of Posttraumatic Stress Disorder, 2008 [14].	2c	C
Fluoxetine		
Failed Efficacy of Fluoxetine in the Treatment of Posttraumatic Stress Disorder, 2007 [15].	2b	C
Ganaxolone		
A randomized controlled trial of ganaxolone in posttraumatic stress disorder, 2017 [16].	2b	C
Ketamine		
Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder: A Randomized Clinical Trial, 2014 [17].	2b	D

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Paroxetine		
Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study, 2001 [18].	2b	B
Prazosin		
Efficacy of Prazosin in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis, 2016 [19].	3b	C
Pregabalin		
Effect of Pregabalin Augmentation in Treatment of Patients with Combat-Related Chronic Posttraumatic Stress Disorder, 2014 [20].	4	C
Propranolol		
Reduction of PTSD Symptoms with Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial, 2012 [21].	2b	C
Quetiapine		
Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial, 2016 [22].	2b	B
Rivastigmine		
Effect of Rivastigmine Augmentation in Treatment of Male Patients with Combat-Related Chronic Posttraumatic Stress Disorder, 2017 [23].	4	C
Sertraline		
Effect and safety of sertraline for treating posttraumatic stress disorder: a multicenter randomized controlled study, 2017 [24].	2b	B

A randomized, double-blind, placebo-controlled trial on the efficacy and tolerability of sertraline in Iranian veterans with post-traumatic stress disorder, 2011 [25].	2b	B
Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder, 2001 [26].	2b	B
Tiagabine		
The Efficacy and Tolerability of Tiagabine in Adult Patients with Post-Traumatic Stress Disorder, 2007 [27].	4	C
Topiramate		
Topiramate as Monotherapy or Adjunctive Treatment for Posttraumatic Stress Disorder: A Meta-Analysis, 2018 [28].	1a	C
Venlafaxine		
Venlafaxine Extended Release in Posttraumatic Stress Disorder, 2006 [29].	1b	B
Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial, 2006 [30].	2b	B

PTSD: Post-traumatic stress disorder; **SR:** Sustained Release.

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ANNEXES

Annex 1. Critical appraisal skills programme questionnaire for clinical trials

SECTION A	Is the basic study design valid for a randomized controlled trial?
1	Did the study address a clearly focused research question?
2	Was the assignment of participants to interventions randomized?
3	Were all participants who entered the study accounted for at its conclusion?
SECTION B	Was the study methodologically sound?
4A	Were the participants 'blind' to intervention they were given?
4B	Were the investigators "blind" to the intervention they were giving to participants?
4C	Were the people assessing/analyzing outcome/s 'blinded'?
5	Were the study groups similar at the start of the randomized controlled trial?
6	Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?
SECTION C	What are the results?
7	Were the effects of intervention reported comprehensively?
8	Was the precision of the estimate of the intervention or treatment effect reported?
9	Do the benefits of the experimental intervention outweigh the harms and costs?
SECTION D	Will the results help locally?
10	Can the results be applied to your local population/in your context?
11	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

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Annex 2. Clinician-administered post-traumatic stress disorder scale questionnaire for systematic reviews and meta-analyses

SECTION A	Are the results of the review valid?
1	Did the review address a clearly focused question?
2	Did the authors look for the right type of papers?
3	Do you think all the important, relevant studies were included?
4	Did the review's authors do enough to assess the quality of the included studies?
5	If the results of the review have been combined, was it reasonable to do so?
SECTION B	What are the results?
6	What are the overall results of the review?
7	How accurate are the results?
SECTION C	Will the results help locally?
8	Can the results be applied to the local population?
9	Were all important outcomes considered?
10	Are the benefits worth the harms and costs?

Annex 3. Oxford center for evidence-based medicine 2019 levels of evidence classification

Level	**Therapy, Prevention, Aetiology, Harm**
1st	Systematic Review (with homogeneity) of Randomized Controlled Trials
1b	Individual Randomized Controlled Trial (with narrow Confidence Interval)
1c	All of none
2nd	Systematic Review (without homogeneity)
2b	Individual cohort study (including low quality Randomized Controlled Trial)
2c	"Outcomes" Research; ecological studies
3rd	Systematic Review (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Grades of Recommendation	
A	Consistent Level 1 studies
B	Consistent Level 2 or 3 studies ***or*** Extrapolations from Level 1 studies
C	Level 4 studies ***or*** Extrapolations from Level 2 or 3 studies
D	Level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

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Annex 4. *Critical appraisal skills programme* questionnaire administered in randomized clinical trials

A Placebo-Controlled Trial of Bupropion SR in the Treatment of Chronic Posttraumatic Stress Disorder, 2007[12]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	NO
SECTION D	
10	YES
11	NO
Divalproex in the Treatment of Posttraumatic Stress Disorder, 2008[14]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES

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8	YES
9	NO
SECTION D	
10	YES
11	NO
Failed Efficacy of Fluoxetine in the Treatment of Posttraumatic Stress Disorder, 2007[15]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	NO
SECTION D	
10	YES
11	NO
A randomized controlled trial of ganaxolone in posttraumatic stress disorder, 2017[16]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES

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SECTION C	
7	YES
8	YES
9	NO
SECTION D	
10	YES
11	NO
Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder: A Randomized Clinical Trial, 2014[17]	
SECTION A	
1	YES
2	YES
3	YES
SECTION B	
4A	YES
4B	YES
4C	NO
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	NO
SECTION D	
10	YES
11	NO
Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study, 2001[18]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES

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4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	YES
SECTION D	
10	YES
11	YES
Effect of Pregabalin Augmentation in Treatment of Patients with Combat-Related Chronic Posttraumatic Stress Disorder, 2014[20]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	NO
SECTION D	
10	YES
11	NO
Reduction of PTSD Symptoms with Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial, 2012[21]	
SECTION A	

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1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	CAN`T TELL
SECTION D	
10	YES
11	NO
Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial, 2016[22]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	NO
5	NO
6	YES
SECTION C	
7	YES
8	YES
9	YES
SECTION D	
10	YES
11	YES

https://doi.org/10.25118/2763-9037.2023.v13.1037

Effect of Rivastigmine Augmentation in Treatment of Male Patients with Combat-Related Chronic Posttraumatic Stress Disorder, 2017[23]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	NO
SECTION D	
10	YES
11	NO
Effect and safety of sertraline for treating posttraumatic stress disorder: a multicenter randomized controlled study, 2017[24]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	

https://doi.org/10.25118/2763-9037.2023.v13.1037

7	YES
8	YES
9	YES
SECTION D	
10	YES
11	YES
A randomized, double-blind, placebo-controlled trial on the efficacy and tolerability of sertraline in Iranian veterans with post-traumatic stress disorder, 2011[25]	
SECTION A	
1	YES
2	YES
3	YES
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	YES
SECTION D	
10	YES
11	YES
Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder, 2001[26]	
SECTION A	
1	YES
2	YES
3	NO

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SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	YES
SECTION D	
10	YES
11	YES
The Efficacy and Tolerability of Tiagabine in Adult Patients with Post-Traumatic Stress Disorder, 2007[27]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	NO
SECTION D	
10	YES
11	NO
Venlafaxine Extended Release in Posttraumatic Stress Disorder, 2006[29]	
SECTION A	

https://doi.org/10.25118/2763-9037.2023.v13.1037

1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	YES
SECTION D	
10	YES
11	YES
Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial, 2006[30]	
SECTION A	
1	YES
2	YES
3	NO
SECTION B	
4A	YES
4B	YES
4C	YES
5	YES
6	YES
SECTION C	
7	YES
8	YES
9	YES
SECTION D	
10	YES
11	YES

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PTSD: *Post-traumatic stress disorder.* **SR:** *Sustained Release*

Annex 5. *Critical appraisal skills programme* questionnaire *administered in systematic reviews and meta-analyses*

The potential role of atypical antipsychotics for the treatment of posttraumatic stress disorder, 2014[11]	
SECTION A	
1	YES
2	YES
3	YES
4	YES
5	YES
SECTION B	
6	GOOD
7	PRECISE
SECTION C	
8	YES
9	YES
10	CAN'T TELL
Use of Medicinal Cannabis and Synthetic Cannabinoids in Post-Traumatic Stress Disorder (PTSD): A Systematic Review, 2019[13]	
SECTION A	
1	YES
2	NO
3	NO
4	NO
5	CAN'T TELL
SECTION B	
6	WEAK
7	NOT PRECISE
SECTION C	
8	NO
9	CAN'T TELL

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10	NO
Efficacy of Prazosin in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis, 2016[19]	
SECTION A	
1	YES
2	YES
3	YES
4	YES
5	YES
SECTION B	
6	GOOD
7	VERY PRECISE
SECTION C	
8	YES
9	YES
10	YES
Topiramate as Monotherapy or Adjunctive Treatment for Posttraumatic Stress Disorder: A Meta-Analysis, 2018[28]	
SECTION A	
1	YES
2	YES
3	YES
4	YES
5	YES
SECTION B	
6	GOOD
7	PRECISE
SECTION C	
8	YES
9	YES
10	NO

PTSD: *Post-traumatic stress disorder.*

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Annex 6. Detailing of included clinical trials

Study, year, PMID	Type of study	Groups	Population	Follow-up period	PTSD measurement (scale/diagnosis)	PTSD diagnostic criteria	Type of trauma	Outcome measures	Result summary (note: p<0.05 is considered significant)
A Placebo-Controlled Trial of Bupropion SR in the Treatment of Chronic Posttraumatic Stress Disorder, 2007[12]	Double blind, placebo controlled, randomized clinical trial	G1: Bupropion (started at 100 mg a day, increasing up to 300 mg a day at the end) G2: placebo	G1: 20 individuals (without gender distinction) G2: 10 individuals (without gender distinction)	8 weeks	CAPS, DTS	DSM-IV	Military, sexual abuse, assault, non-sexual abuse, accidental injury, natural disaster, testimony, unexpected death, unknown	CAPS, DTS, BDI, PANAS, Pittsburgh Sleep	Total PTSD symptom severity [DTS; F(1.21) = 8.67; P < 0.01], symptom severity [CAPS; F(1.20) = 9.21; P < 0.01], re-experiencing PTSD symptoms [Cluster B; F(1.21) = 7.16; P < 0.01], PTSD arousal symptoms [Cluster D; F(1.21) = 11.85; P < 0.01], depressive symptoms [F(1.21) = 10.75; P < 0.01], negative affect [F(1.21) =

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									7.28; P < 0.01], and subjective sleep quality [F(1.21) = 7.86; P < 0.01].
Divalproex in the Treatment of Posttraumatic Stress Disorder, 2008[14]	Double blind, placebo controlled, randomized clinical trial	G1: Sodium valproate (started with 1g a day, increasing progressively up to 3 g a day) (Note: Trazodone - 50 mg daily - was used in participants with insomnia) G2: Placebo	G1: 34 individuals (34 men) G2: 34 individuals (34 men)	8 weeks	CAPS	DSM-IV	Military PTSD	CAPS, TOP-8, MADRS, CGI-S, HAM-A	No significant differences were found between the drug and placebo groups on the CAPS - D subscale, nor on total CAPS, CAPS -B, CAPS -C, TOP -8, CGI-I, CGI-S, MADRS, HAM -A, or Davidson Trauma Scale.
Failed Efficacy of Fluoxetine	Double blind, placebo	G1: Fluoxetine 20 mg daily	G1: 163 individuals (116	12 weeks	CAPS, DTS	DSM-IV	Sexual assault, combat,	TOP-8, CAPS One	CAPS the score for fluoxetine 20 mg decreased from

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in the Treatment of Posttraumatic Stress Disorder, 2007[15]	controlled, randomized, multicenter clinical trial	G2: Fluoxetine 40 mg daily G3: placebo	women and 47 men) G2: 160 individuals (115 women and 45 men) G3: 88 individuals (63 women and 25 men)				domestic violence, accident, incest, witnessing someone else's death	Week Symptom Status Version, Davidson Trauma Scale, MADRS, and Hamilton Anxiety Scale, DES	baseline from +77.7 to -42.9 (p=0.151), for fluoxetine 40 mg from +78.3 to -42.8 (p=0.151), and for placebo from 75.2 to -36.6 (p=0.151). No statistically significant difference between groups.
A randomized controlled trial of ganaxolone in posttraumatic stress	Double blind, placebo controlled, randomized	Phase 1: G1: Ganaxolone G2: placebo (Note: At week six, the study was	G1: 59 individuals (44 men and 15 women)	6 weeks	CAPS, CTQ, LEC and Deployment risk and resilience inventory	DSM-IV	Direct exposure arising from witnessing the trauma, knowing that a relative or	PCL, POMS, PHQ9, ISI, CD-RISC	The group GNX-GNX, treated continuously with ganaxolone, had a mean change in total CAPS score of -28.6 points at week 12 (95% CI and -34.7; -22.4),

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disorder, 2017[16]	clinical trial	opened so that the placebo group started receiving ganaxolone for a final comparison) (Note: biweekly increasing doses 2x a day – 200, 400, and 600 mg) Level 2: G1: Ganaxolone G2': Ganaxolone	G2: 53 individuals (44 men and 9 women)				close friend was exposed to trauma, and indirect exposure to aversive details of the trauma		compared with -26.8 (95% CI and -32.8; -20.9) for the group PLC-GNX (p = 0.69). Changes in PCL scores at week 12 were -15.5 (95% CI -20.1, -10.9) and -13.6 (95% CI -18.0, -9.1), respectively, for the GNX-GNX vs. PLC-GNX groups (p = 0.55). There were also no significant differences between these two groups for the other measures collected in the study (data not shown). Future investigations are necessary.

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		(previously placebo) (Note: G2=G2' - they are the same participants)							
Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder: A Randomized Clinical Trial, 2014[17]	Double blind, placebo controlled, randomized clinical trial	G1: Ketamine (dose= 0.5 mg/kg) G2: Placebo (Midazolam; dose= 0.045 mg/kg)	G1: 22 individuals (13 women and 9 men) G2: 19 individuals (6 women and 13 men)	02 weeks	CAPS	DSM-IV	Military, sexual abuse, assault, non-sexual abuse, accidental injury, natural disaster, testimony, unexpected death, unknown (with associated depression)	IES-R, MADRS, CGI-S, CGI-I, QIDS-SR	Ketamine was associated with a significant and rapid reduction in PTSD symptom severity when measured 24 hours after infusion compared with midazolam (mean difference in revised Event Impact Scale score, 12.7 [95% CI and 2.5; 22.8] and P = 0.02). Low quality RCT. Preliminary results. Efficacy and

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									safety not sufficient for recommendation.
Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study, 2001[18)]	Double blind, placebo controlled, randomized clinical trial	G1: Placebo G2: Paroxetine 20mg G3: Paroxetine 40mg	G1: 186 individuals (62 men and 142 women) G2: 183 individuals (57 men and 126 women) G3: 182 individuals (55 men and 127 women)	12 weeks	CAPS	DSM-IV	Direct exposure arising from witnessing the trauma, knowing that a relative or close friend was exposed to trauma, and indirect exposure to aversive details of the trauma	Caps, Davidson trauma scale, Treatment outcome PTSD scale, Sheehan total disability scale, and Montgomery-Asberg depression rating scale	Paroxetine reduced PTSD symptoms significantly more than placebo in both subgroups on the CAPS scale (non-depressed: F=12.33, df=2, 229, p < 0.001; paroxetine 20 mg/day and placebo: mean=-16.8 point change in score, 95% confidence interval=-23.7 to -9.8, p < 0.001; paroxetine 40 mg and placebo: Mean=-12.7 points change in score, 95% CI=-19.8 to -5.6, p < 0.001) (depressed: F=4.07, df=2, 181, p < 0.02; paroxetine

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									20 mg/day and placebo: mean change=-11.0 points in score, 95% CI=-20.4 to -1.7, p < 0.03; paroxetine 40 mg/day and placebo: mean=-11.8 points change in score, 95% CI=-20.9 to -2.7, p < 0.02).
Effect of Pregabalin Augmentation in Treatment of Patients with Combat-Related Chronic Posttraumatic Stress Disorder, 2014[20]	Double blind, placebo controlled, randomized clinical trial	G1: Pregabalin (received citalopram 10-40 mg day or sertraline 50-200 mg day and valproate 1000-1800 mg day for 1 month; then,	G1: 18 individuals (18 men) G2: 19 individuals (19 men)	6 weeks	CAPS, DTS	DSM-IV	Military PTSD (with symptoms of depression)	Hamilton Rating Scale for Depression, Hamilton Anxiety Rating Scale, Spitzer Quality of Life Index, PTSD	Although depression and anxiety scores decreased significantly in both groups (p = 0.001), the comparison of the efficacy of pregabalin and placebo showed no significant differences in depression, anxiety, and quality-of-life scores (p = 0.614, p = 0.144,

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		pregabalin 300 mg day) G2: placebo						Checklist-Military Version	and p=0.076, respectively). Very low-quality RCT. Not sufficient for recommendation. Negative results.
Reduction of PTSD Symptoms with Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial, 2012[21]	Double blind, placebo controlled, randomized clinical trial	G1: Propranolol (We administered 0.67 mg/kg of conventional short-acting propranolol plus 1.0 mg/kg of long-acting propranolol G2: placebo	G1: 30 individuals (19 women and 11 men) G2: 30 individuals (16 women and 14 men)	6 weeks	CAPS, PCL-S	DSM-IV	Sexual abuse, assault, non-sexual abuse, accidental injury, natural disaster, witness, unexpected death, Unknown	CAPS, PCL-S	The estimated difference score by group after the last week was +14.58 (p<0.001) for the intention-to-treat analysis and +16.74 (p<0.001) for the per-protocol analysis. Low-quality RCT. Replication studies using a long-term follow-up in various trauma populations are required.
Efficacy of Quetiapine Monotherapy in	Double blind, placebo controlle	G0: Placebo (Phase 1: single-blind, patients	G0: 119 individuals (no	12 weeks	CAPS-DX, SCID-I/P	DSM-IV	Military PTSD	CAPS total score, PANSS,	Mean total CAPS scores were similar in the quetiapine and placebo groups, 75

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Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial, 2016[22]	d, randomized clinical trial	received 1 week of placebo. The placebo non-responders were then reassigned into 2 new groups for the study) G1: Quetiapine (25 mg before bedtime for the first two weeks, increasing to 400 mg when tolerated. Thereafter, a limit of 50 mg to 800	gender data) G1: 42 subjects (38 men and 4 women), but 29 completed G2: 38 individuals (37 men and 1 woman), but 18 completed (Note: G2+G3= 80 - who					CGI, HAM-D, HAM-A, Pittsburgh Sleep Quality Index	(SD = 16) versus 71 (SD = 12) (t =20.76, p=0.45). However, DSM-IV cluster B (reliving) scores were higher in the quetiapine group (mean = 21, SD = 7) than in the placebo group (mean = 17, SD = 15) (t = 2.4, p=0.02). A significant interaction effect was found between visit and treatment condition (F = 2.88, df = 4, 240, p = 0.03), suggesting that the quetiapine group had a greater decrease in CAPS total score than the placebo group. A logistic regression of the binary variable

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		mg daily was established depending on patient acceptability). G2: placebo	actually participated in the quetiapine study						for dropouts was not significant (p=0.50), suggesting that study dropouts were "completely random" and were not related to the subject's last CAPS score or which treatment group the subject was in (p=0.42). An intention-to-treat analysis of the complete repeated measures model (ANCOVA) revealed a significant treatment interaction per visit (F = 2.94, df = 4, 312, p = 0.02). Low quality RCT.
Effect of Rivastigmine Augmentati	Double blind, placebo controlle	G1: Rivastigmine (1.5 mg 2x daily for 4	G1: 12 individuals (12 men)	12 weeks	PCL-M	DSM-IV	Military PTSD	PCL-M	The only significant difference between groups in terms of total PCL-M scores

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on in Treatment of Male Patients with Combat-Related Chronic Posttraumatic Stress Disorder, 2017[23]	d, randomized clinical trial	weeks, then 3mg 2x daily for 8 weeks) G2: placebo G3: Previous treatment (used previously)	G2: 12 individuals (12 men) G3: 12 individuals (12 men)						was observed at week 4. Statistically significant reductions were seen in the total military PTSD score, the avoidance subscale, and the reliving subscale, but no reduction was seen in the hyperarousal subscale. Very low-quality RCT. Evidence not sufficient for recommendation.
Effect and safety of sertraline for treating posttraumatic stress disorder: a multicenter randomized controlled	Double blind, placebo controlled, randomized clinical trial	G1: Sertraline (135mg daily) G2: placebo	G1: 36 individuals (31 men and 5 women) G2: 36 individuals (32	12 weeks	HEI-R	DSM-IV	Sexual abuse, assault, non-sexual abuse, accidental injury, natural disaster, witness,	IES-R, CGI-S	The proportion of patients in the sertraline group (49% of subjects) who met the response criteria was significantly higher than in the placebo group (6% of subjects; p=0.0057).

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study, 2017[24]			men and 4 women)				unexpected death, unknown		The proportion of IES-R responders in the sertraline group. The proportion of patients in the sertraline group (49% of subjects) who met the response criteria was significantly higher than in the placebo group (6% of subjects; p=0.0057). The proportion of IES-R responders was also significantly higher in the sertraline group than in the placebo group (sertraline: 100% of subjects; placebo: 70% of subjects; p=0.043). Based on the proportion of IES-R responders,

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									symptoms decreased in all 36 subjects in the sertraline group, while 25 patients in the control group achieved remission. Low quality RCT.
A randomized, double-blind, placebo-controlled trial on the efficacy and tolerability of sertraline in Iranian veterans with post-traumatic stress	Double blind, placebo controlled, randomized clinical trial	G1: Sertraline (50-200mg 1x a day) G2: placebo	G1: 33 individuals (32 men) G2: 30 individuals (30 men)	10 weeks	HEI-R	DSM-IV	Military PTSD	IES-R, CGI-S, CGI-I	It indicates significant therapeutic efficacy of sertraline on all three efficacy measures assessed: the IES-R, CGI-I, and CGI-S scales ($p < 0.001$). Low quality RCT.

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disorder, 2011[25]									
Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder, 2001[26]	Double blind, placebo controlled, randomized clinical trial	G1: Sertraline (started with 50 mg a day, increasing progressively up to 200 mg a day) G2: Placebo	G1: 100 individuals (84 women and 16 men) G2: 108 individuals (78 women and 30 men)	12 weeks	CAPS	DSM-III	Military, sexual abuse, assault, non-sexual abuse, accidental injury, natural disaster, witness, unexpected death, unknown	CAPS, IES, CGI-S, CGI-I, Davidson PTSD scale, HAM-D, HAM-A, Pittsburgh Sleep Quality Scale	The analysis of the effects revealed more significant improvements for sertraline compared with placebo on CAPS -2 (t = 2.96, P = 0.003), IES (t = 2.26, P = 0.02), CGI-I (t = 3.62, P < 0.001), and on CGI-S score (t = 4.40, P < 0.001).
The Efficacy and Tolerability of Tiagabine in Adult	Double blind, placebo controlled, randomized,	G1: Tiagabine (started with 4mg a day, progressively increasing to 16 mg a day)	G1: 116 individuals (without gender distinction)	12 weeks	CAPS, DTS	DSM-IV	Physical and sexual aggression/ violence; witnessing harm or death;	CAPS, DTS and Treatment Outcome PTSD Scale	There were no significant differences in the change in CAPS total score at study end for tiagabine compared

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Patients with Post-Traumatic Stress Disorder, 2007[27]	multicenter clinical trial	G2: placebo	G2: 116 individuals (without gender distinction)				accident/fire/serious injury; combat; natural disaster	(TOP-8), CGI-C), Connor-Davidson Resilience Scale, Sheehan Disability Scale, and a patient-rated evaluation of sleep (sleep questionnaire), MGSQ, MADRS	with placebo (P = 0.85). Very low-quality RCT.
Venlafaxine Extended Release in Posttraumatic Stress	Double blind, placebo controlled, randomi	G1: Venlafaxine (75 – 300 mg/day)	G1: 179 individuals (without gender	12 weeks	CAPS-SX17, STD	DSM-IV	Sexual abuse, assault, non-sexual abuse, accidental	CAPS-SX17, DTS, SVS, CGI-S,	Remission rates at the end of the study were 30.2% for venlafaxine ER (P < 0.05 vs. placebo), 24.3% for sertraline,

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Disorder, 2006[29]	zed clinical trial	G2: Sertraline (50 – 200 mg/day) G3: placebo	distinction) G2: 173 individuals (without gender distinction) G3: 179 individuals (without gender distinction)				injury, natural disaster, witness, unexpected death, unknown	GAF, HAM-D17	and 19.6% for placebo.
Treatment of posttraumatic stress disorder with venlafaxine	Double blind, placebo controlled, randomized	G1: Venlafaxine (37.5-300 mg/day) G2: placebo	G1: 161 individuals (72 men and 89 women)	24 weeks	CAPS	DSM-IV	Military, sexual abuse, assault, non-sexual abuse, accidental	CAPS, CGI-S, GAF, HAM-D17, full CD-RISC, SVS, Q-	The mean changes from baseline on the CAPS scale at the end of the study were -51.7 for venlafaxine ER and -43.9 for placebo (P =

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extended release: a 6-month randomized controlled trial, 2006[30]	clinical trial		G2: 168 individuals (79 men and 89 women				injury, natural disaster, witness, unexpected death, unknown	LES-Q-SF, SDS	0.006). Low quality RCT.

BDI: *Beck depression inventory*. **CD-RISC:** *Connor-Davidson resilience scale.* **CGI:** *Clinical global impression.* **CGI-I:** *Clinical global impression – improvement.* **CGI-S:** *Clinical global impression – severity of illness*. **CTQ:** *Childhood trauma questionnarie.* **DST:** *Dexamethasone suppression test.* **DTS:** *Davidson trauma scale*. **GAF:** *Global assessment of functioning scores*. **HAM-A:** *Hamilton rating scale for depression for anxiety*. **IES:** *Impact of events scale*. **IES-R:** *Impact of events scale – revised*. **ISI:** *Insomnia severity index.* **LEC:** *Life events checklist*. **MADRS:** *Montgomery–Asberg depression rating scale.* **MGSQ:** *Massachusetts general hospital sexual functioning questionnaire*. **PANAS:** *Positive and negative affect schedule*. **PANSS:** *Positive and negative syndrome scale*. **PCL:** *Posttraumatic stress disorder checklist*. **PHQ9:** *9-Question patient health questionnaire.* **POMS:** *Profile of mood states*. **PTSD:** *Post-traumatic stress disorder*. **Q-LES:** *Quality of life enjoyment questionnaire*. **Q-SF:** *Quality of satisfaction questionnaire*. **QIDS-SR:** *Quick inventory of depressive symptomatology self-report version*. **SCID-I/P:** *Structured clinical interview – patient edition*. **SDS:** *Sheehan disability scale*. **SR:** *sustained release*. **SVS:** *Sheehan vulnerability to the effects of stress scale.* **TOP-8:** *Treatment-outcome post-traumatic stress disorder scale.*

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