American Journal of Internal Medicine
2022; 10(3): 39-50
http://www.sciencepublishinggroup.com/j/ajim
doi: 10.11648/j.ajim.20221003.12
ISSN: 2330-4316 (Print); ISSN: 2330-4324 (Online)

Curative Drug Treatments for Post-Traumatic Stress Disorder: A Systematic Review of the Effectiveness of Recent Treatments

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To cite this article:

Cyril Coquemont, Cyril Georges, Bernard Massoubre, Catherine Massoubre, Caroline Boulliat. Curative Drug Treatments for Post-Traumatic Stress Disorder: A Systematic Review of the Effectiveness of Recent Treatments. *American Journal of Internal Medicine.* Vol. 10, No. 3, 2022, pp. 39-50. doi: 10.11648/j.ajim.20221003.12

Received: March 17, 2022; **Accepted**: April 13, 2022; **Published**: May 10, 2022

Abstract: Post-traumatic stress disorder (PTSD) is a severe anxiety disorder with clinical and social repercussions. The first line of treatment is psychotherapy, but the most advanced forms require, in addition, a drug treatment. Currently, the treatments used are few in number and not very effective. The objective is to review the recent literature on curative drug treatments for PTSD. We conducted a literature review on the Medline database to include articles less than 10 years old dealing with curative drug treatments for PTSD. We identified inclusion and exclusion criteria to frame our research. We first selected articles by reading the title, then the abstract, and finally the full text. Each clinical study was placed in a table with its main characteristics and then analyzed in order to determine the effectiveness of the treatment studied. 51 references were included. Beta-blockers, corticosteroids and D-cycloserine show positive results in combination with various psychotherapy methods. Antiepileptics, oxytocin, atypical antipsychotics and prazosin showed divergent results. The use of prazosin, currently used to treat PTSD-induced sleep disorders, is being questioned. Ketamine, MDMA and cannabinoids have shown satisfactory results in terms of efficacy, but the question of their safety of use remains. The risks of overdose and illegal use should not be overlooked. Molecules such as ketamine, MDMA or cannabinoids will require further studies to conclude their efficacy and safety. They appear to be the most promising molecules currently available for the treatment of PTSD.

Keywords: PTSD, Pharmacotherapy, Psychotherapy, Treatment, Drug

1. Introduction

Formerly called "war neurosis" or "Kriegsneurosis" in the scientific literature, the term Post-Traumatic Stress Disorder has been widely recognized since its appearance in the third edition of the Statistical Manual of Mental Disorders (DSM-III) published in 1952. This pathology includes a set of symptoms known since antiquity.

Post-traumatic Stress Disorder (PTSD) is defined as the onset of symptoms following direct or indirect exposure to a traumatic event, during which the subject was confronted with death, threats of death, or sexual violence suffered by one or more people. The diagnosis of PTSD is made on the basis of eight criteria defined in the DSM-V. These criteria include exposure to a traumatic event, symptoms of intrusion, avoidance, cognitive impairment, and alertness, disruption for more than one month, clinical, social, or occupational distress, and an absence of other triggers. [1] PTSD affects 3 to 5% of the general population at least once in their lifetime [2] and is more prevalent in war zones. The main risk factors are female gender, psychiatric history, and low socioeconomic status. The treatment of this disorder is primarily based on psychotherapy. However, as a second-line

treatment, medication is part of the therapeutic arsenal. Health authorities in different countries agree on the effectiveness of Selective Serotonin Reuptake Inhibitors (SSRIs). However, their conclusions are divergent for second-line drug treatments. While the British authorities recommend the prescription of risperidone as a second-line treatment, the American authorities contraindicate it. These discrepancies indicate a low level of effectiveness of the second-line treatments currently prescribed. [3].

This literature review is part of the search for new treatments. Over the past ten years, studies on innovative treatments for PTSD have been conducted. The objective is to analyze these studies in order to extract the molecules that have shown convincing results in the treatment of PTSD.

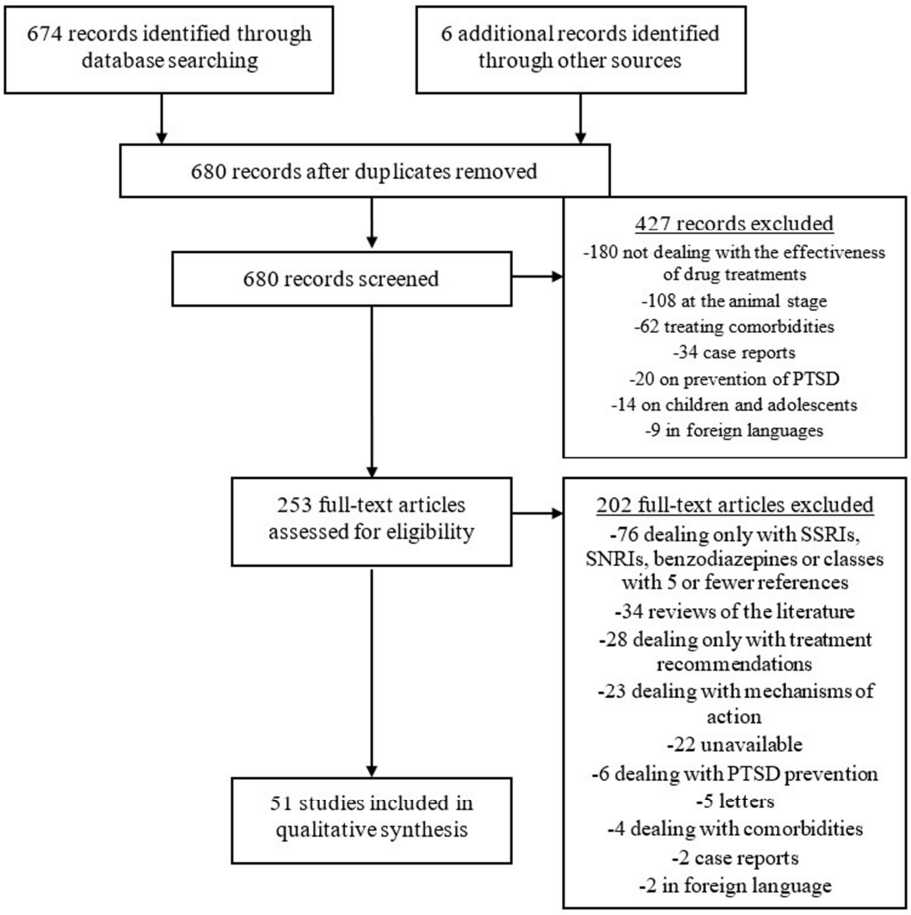

Figure 1. *Flow diagram.*

2. Material and Methods

This literature review is based on a Medline search of articles from the last 10 years to January 1, 2021 with the following equation:

("Stress Disorders, Post-Traumatic/therapy" [Majr]) AND ("drug therapy" [all fields] OR "pharmacotherap" [all fields]).*

The bibliographies of the articles searched were reviewed in order to implement our sources. The objective was to obtain all types of studies on the pharmacotherapy of PTSD.

The selection process of articles of interest is done in three steps, firstly by reading the title, then the abstract and finally the full article.

At each stage, two reviewers selected articles dealing with curative treatments of PTSD or ones allowing the reduction of symptoms in adults, regardless of whether they be civilian or military. The aim of these articles was to study the effectiveness of the molecules in humans. The drug treatments studied could be associated with psychotherapy or not. Where there was a doubt, the article was passed on to the next reading stage, which allowed us not to exclude any articles for lack of information in the title or the abstract.

We excluded from the selection case series which do not provide solid scientific evidence. Articles dealing only with preventive treatments of PTSD were excluded, as were studies in children and adolescents, studies dealing with co-treatment of PTSD and an associated comorbidity, animal studies or meta-analyses dealing only with studies conducted in 2010 or earlier. Only articles in French or English were retained.

For each study selected, the data necessary to determine the conclusions of the study were extracted. We thus selected for each study: the type of study, the number of patients included, the treatment studied, the comparator, the events studied and the significant results demonstrated by the study. The comparator could be a placebo or a reference treatment such as SSRIs. The events studied allowed the study treatment to be compared with the comparator, and took the

form of reference scores for the diagnosis of PTSD or for assessing the intensity of symptoms.

In order to focus on the most promising molecules, we have chosen to focus on the drug classes covered by more than five articles and have decided not to address the case of SSRIs and SNRIs considered as references and benzodiazepines recognized as contraindicated.

3. Results

674 articles were selected from the Medline search. Of those, 6 articles were identified as being of interest from the bibliographies of the literature reviews present among the 674 articles. No duplicates were found. 253 articles were read in full and of them, 76 were excluded because they were SSRIs, SNRIs, benzodiazepines or drug classes for which we found 5 or fewer articles. Articles that did not address our original topic or were in a literature review format were discarded. We thus ultimately included only 51 studies in our review.

Several drug classes have been studied by five or fewer articles in recent years and were therefore excluded: nitrous oxide, benzodiazepine relatives, 1st-generation antipsychotics, orexin antagonists, melatoninergic agonists, angiotensin-2 antagonists, converting enzyme inhibitors, neurokinin-1 antagonists, opioids, immunosuppressants, acetylcholine esterase inhibitors, probiotics, neuropeptides, presynaptic alpha2-adrenergic receptor blockers, alpha2-selective alphamimetics, NMDA receptor antagonists, thymoregulators, insulin, and antidepressants with an unclear mode of action such as tianeptine.

Clinical studies are listed in tables.

3.1. Antiepilectics

The most studied antiepileptic drug in the indication of PTSD is topiramate, the other studied treatments being tiagabine and pregabalin. Topiramate acts by blocking voltage-gated sodium channels, by blocking the excitatory activity of glutamate and by potentiating gamma-aminobutyric acid. Tiagabine inhibits the reuptake of GABA, increasing its concentration in the synaptic cleft. Pregabalin increases GABAergic transmission.

Table 1. *Characteristics of included clinical studies of antiepileptic drugs.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Shiner et al. 2018 [5]	Retrospective comparative study	2931	Fluoxetine, paroxetine, sertraline, topiramate, venlafaxine	Same patients before treatment	PCL	No significant difference in symptomatology improvements between the 5 treatments
Krystal et al. 2014 [6]	Open test	20	Tiagabine (2-12mg)	Same patients before treatment	PSG WASO SPRINT	Improved sleep quality and SPRINT. SPRINT is correlated with PSG and WASO
Yeh et al. 2011 [7]	Randomized trial	26	Topiramate (25-200mg)	Placebo	CAPS BDI CGI	Greater CAPS, CAPS-B and CAPS-C improvement in the Topiramate group
Baniasadi et al. 2014 [8]	Randomized trial	18	Pregabalin (300mg)	Placebo	PCL-M	Greater PCL-M improvement with pregabalin but no improvement in quality of life, anxiety and depression.

Meaning of acronyms: PCL: Posttraumatic Checklist; PSG: Polysomnographic; WASO: Wake time after sleep onset; SPRINT: Short PTSD Rating Interview; CAPS: Clinician-Administered Posttraumatic Stress Scale; BDI: Beck Depression Inventory; CGI: Clinical Global Impression; PCL-M: Posttraumatic Checklist Military.

Since 2010, four studies of antiepileptic drugs have been conducted, two involving topiramate [5, 7] one involving tiagabine [6] and one involving pregabalin. The randomized trial of topiramate [7] showed efficacy in reducing CAPS as well as reducing "re-experiencing" and avoidance symptoms. A retrospective comparative study of 2931 American veterans showed that symptoms did not decrease differently depending on whether the subject was treated with an SSRI, venlafaxine or topiramate [5]. An open-label trial of tiagabine [6] showed an increase in sleep duration and a decrease in PTSD-related symptoms. A randomized trial of pregabalin [8] showed an improvement in symptomatology without improving subjects' quality of life.

3.2. Beta-blockers

The β-receptor antagonists, or beta-blockers, are an old drug class with a significant safety record. PTSD induces noradrenergic activation. It is from this discovery, that this research on beta-blockers stems.

In the last ten years, only two studies - both on propranolol - have been conducted to determine their efficacy in the indication of curative treatment of PTSD. A randomized trial of 41 people showed no difference in symptomatology reduction between propranolol and placebo. This trial simply concluded that cognitive function improved with propranolol. The second randomized trial [9] showed a greater improvement in symptomatology in the propranolol group.

3.3. Steroids

Two types of steroids have been studied in the last decade: glucocorticoids and neurosteroids. Glucocorticoids are analogues of cortisol with numerous metabolic effects. Neurosteroids act as modulators of GABAA receptors resulting in reduced neurotransmission.

Four randomized trials have observed the effects of glucocorticoids on changes in different diagnostic scores for PTSD, or on neurovegetative action in the presence of a frightening signal. In 2015, one such trial [14] compared the combination of hydrocortisone and prolonged exposure to prolonged exposure alone. Prolonged exposure had better results when combined with hydrocortisone. Hydrocortisone used alone, on the other hand, has no effect on the number of intrusions, which can be defined by the reliving of traumatic memories. [13] Dexamethasone has been shown to be effective in extinguishing fear and discriminating cues, two Pavlovian concepts characterized by decreased sensitivity to memories of traumatic events [11]. It has also shown efficacy in reducing PTSD symptoms at 1 and 3 months, but this result is not found at 6 months. [12].

Table 2. *Characteristics of included clinical studies of beta-blockers drugs.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Brunet et al. 2018 [9]	Randomized trial	60	Propranolol	Placebo	CAPS PCL-S	Greater reduction in CAPS and PCL-S in the propranolol group
Mahabir et al. 2015 [10]	Randomized trial	41	Propranolol (1mg/kg)	Placebo	WAIS-III IES-R	No significant difference in IES-R. Processing speed is higher in the Propranolol group than in the placebo group

Meaning of acronyms: CAPS: Clinician-Administered Posttraumatic Stress Scale; PCL-S: Posttraumatic Checklist-Specific; WAIS: Wechsler Adult Intelligence Scale; IES-R: Impact of Event Scale Revised.

Table 3. *Characteristics of included clinical studies of steroid drugs.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Michopoulos et al. 2017 [11]	Randomized trial	25	Dexamethasone	Placebo	Palpebral flinch after listening to a frightening sound	Improvement of the "fear extinction" and "signal discrimination
Suris et al. 2017 [12]	Randomized trial	54	Dexamethasone	Placebo	PCL	Reduction of PCL at 1 and 3 months compared to placebo, not significant at 6 months
Ludäscher et al. 2015 [13]	Randomized trial	30	Hydrocortisone 10 or 30mg	Placebo	IES-R	No significant difference in the number of intrusions
Yehuda et al. 2015 [14]	Randomized trial	24	Hydrocortisone 30mg + PE	PE only	CAPS	Increased efficacy of EP, especially in good responders to glucocorticoids
Rasmusson et al. 2017 [15]	Randomized trial	112	Ganaxolone	Placebo	CAPS	No significant difference

Meaning of acronyms: PCL: Posttraumatic Checklist; CAPS: Clinician-Administered Posttraumatic Stress Scale; IES-R: Impact of Event Scale Revised.

Table 4. *Characteristics of included clinical studies of D-cycloserine.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
De Kleine et al. 2015 [16]	Randomized trial	67	DCS (50mg) + exposure therapy	Placebo + exposure therapy	PSS-SR Extinction learning	DCS has no significant effect on extinction learning
Rothbaum et al. 2014 [17]	Randomized trial	156	DCS + virtual reality	Alprazolam or placebo + virtual reality	CAPS PSS	No influence on scores. Less startle and cortisol production than in the placebo group
Difede et al. 2013 [18]	Randomized trial	25	DCS (100mg) + virtual reality	Placebo + virtual reality	CAPS BDI-II STEI-II	Significantly greater reduction in CAPS at 6 months
Litz et al. 2012 [19]	Randomized trial	26	DCS (50mg) + exposure therapy	Placebo + exposure therapy	CAPS	Greater CAPS reduction with placebo

Meaning of acronyms: PSS-SR: Posttraumatic Stress Symptom Scale - Self Report; CAPS: Clinician-Administered Posttraumatic Stress Scale; BDI: Beck Depression Inventory; STEI: State-Trait Anger Expression Inventory.

Only one randomized trial has been conducted with ganaxolone, a neurosteroid in development. It showed no difference in CAPS reduction between the ganaxolone group and the placebo group.

3.4. D-Cycloserine

D-Cycloserine is a molecule derived from cycloserine, a second-line antituberculosis drug. It is a partial agonist of NMDA receptors, facilitating the glutamatergic signaling pathway and by extension the capacity for learning and memory.

Four randomized trials have been conducted in the last ten years. Three trials concluded with the ineffectiveness of D-Cycloserine on the reduction of the PTSD score. Combined

with exposure psychotherapy or virtual reality psychotherapy, it showed no added value to psychotherapy alone in these three studies in terms of scores. The 156-subject trial showed that startle was less present during traumatic situations in subjects treated with D-Cycloserine. Only the combination of 100mg of D-Cycloserine with virtual reality psychotherapy showed superiority in terms of score reduction compared to virtual reality alone in 25 subjects suffering from PTSD following the World Trade Center attacks. In this condition, the CAPS score showed a greater reduction at 6 months.

3.5. MDMA

MDMA is a sympathicomimetic and psychostimulant amphetamine. It causes the release of neurotransmitters such as serotonin, dopamine or noradrenaline. It indirectly induces the release of oxytocin.

Seven randomized trials have studied the efficacy of MDMA. In these trials, active and non-active doses of MDMA were distinguished, serving as controls and allowing the preservation of double-blindness. [27].

The trial with the largest number of subjects [20] demonstrated a significantly greater reduction in short- and long-term CAPS with active doses of MDMA combined with psychotherapy compared to non-active doses combined with psychotherapy. Similar results had previously been found with a smaller sample of 28 individuals, but only on a per-protocol, not an intention-to-treat basis. [21].

Mithoefer et al. in 2018 even demonstrated that a low active dose of 75mg was more effective in reducing symptoms than a high active dose of 125mg, which in turn was more effective than a non-active dose of 30mg, these doses always being combined with psychotherapy. [22].

Oehen et al. found no significant differences in CAPS reduction between MDMA and placebo combined with psychotherapy. The severity of symptoms assessed by the PDS was, however, significantly more reduced with MDMA. [25].

The pilot study by *Mithoefer et al*. [26] yielded three papers. This study of 23 subjects demonstrated a significantly greater decrease in CAPS in the MDMA arm compared with the placebo arm. A 2016 study by *Corey et al* [23] demonstrated that when interviewing patients in the pilot study, the terms used by patients on MDMA were significantly more related to empathy, their perception of themselves, or their contact with others. The pilot study also provided the basis for a study by *Mithoefer et al*. two years later, which showed that the decrease in CAPS persisted over the long term, between 17 and 74 months after. [24].

3.6. Oxytocin

Oxytocin is a neuropeptide secreted by the hypothalamus. Used for its impacts on the muscles of the uterus and mammary glands, it is said to be effective in treating psychiatric disorders by reducing stress.

Table 5. *Characteristics of included clinical studies of MDMA.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Jerome et al. 2020 [20]	Randomized trial	107	MDMA (75-125mg) combined with psychotherapy	MDMA (0-40mg) + psychotherapy	CAPS LTFUQ	Significantly greater reduction in CAPS-IV in the short and long term compared to the control
Ot'alora et al. 2018 [21]	Randomized trial	28	MDMA (100-125mg) + psychotherapy	MDMA (40mg) + psychotherapy	CAPS BDI-II PSQI DES-II CAPS-IV	Significantly greater decrease in CAPS-IV compared to control. Only per protocol, not intention to treat
Mithoefer et al. 2018 [22]	Randomized trial	26	MDMA (75-125mg) combined with psychotherapy	MDMA (30mg) + psychotherapy	BDI-II PSQI PTGI NEO-PI-R DES-II GAF	Significantly greater reduction in symptoms with 75mg of MDMA than with 125mg, itself greater than with 30mg
Corey et al. 2016 [23]	Randomized trial	23	MDMA (125mg)	Placebo	Patients' feelings during medical interviews. Searching for terms related to empathy, changing their self-representation or contact with others	MDMA patients used significantly more terms related to the feelings discussed above than placebo patients. A high number of occurrences of the desired terms is statistically related to a low CAPS
Mithoefer et al. 2013 [24]	Open study	16	MDMA + psychotherapy	MDMA + Psychotherapy	CAPS IES	No statistically significant differences in CAPS and IES between 2 months and the long term
Oehen et al. 2012 [25]	Randomized trial	14	MDMA (125 + 62.5mg) + psychotherapy	MDMA (25 + 12.5mg) + psychotherapy	CAPS PDS	No statistically significant difference in CAPS reduction between the two arms. Higher SDB improvement with active dose of MDMA.

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Mithoefer et al. 2011 [26]	Randomized trial	23	MDMA (125 + 62.5mg) + psychotherapy	Placebo + psychotherapy	CAPS IES-R SCL-90-R	Significantly greater decrease in CAPS-IV compared to control

Meaning of acronyms: CAPS: Clinician-Administered Posttraumatic Stress Scale; LTFUQ: Long-term follow-up questionnaire; BDI: Beck Depression Inventory; PSQI: Pittsburgh Sleep Quality Index; DES-II: Dissociative Experiences Scale-II; PTGI: Post-Traumatic Growth Inventory; NEO-PI-R: Neuroticism-Extroversion-Openness Personality Inventory-Revised; GAF: Global Assessment of Functioning; IES-R: Impact of Event Scale Revised; PDS: Posttraumatic Diagnostic Scale; SCL-90-R: Symptom Checklist 90-Revised.

Table 6. *Characteristics of included clinical studies of oxytocin.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Flanagan et al. 2018 [28]	Randomized trial	34	Oxytocin (24 IU)	Placebo	n-back" memory exercise Functional MRI	Significantly fewer errors with oxytocin
Flanagan et al. 2018 [29]	Randomized trial	17	Oxytocin (40 IU) + PE	PE	CAPS PCL BDI	No significant difference
Sack et al. 2017 [30]	Randomized trial	35 women with childhood trauma	Oxytocin (24 IU)	Placebo	RSDI	Decreased avoidance but not recurrence of symptoms
Nawijn et al. 2016 [31]	Randomized trial	72 patients with or without PTSD	Oxytocin (40 IU)	Placebo	Social incentive task Functional MRI	With placebo, PTSD+ patients have a lower response to social rewards than PTSD- subjects. The results are comparable between PTSD+ subjects with oxytocin and PTSD- with placebo.
Palgi et al. 2017 [32]	Randomized trial	32 patients with PTSD, 30 patients without PTSD	Oxytocin (24 IU)	Placebo	Emotional empathy: Biological motion task Cognitive empathy: ToM task	No improvement in empathy with oxytocin

Meaning of acronyms: CAPS: Clinician-Administered Posttraumatic Stress Scale; PCL: Posttraumatic Checklist; BDI: Beck Depression Inventory; RSDI: Responses to Script-Driven Imagery Scale.

Since 2011, four randomized trials have been conducted with and without the prolonged exposure psychotherapy technique. The 2016 study by *Nawijn et al.* [31] on subjects with and without PTSD showed that PTSD+ subjects had significantly less activation of their reward circuitry. Oxytocin corrects this deficit to the same level of activation as in a healthy person. A 2017 study by *Sack et al* [30] shows that PTSD recurrence symptoms are not affected by oxytocin intake. By contrast, avoidance behavior decreases significantly more with oxytocin than with placebo. The addition of oxytocin during prolonged exposure psychotherapy has no influence on the reduction of symptoms [29]. It does, however, appear to have an effect on memory. In fact, the randomized trial in 34 subjects with PTSD showed that oxytocin-treated subjects made fewer errors on the n-back memory exercise than placebo-treated subjects. [28] Finally, the randomized trial by *Palgi et al*. showed no improvement in empathy after oxytocin administration in subjects with PTSD. [32].

3.7. Prazosin

Prazosin is an antihypertensive, alpha-1 receptor antagonist indicated as a second-line treatment for high blood pressure, Raynaud's syndrome or benign prostatic hypertrophy. It is indicated in the treatment of PTSD to treat the nightmares associated with it. Six randomized trials of prazosin have been conducted in the last 10 years. The control chosen was either a placebo [33, 35-38] or hydroxyzine with a hypnotic effect [34] or a psychotherapy called "Behavioral Sleep Intervention" [38]. Three studies demonstrated the superiority of prazosin over control in 50 [38], 67 [35] and 100 [34] patients, with the control in each study being different. Two studies did not show superiority of prazosin over placebo, including one study with 304 subjects, the largest one conducted in the last 10 years on this subject. [33, 36].

3.8. Ketamine

Ketamine is a potent antagonist of the N-methyl-D-aspartate (NMDA) receptor. Activation of this receptor by glutamate requires glycine as a co-agonist. Ketamine will non-competitively inhibit the activation of the NMDA receptor by glutamate.

Its most common indication is as a non-barbiturate general anesthetic. It can be administered by IV or IM.

In 2014 *Feder et al.* looked at ketamine use in patients with PTSD in a randomized, double-blind, cross-over study. This study found that IV ketamine use resulted in a rapid and significant reduction in the severity of PTSD symptoms compared with midazolam. [39].

In 2017 *Hartberg* et al. conducted a retrospective study of

oral ketamine in patients with PTSD, or depression resistant to conventional treatments. In patients on this treatment, hospital length of stay was reduced by 70% and admissions were reduced by 65%. [40].

Table 7. *Characteristics of included clinical studies of prazosin.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
McCall et al. 2018 [33]	Randomized trial	20	Prazosin at bedtime	Placebo	NMSU SSI C-SSRS HRSD CGI-S	Lower sleep improvement in the prazosin group
Ahmad-panah et al. 2014 [34]	Randomized trial	100	Prazosin	Hydroxyzine	Quality of sleep	Increased sleep duration, reduced nightmares
Raskind et al. 2013 [35]	Randomized trial	67	Prazosin	Placebo	Quality of sleep	Increased quality of sleep, fewer nightmares
Raskind et al. 2018 [36]	Randomized trial	304	Prazosin	Placebo	CAPS-B2 PSQI CGI-C	No significant results
Raskind et al. 2016 [37]	Randomized trial	67	Prazosin	Placebo	CAPS	The higher the baseline blood pressure, the more prazosin reduces the CAPS score
Germain et al. 2012 [38]	Randomized trial	50	Prazosin	BSI, placebo	CGI-I ISI PSQI PSQI-A PghSD	Reduction in the frequency of nightmares, improved sleep

Meaning of acronyms: DDNSI: Disturbing Dreams and Nightmare Severity Index; SSI: Scale for Suicide Ideation; C-SSRS: Columbia Suicide Severity Rating Scale; HRSD: Hamilton Rating Scale for Depression Clinician-Administered Posttraumatic Stress Scale; PSQI: Pittsburgh Sleep Quality Index; CGI-C: Clinical Global Impression of Change; CGI-I: Clinical Global Impression - Improvement; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; PghSD: Pittsburgh Sleep Diary.

Table 8. *Characteristics of included clinical studies of ketamine.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Feder et al. 2014 [39]	Randomized trial	41	Ketamine IV (0.5 mg/kg)	Midazolam (0.045 mg/kg)	IES-R MADRS QIDS-SR CGI-S CGI-I	Significant effectiveness
Hartberg et al. 2018 [40]	Retrospective study	37	Final dose of ketamine between 0.5 and 7.0 mg/kg	Situation before / after treatment	Pairwisettests	70% reduction in length of stay and 65% reduction in hospitalizations

Meaning of acronyms: IES-R: Impact of Event Scale Revised; MADRS: Montgomery-Asberg Depression Rating Scale; QIDS-SR: Quick Inventory of Depressive Symptomatology - Self-Report; CGI-S: Clinical Global Impression - Severity; CGI-I: Clinical Global Impression – Improvement.

Table 9. *Characteristics of included clinical studies of cannabinoids.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Rabinak et al. 2020 [41]	Randomized trial	71	7.5mg THC	Placebo	Functional MRI	THC reduced threat-related amygdala reactivity, increased mPFC (medial prefrontal cortex) activation during threat
Bonn-Miller et al. 2014 [42]	Pilot study	170	Cannabis	Patients without PTSD	PCL-C CMMQ MSHQ IDAS	Improvement of sleep disorders
Bonn-Miller et al. 2014. [43]	Pilot study	217	Cannabis	Patients without PTSD	Benefits felt by patients	Non-significant improvement in PTSD symptoms
Cameron et al. 2014 [44]	Retrospective study	104	Nabilone Average starting dose: 1.4mg/d Average final dose: 5mg/d	Situation before / after treatment	PCL-C GAF	Significant improvement
Greer et al. 2014. [45]	Retrospective study	80	Cannabis	Situation before / after treatment	CAPS	Reduction of symptoms

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Roitman et al. 2014 [46]	Open study	10	THC	Situation before / after treatment	CAPS CGI PSQI NFQ NES	Reduced nightmares and improved sleep quality
Jetly et al. 2015 [47]	Randomized trial	10	Nabilone	Placebo	CAPS CGI-C WBQ	Reduction of nightmares
Wilkinson et al. 2015 [48]	Retrospective cohort study	2276	Cannabis	Consumer Weaned New consumers	ASI MISS	Deleterious effects
Johnson et al. 2016 [49]	Case-control study	700	THC	Placebo	PCL-C	No association between cannabis use and PTSD symptom severity

Meaning of acronyms: PCL-C: Posttraumatic Checklist-Civilian; CMMQ: The Comprehensive Marijuana Motives Questionnaire; MSHQ: Marijuana Smoking History Questionnaire; IDAS: Inventory of Depression and Anxiety Scale; GAF: Global Assessment of Functioning; CAPS: Clinician-Administered Posttraumatic Stress Scale; CGI: Clinical Global Impression; PSQI: Pittsburgh Sleep Quality Index; NFQ: Nightmare Frequency Questionnaire; NES: Nightmare Effects Survey; CGI-C: Clinical Global Impression of Change; WBQ: Well Being Questionnaire; ASI: Addiction Severity Index; MISS: Mississippi Short Form scale.

Table 10. *Characteristics of included clinical studies of antipsychotics.*

Name of the study	Type of study	Number of patients included	Treatment studied	Comparator	Measurements made	Significance
Naylor et al. 2015 [51]	Randomized trial	16	Aripiprazole 10mg	Placebo	CAPS SPRINT PSS	No significant effect
Krystal et al. 2011 [52]	Randomized trial	247	Risperidone 4mg	Placebo	CAPS CGI MADRS HAMA PANSS SF-36V BLSI	No significant effect
Villarreal et al. 2016 [53, 54]	Randomized trial	80	Quetiapine On average 258 mg (from 50-800 mg)	Placebo	CAPS PANSS CGI HAM-D HAM-A	Significant effectiveness
Carey et al. 2012 [55]	Randomized trial	28	Olanzapine 5-15 mg	Placebo	CAPS CGI CAPS subscales DTS SDS	Significant effectiveness
Youssef et al. 2012 [56]	Pilot study	10	Aripiprazole 5-30mg/day	Before and after	CGI	Significant improvement
Richardson et al. 2011 [57]	Retrospective study	27	Aripiprazole variable dose	Before and after	PCL-M BDI SF-36	Significant improvement
Hamner et al. 2019 [58]	Randomized trial	24	Ziprasidone (120-160mg)	Placebo	CAPS	No significant effect

Meaning of acronyms: CAPS: Clinician-Administered Posttraumatic Stress Scale; SPRINT: Short PTSD Rating Interview; PSS: Posttraumatic Stress Symptom Scale; CGI: Clinical Global Impression; MADRS: Montgomery-Asberg Depression Rating Scale; HAM A: Hamilton Anxiety Rating Scale; PANSS: Positive and Negative Syndrome Scale; SF-36V: Veterans RAND 36-Item Health Survey; BLSI: Boston Life Satisfaction Inventory; HAM D: Hamilton Depression Rating Scale; DTS: Davidson Trauma Scale; SDS: Sheehan Disability Scale; CGI: Clinical Global Impression; PCL-M: Posttraumatic Checklist-Military; SF-36: RAND 36-Item Health Survey.

3.9. Cannabinoids

3.9.1. THC

A randomized double-blind trial by *Rabinak et al* in 2020 showed that THC, compared with placebo, decreased amygdala reactivity to threat and increased medial prefrontal cortex activation during threat. These data suggest that in individuals exposed to trauma, THC modulates threat-related processing. [41].

A preliminary pilot study conducted by *Roitman et al.* in 2014 on the safety and tolerability of oral THC use as a supplement to standard treatment for PTSD found statistically significant improvements in overall symptoms,

sleep quality, nightmare frequency, and arousal symptoms related to PTSD [46].

3.9.2. Cannabis

In 2014 *Bonn-Miller et al.* conducted a preliminary pilot study in patients using cannabis at least once a week. Improvement in PTSD-related sleep disturbance was found, but only 8 of 40 subjects had a reduction in PTSD symptoms. [42].

A reduction in PTSD symptoms was found in a second 2014 study by *Bonn-Miller et al.* [43]. This reduction in PTSD symptoms was also found by *Greer et al.* in 2014 [45].

Not all studies support this however. A retrospective cohort study conducted by *Wilkinson et al.* in 2015 on cannabis use in PTSD patients showed that stopping cannabis use improves PTSD symptoms. A start of use in a PTSD patient creates a worsening of symptoms. Finally, at follow-up, quitters who had never used cannabis had lower levels of PTSD symptoms, and starters had the highest levels of violent behavior. [48].

The lack of association between cannabis use and the presence of fewer PTSD symptoms was found in a case-control study by *Johnson et al.* (2016). [49].

Ruglass et al. conducted a statistical study in 2017 on possible associations between weekly cannabis use and completion of treatment for PTSD symptoms. Neither positive nor negative associations could be established. [50].

3.9.3. Nabilone

In 2014, *Cameron et al.* conducted a retrospective study in PTSD patients undergoing treatment with nabilone. A significant improvement in PTSD-related insomnia and nightmares as well as PTSD symptoms was noted [44]. The reduction in nightmares thanks to nabilone was confirmed in a randomized, double-blind, placebo-controlled study by *Jetly et al.* in 2015. [47].

3.10. Atypical Antipsychotics

In 2011 a pilot study by *Youssef et al.* and a retrospective study by *Don Richardson et al.* demonstrated a reduction in PTSD symptoms after treatment or addition of aripiprazole. [56, 57].

However, since then a randomized trial aripiprazole vs placebo, conducted by *Naylor et al.* in 2015, showed no significant effects on PTSD symptoms. [51].

A 2015 randomized double-blind risperidone vs. placebo trial by *Krystal et al.* showed no significant effects on reducing PTSD symptoms.

Quetiapine showed efficacy as monotherapy on military personnel with PTSD in a 2016 randomized quetiapine vs. placebo trial conducted by *Villarreal et al*. [53].

Olanzapine demonstrated superior efficacy to placebo in patients with PTSD in a randomized, double-blind trial by *Carey et al*. [55].

A randomized trial was conducted in 2019 on ziprasidone. This one did not show significant results however. [58].

4. Discussion

The place of this study in the scientific literature:

Psychotherapy is the first line of treatment for PTSD. Many studies therefore focus on this subject. Clinical studies and reviews of the literature specific to drug treatments are few. In contrast to the studies present in the literature, this article identifies all therapeutic drug perspectives in the indication of curative treatment of PTSD. No recent study had investigated the entire spectrum of possible treatments until now. The present one ranges from prazosin to MDMA or ketamine.

This permitted the inclusion of studies dealing with the efficacy of old molecules as well as future perspectives. This objective confrontation between the two categories is the strength of this study and promising results have been found.

The place of drug therapy in the therapeutic arsenal of PTSD:

A person exposed to a traumatic event, such as a confrontation with death, may develop PTSD. The appearance of symptoms of intrusion, avoidance or hyperstimulation will lead to this diagnosis.

In France, the first line of treatment is psychotherapy using CBT (Cognitive Behavioral Therapy) or EMDR (Eye Movement Desensitization and Reprocessing). However, psychotherapy is not 100% effective because of dropouts during therapy, contraindications to psychotherapy, insufficient reduction of symptoms or relapses.

The second line of treatment is the concomitant use of antidepressants with psychotherapy. The antidepressants used are SSRIs. Only paroxetine and sertraline are approved for the treatment of PTSD. Hypnotics, such as benzodiazepines, may be indicated for symptoms of hypervigilance leading to sleep disturbance.

The effectiveness of the treatment of patients suffering from PTSD is not optimal despite the recommendations set out above. In fact, beyond the failures and non-adherence to psychotherapy, some patients may prove to be resistant to conventional antidepressants. Psychiatrists will then turn to treatments outside the MA.

In order to ensure optimal patient management, exploration of the clinical efficacy of other drug classes is necessary, as the therapeutic arsenal of drugs within the framework of a marketing authorization is currently limited to SSRIs.

Over the last ten years, research on drug treatments for PTSD has turned resolutely towards new atypical therapeutic classes such as MDMA, ketamine or cannabis derivatives. Traditional treatments have definitely shown their limits. Of the ten therapeutic classes studied, none of the seven traditional classes has shown an undeniable efficacy, but some of them are nonetheless still of interest.

Effective traditional treatments combined with psychotherapy:

Beta-blockers, dexamethasone or hydrocortisone and D-cycloserine may be effective when combined with

psychotherapy. The combination of several memory reactivation sessions and the use of beta-blockers seems to be complementary. Dexamethasone and hydrocortisone, on the other hand, are only useful when used in conjunction with prolonged exposure psychotherapy. Finally, D-cycloserine would only be effective in combination with virtual reality psychotherapy.

Traditional treatments with divergent results:

The antiepileptic drugs tested in recent years, topiramate, tiagabine and pregabalin, show encouraging results, even if the improvement of certain symptoms is not found with pregabalin.

Oxytocin induces a return to normal brain circuitry visible on MRI, but this does not translate into PTSD symptomatology scores.

Prazosin has long been considered the gold standard for treating PTSD-induced sleep disorders. Two 2018 randomized, double-blind, controlled studies cast doubt on this efficacy however.

Atypical antipsychotics also show divergent results. Quetiapine and olanzapine still seem to do well, while risperidone is ineffective.

Atypical treatments, consequences of a new consideration for certain substances:

MDMA has shown almost exclusively positive results in studies over the last ten years. However, it seems clear that this molecule does not only have advantages in use. At the doses used in the trials, no serious adverse effects occurred, though the question of overdosing or trafficking of this substance may arise.

Cannabis derivatives, on the other hand, have not shown significant efficacy, except for nabilone, which has only positive results. This difference in results may be due to the unregulated use of cannabis. In fact, not all the patients included consume the same quantities of cannabis nor do they obtain the same varieties. Thus the amount of THC and CBD assimilated by the patients during the studies is not the same.

Ketamine could also be a treatment for PTSD to consider, given its effectiveness.

Multiple scores, making interpretation difficult:

An analysis of the results of the effectiveness of PTSD treatments is delicate because the scores used to define PTSD are so divergent. Of the 51 studies considered, there are many different comparators. The "gold standard" being the CAPS, it would seem interesting to harmonize the studies around it.

Drug treatment of PTSD, interest varies from country to country.

Although the operational commitment of French military personnel is currently significant, very few studies have been conducted in France on this subject. In fact, the 51 clinical studies included were carried out mainly in the USA with 34 studies, followed by Canada with 5 studies, Germany, the Netherlands, Iran and Israel with 2 studies each and finally Brazil, Switzerland, Australia and South Africa with 1 study each.

There are prospects for research in France to improve the management of PTSD victims, while the United States is studying this subject with interest and has been publishing for several years.

5. Conclusion

Many preliminary studies in the treatment of PTSD seem promising. Nevertheless, before being integrated into the therapeutic arsenal and concretely modifying clinical practice, the promising molecules will have to undergo new randomized trials in order to ensure their safety of use and their effectiveness. These molecules will also have to face the reluctance of the health authorities to authorize as treatment addictive molecules that can be trafficked. Traditional molecules will have to be included in large-scale studies so that clear and uniform recommendations can be made concerning the treatment of PTSD.

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