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Targeting the Noradrenergic System in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis of Prazosin Trials

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Abstract: Post-traumatic stress disorder (PTSD) is a chronic psychiatric disorder that may develop after exposure to a life-threatening trauma. As veterans and armed forces may deal with diverse health problems compared with civilians, they have a greater risk for psychiatric disorders, including PTSD, than civilians, even if the disorder may be also frequent in the general population. PTSD is associated with significant comorbidity, especially with mood disorders and substance abuse. Moreover, the suicide risk is higher in PTSD patients than in the general population. Selective Serotonin Reuptake Inhibitors (SSRIs), atypical antipsychotics and benzodiazepines are commonly employed in the management of PTSD, but often these treatments fail or are discontinued due to adverse effects. It has been demonstrated that high noradrenergic activity may be associated with hyperarousal, trauma nightmares and sleep disturbances in PTSD subjects, probably through the stimulation of α-1 adrenergic receptors in the brain prefrontal cortex. The α-1 adrenoreceptor antagonist prazosin decreases noradrenaline effects at brain α-1 adrenoreceptors and may be a promising agent in the treatment of PTSD, as some studies have found it effective and well tolerated. Therefore, the present review is aimed to examine the role of noradrenergic system in the pathophysiology of PTSD. Moreover, we conducted a systematic review to evaluate the effectiveness and tolerability of prazosin in PTSD patients. Meta-analysis was used to combine data from multiple studies and better estimate the effect of prazosin on specific outcomes. We found prazosin to be significantly more efficacious than placebo in reducing distressing dreams in PTSD patients, even though our results should be interpreted with caution due to the small number of studies included in our quantitative synthesis.

Keywords: Efficacy, hyperarousal, nightmares, post-traumatic stress disorder, prazosin, noradrenergic system, tolerability.

INTRODUCTION

The treatment of PTSD equally accounts a number of different approaches, although the effectiveness of both psychotherapeutic and pharmacological interventions for PTSD (the ones having higher cumulative evidence), is far away from allowing a conclusive statement in their support or discharge. Specifically, concerning the psychopharmacological approaches to PTSD, the Selective Serotonin Reuptake Inhibitors (SSRIs), benzodiazepines, as well as recently introduced second-generation antipsychotics (SGAs) have all being considered as part of a multi-disciplinary approach, yet, both acute and long-term tolerability issues often limited their clinical use [1,2]. Therefore, a number of pharmacological agents from different classes of drugs have been further accounted in the management of non-responding or partial responding cases of PTSD, primarily targeting the central

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nervous system (CNS) norepinephrinergic transmission, a classical neurobiological paradigm accounted in pathophysiology of PTSD [3].

Such alternative pharmacological approach is exemplified by some anti-hypertensive drugs, including α-2 presynaptic and α-1 postsynaptic blockers that can cross the blood–brain barrier (BBB), thus exerting their effects also at the CNS, either at the locus coeruleus (LC) or at other areas of the brain engaged in the fear-anxiety response, such as the prefrontal cerebral cortex [4]. To date, prazosin, a selective α-1-adrenergic blocker, represents the main promising sympatholytic drug in the treatment of hypertension, reported effective also in the management of PTSD, as well as in general anxiety and panic disorders [5]. Moreover, animal data suggests a melatonergic MT1 and MT2 antagonism for prazosin [6], which may explain the clinical benefits from this drug for many veterans, frequently complaining recurrent nightmares and flashbacks in the presence of markedly impaired circadian rhythm and architecture of sleep [7,8].

Thereafter, stating the suggestive potential clinical role of prazosin even in the management of PTSD, a systematic review of published data on the matter is herein presented, alongside with a critical dissertation on the function of the norepinephrinergic system in the pathogenesis of PTSD as a primary target of prazosin itself.

Sleep Disturbances in PTSD as a Marker of Disease Severity

Sleep disturbances are a common and central complaint among PTSD sufferers [9,10]. In fact, sleep disorders are incorporated in the DSM-V criteria for PTSD. These are the re-experiences of traumatic symptoms (nightmares, critera B) as well as alterations in arousal and reactivity (sleep disturbance, critera E).

The most commonly reported complaints of such patients are difficulties in falling asleep, regular awakenings (with difficulties in falling back to sleep), reduced sleep duration, restless sleep, fatigue, and, above all, anguished nightmares and anxiety dreams. The 44%–90% of veterans with PTSD reported some sleep disturbances, and 52%–87% reported having persistent nightmares [11]. In fact, nightmares are the most constant finding in the majority of questionnaire studies that have investigated sleep complaints associated with PTSD [12,13].

It has been suggested that sleep disturbances may be considered as core symptoms of PTSD [14]. A couple of data showed that sleep disturbances were correlated with exposure to traumatic events and development of PTSD [15-18]. For instance, sleep disturbances were the prevalent symptoms among persons who survived the 1995 Hanshin earthquake in Japan [19] and among survivors of the Holocaust [20]. Moreover, several studies pointed out that sleep disturbances were strongly related to overall PTSD severity and associated with poorer psychological outcomes in military personnel stationed at war zones [21].

The relationships between exposure to traumatic events and sleep disturbances are the most evident among subjects who do not recover from early symptomatic responses to such exposures, including patients with PTSD [22]. Certainly, about 70% of PTSD patients also have co-occurring sleep disturbances and report greater difficulties in initiating and maintaining sleep compared to individuals without PTSD [13]. These data highlight that sleep problems commonly occur among people exposed to a traumatic event.

In addition, it was demonstrated that post traumatic nightmares have a propensity to persist for several years, impairing daytime functioning and psychological well-being [23]. In a recent study [24] it has been found that the exposure to a traumatic disaster (L'Aquila earthquake on April 6, 2009) was related to a significant deterioration of sleep quality and an increased occurrence of disturbing nocturnal behaviors [25] even in the long term (two years after the event).

Therefore, taken together, these findings support the notion that sleep disturbances play a significant role in PTSD, suggesting the importance of preventive strategies to improve sleep quality in the aftermath of an extremely stressful event.

Neuroimaging of Sleep Disturbances in PTSD

As traumatic nightmares, disturbed sleep and hyperarousal are core symptoms of PTSD, their neural correlates may be clarified by means of neuroimaging techniques. Alterations in REM sleep have been associated to impaired fear extinction throughout a reduced activation of ventromedial prefrontal cortex (vmPFC), mediated by the brainstem [26].The vmPFC has a crucial role in the extinction learning, because it exerts a top-down inhibitory control over the amygdala [27]. So, when a hypoactivation of vmPFC occurs, a hyperactivation of the amygdala is observed and the subject fails to diminish or inhibits his response to learned fears. Moreover, in PTSD patients, when the amygdala escapes the prefrontal control, it may react in an abnormal way not only during negative emotion processing [28,29], but also during neutral and harmless stimuli [30,31], as a result of hypoarousal or altered coping strategies for emotional events. Several functional connectivity studies confirmed a disrupted communication between limbic and prefrontal areas in PTSD [32-35]. In a recent study [36], when PTSD patients were compared to traumatized subjects who did not develop psychiatric symptoms, they showed a prolonged excitation and higher tonic component of autonomic activity during fear processing, hence indicating an abnormal "attack - escape" response mediated by the autonomic nervous system. In normal volunteers, an enhanced noradrenergic transmission increases the amygdala response to fear [37], thus suggesting that drugs interacting with the noradrenergic system may be effective in PTSD treatment.

Another role of both slow wave and REM sleep is to improve synaptic plasticity and consolidate memories in the hippocampal circuitry [38]. Having a reduced hippocampal volume was reported as a risk factor for PTSD in monozygotic twins not concordant for trauma exposure [39]. Several structural studies reported a volume reduction in the whole hippocampus or in specific hippocampal subregions in PTSD patients [40]. Neylan and colleagues [41] found a significant association between a reduced volume in the cornu ammonis-sector 3 (CA3) and dentate gyrus (DG) of the hippocampus and the severity of insomnia, and suggested that

chronic sleep disruption, as a result of traumatic events, may decrease the neurogenesis in these regions. However, in a recent study by Chao *et al.* [42], the hippocampal and fronto-limbic abnormalities observed in current PTSD were not confirmed in remitted patients, so the authors hypothesized that PTSD recovery may be characterized by a restoration of brain tissue.

The Role of Noradrenergic System in PTSD: Complex Interactions Among Stress Hormones from the Physiology of Memory Consolidation to the Pathology of Fear Extinguishing Failure

The neurobiology of PTSD is basically the neurobiology not only of sleep, but also of memory retaining and consolidation. During our lives we are daily exposed to emotively striking and stressful experiences that activate mnesic traces writing and time-dependent cellular storage processes in the brain areas involved in representation of each specific kind of memory (i.e. cortex, hippocampus, nucleus striatum etc.). More than a century of studies on memory consolidation have demonstrated that emotional arousal of events may play a crucial role in enhancing memory retaining, thus the more emotional the events are the better they are recorded in our memories [43].

Increasing evidence suggests that the interaction between the corticosteroid system and the noradrenergic system during memory encoding is pivotal for a correct consolidation of emotionally arousing experiences, and that the Baso-lateral nucleus of the Amygdala (BLA) is the core region deputed to the modulation of memory consolidation [44,45]. However, recent findings have also demonstrated a modulatory role of endocannabinoids on the noradrenaline-corticosteroids integrated memory-consolidating system [46]. Therefore, noradrenergic system may be logically considered as having the leading role in memory formation, as well as in the pathophysiology of psychiatric disorders in which memory consolidation and recalling are disrupted, such as PTSD.

The most part of noradrenergic projections originates in the locus coeruleus (which contains almost 40% of the brain noradrenergic neurons), and from the lateral tegmental system (which comprises the dorsal motor nucleus of the vagus nerve, the nucleus tractus solitarii and the lateral tegmental nucleus). Locus coerules neurons project mainly to cerebral cortex, amygdala and hippocampus [47], whereas the lateral tegmental neurons are mainly involved in controlling vegetative nervous system functions, such as blood pressure, in modulating the wakefulness status and eating behaviors, as well as in controlling endocrine system secretions (e.g. ACTH, TSH, GH). Moreover, noradrenaline, together with adrenaline, are also produced by the medulla of the adrenal glands (respectively 80% adrenaline and 20% noradrenaline) in response to stressful events. Overall, the noradrenergic systems seem to exert two main functions: the first one is to maintain a basal sensory status in the forebrain, which is necessary to acquire information, and the second one is to rapidly respond to emotionally arousing events by modulating sensory, motor and memory processes [48].

Studies have repeatedly shown the essential role of noradrenaline in memory formation, both in animals and in humans. Indeed, adrenergic agonists, or generically blood raising in noradrenaline/adrenaline levels may enhance memory performances in experimental animals, whereas different types of beta-blocking drugs may improve memory consolidation [26, 28]. Similarly, in healthy humans the administration of propranolol (a beta1/beta2-adrenergic receptors blocker which passes the blood-brain barrier) has been demonstrated to impair the memory consolidation of emotionally arousing experiences (emotional slide shows) [49]. Notably, beta-blocking drugs with exclusive peripheral actions (i.e. nadolol) have been demonstrated to have no effects on memory consolidation in healthy subjects, thus confirming the key role of central noradrenergic system in these functions [50].

Although the role of noradrenaline in formation of emotional memory is unquestionable, increasing evidence points out that other stress hormones act in the final consolidation of memories in the brain, such as corticosteroids and endocannabinoids. First of all, it is noteworthy to highlight that extensive evidence has demonstrated that the main playground in which all these interactions take place, in both animals and humans, is the Amygdala, and, in particular, the BLA [51]. Indeed, the increase in noradrenaline levels in the BLA, but not in the adjacent Central Nucleus of the Amygdala (CeA), has been shown to increase memory consolidation in different emotionally arousing tasks, whereas beta-blocking drugs BLA infusion may provoke memory consolidation impairments [52]. These effects seem principally mediated by beta-adrenergic receptors, with α1-adrenergic receptors exerting a potentiating action on them [53].

At the level of BLA, noradrenaline and glucocorticoids appear to interact in multiple ways in order to enhance and fine-tune memory consolidation process. For example, in Pavlovian contextual fear conditioning animal models (wherein an animal quickly learns to connect a previously neutral or harmless sensory stimulus [conditioned stimulus], such as light or an auditory tone, with a concurrent aversive stimulus [unconditioned stimulus] such as a mild bodyshock) the administration of glucocorticoid receptors agonists in the BLA has been demonstrated to improve consolidation of memory, whereas antagonist may impair it [54,55]. However, glucocorticoids have been demonstrated to be unable to establish memory formation by themselves, but they act by potentiating noradrenaline G-protein-mediated actions in the amygdala neurons [55].

Thus, the most up-to-date model of emotional memory consolidation takes into account a complex interaction between adrenal stress hormones and BLA noradrenergic system in order to establish a correct memory consolidation. Adrenaline, indeed, is released by adrenal glands in response to stressful, or emotionally arousing, events. However, adrenaline cannot cross the BBB, but it may activate beta-adrenergic receptors situated on the vagal afferents of the nucleus tractus solitarii, which in turn sends direct projections to the BLA. Moreover, indirect projections from the nucleus tractus solitarii may enhance noradrenaline release from the locus coeruleus to the BLA and to other forebrain regions (e.g. hippocampus, cortex) [56]. Finally, the BLA may influence the consolidation of different kind of memories in several brain regions through its multiple projections,

for example to the nucleus striatum and to the hippocampus [57,58].

However, recent findings have demonstrated that corticosteroid-noradrenaline-mediated memory consolidation may involve other brain regions other than BLA. Indeed, the infusion of a beta-blocking drug in the medial prefrontal cortex may prevent the memory consolidation in an animal model of inhibitory avoidance [59]. Moreover, the infusion of glucocorticoids in the insular cortex may enhance memory formation in animal cognitive tasks [60].

What are the final effects of corticosteroid-mediated noradrenergic signaling potentiation in BLA? Several studies have demonstrated that the synaptic consolidation of memory consists of multiple non-genomic and genomic neuroplastic changes occurring in BLA neurons with precise time-dependence from initial stimulus. Non-genomic changes occur rapidly after stimuli and may range from a rapid rise in presynaptic glutamate release [61] to increase in AMPA glutamate receptors in postsynaptic membrane [62]. Both events may increase synaptic strength of BLA neurons. In turn, BLA projections have been demonstrated to be able to promote synaptic plasticity in other cerebral regions, as striate nucleus [63] and hippocampus [64]. Moreover, promising evidences indicate that endocannabinoids may play a role in the modulation of glucocorticoids-mediated non-genomic rapid effects on noradrenergic targets. The more recent models, indeed, demonstrated that glucocorticoids, concurrently to the enhancement of G-protein-mediated noradrenergic postsynaptic signaling, may stimulate endocannabinoids postsynaptic secretion which in turn promote the retrograde suppression of glutamate release, with the final feedback decrease of corticosteroids secretion [65].

Although the role of stress hormones interactions in memory consolidation is becoming quite clear, the pathophysiological mechanisms by which emotionally arousing memories fails to be extinguished in anxiety disorders, such as PTSD, is still controversial. According to recent neurobiology studies, PTSD is often conceptualized as a memory disorder in which a strong Pavlovian fear conditioning is not accompanied by an equally well-working fear extinction [66]. Recent studies have demonstrated that PTSD subjects, as well as healthy people who have been exposed to trauma, show significant lower levels of blood cortisol as compared to healthy subjects not exposed to traumas [67]. In PTSD diagnosed patients have been also found reduced levels of circulating endocannabinoids, positively associated with corticosteroid dysregulations in these individuals [68]. Moreover, positron emission topography studies revealed a reduced number of noradrenaline transporter in the locus coeruleus of PTSD patients than healthy subjects, and a positive correlation with PTSD severity [69]. Finally, in order to confirm the role of corticosteroids-noradrenaline interaction in PTSD pathophysiology, a recent study demonstrated that, after the exposure to negative emotional stimuli, PTSD patients show increased noradrenaline saliva levels, which are correlated to a greater intrusive negative memories recalling than healthy subjects. Moreover, the cortisol-noradrenaline saliva levels interactions may predict the recall of negative intrusive memories in these patients [70].

Animal model studies may help to better understand human findings of altered corticosteroid-noradrenaline interactions in PTSD. For instance, animals undergoing prolonged stress tend to show lower spontaneous activity of locus coeruleus neurons, but higher evoked responses and impaired recovery after the inhibition after stimulus [71]. In these animals, moreover, tyrosine hydroxylase levels appear lower than normal at baseline, but may have huge increases after stress exposure.

However, a clear characterization of PTSD models is far from be drawn. A recent PTSD model developed by Olson *et al.* [95] suggests interesting considerations on possible subclasses of PTSD pathophysiology. In rats exposed to stressful events with successive remainders (TERS, Traumatic Experience with Remainders of Stress), the Acustic Startle Response test may subdivide subjects in susceptible and resilient individuals, where resilience is not correlated to fear extinction. Interestingly, these two groups show different neural activation (measured with c-fos gene expression in diverse cerebral regions) and different responses to adrenergic blockade, thus demonstrating distinct plastic changes in noradrenergic system.

From a "synaptic" point of view, we have seen above that memory consolidation is accompanied by an increase in synaptic strength, due to both potentiation of presynaptic glutamate release and to postsynaptic AMPA receptors membrane recruitment. The development of PTSD dysregulated memory consolidation may thus derive from altered mechanisms of synaptic strengthening. Recent studies, indeed, have demonstrated that cosrticosteroids and stress, when combined with threatening events, may induce PTSD-like impairment of memory consolidation in mice [72]. Maybe, it is possible that a dysregulation in corticosteroids-noradrenaline interaction may push the formation of indelible fear memories. However, as we have seen, cortisol levels are dimished in PTSD patients. Since corticosteroids may be considered as regulators of noradrenaline functions of synaptic amygdalar strength, it could be feasible that a reduced corticosteroids-mediated control on noradrenaline response to fearful events may be unable to normalize synaptic potentiation after these events, thus triggering an exaggerated PTSD-like memory consolidation of stressful experiences.

Mechanism of Action of Prazosin in PTSD

Evidence is emerging in recent years that the therapeutic action of prazosin (and generally of drugs acting on the noradrenergic system) in PTSD has much to deal with modifications in memory trace processing, including aversive learning.

Fear responses are essential for surviving in threatening conditions, however their persistence may give raise to maladaptive behaviors. It has been suggested that altered fear inhibition may be the basis of PTSD neurobiology [73]. Similarly to other memory traces, fear memory undergoes distinct steps including: acquisition and consolidation of a new memory trace (e.g. as after a fearful experience); retrieval of the memory trace, which is followed by a labile phase, where the memory trace may be susceptible to manipulation; reconsolidation, where the memory trace is definitely stabilized after first retrieval [74]. The blockade of

reconsolidation has been recently proposed as a putative therapeutic approach in PTSD patients [75] and may be obtained by drugs that interfere with molecular mechanisms of memory formation in the early post-retrieval labile phase.

It has been shown that activation of noradrenergic system potentiates fear memory consolidation and reconsolidation. The administration of yohimbine, an α-2 receptor antagonist associated with an enhanced central noradrenergic activity, caused a marked and significant increase of freezing expression (a rodent behavior denoting fear), either when administration was carried out immediately after the acquisition or after the retrieval of a fear memory trace [76].

Blockade of postsynaptic α-1 adrenergic receptors induced by prazosin showed to disrupt the reconsolidation of fear memories [77,78]. It has been demonstrared that, in mices, fear conditioning is attenuated after prazosin microinjection in the prelimbic area of the medial prefrontal cortex (mPFC) [77], while drug conditioning is attenuated after prazosin microinjection in the BLA [78]. Prelimbic mPFC is a core cerebral region for acquisition of olfactory fear memory [79] and is strongly interconnected with BLA [80]. Both regions may therefore be crucially implicated in fear memory formation and may represent basic target sites for prazosin action. One putative mechanism by which prazosin may exert its therapeutic action is restoring PFC control over amygdala and preventing this brain nucleus to enhance its activity, which has been related to reinforcement of fear conditioning [81,82].

However, modulation of α-1 adrenergic receptors to attenuate fear memory responses should be carried out very cautiously. Indeed, prazosin has been shown in multiple paradigms to impair, rather than ameliorate, fear extinction [83,84]. Moreover, terazosin, an analog of prazosin, facilitated fear conditioning, both when given systematically and when microinjected in the lateral amygdala, before exposure to the aversive stimulus [85].

In humans, prazosin was effective in attenuating nightmares and ameliorating sleep in those suffering from PTSD. It has been observed that fear-conditioned rodents have increased rapid eye movement (REM) sleep fragmentation, which may be consistent with the report of disturbed sleep in human PTSD [86]. These observation led to the idea that prazosin may reduce REM sleep fragmentation in fear-conditioned rats. Accordingly, in fear-conditioned Wistar-Kyoto rats, administration of prazosin was associated to a significant reduction of REM sleep fragmentation [87]. Moreover, prazosin administration also significantly reduced non-REM sleep latency and non-REM sleep arousals, demonstrating that it may be useful in reducing REM sleep fragmentation and non-REM sleep discontinuity.

Prazosin has also been shown to improve alterations in startle response, which depends on the well-characterized role of the brain noradrenergic systems in attention, arousal, and vigilance [88]. Increased startle response is a main PTSD symptom, maybe caused by hyperactive noradrenergic tone associated to stress. One measure of sensorimotor gating is prepulse inhibition (PPI), i.e. the blunting of startle response when a soft prestimulus comes first the startling stimulus [89]. Manipulations of α-adrenergic receptors have been observed to affect PPI. Agonists at α-1 receptors disrupt PPI in rats, and enhanced sensitivity of these receptors has been described in sensorimotor gating deficits in neonatal rats with ventral hippocampal lesion (NVHL) [90,91]. Deletion of α-2 receptors has been observed to reduce PPI [92]. Taken together, these reports seem to implicate that an increase in noradrenergic tone may impair PPI and overall startle responses, which is consistent with a condition of hyperarousal. A recent study has investigated whether increased locus coeruleus (LC) tone may disrupt PPI [93]. Activation of LC noradrenergic fibers, by peri-LC infusion of a muscarinic cholinergic receptor agonist or a glutamate AMPA-receptor agonist, significantly disrupted PPI. These PPI deficits were completely reverted by peri-LC infusion of clonidine and, more intriguingly, by systemic administration of prazosin [93]. Therefore, pretreatment of rats by prazosin abolishes PPI deficits caused by excessive stimulation of the LC. Moreover, it has been demonstrated that prazosin administration after traumatic experience decreased acoustic startle response and aggressive behaviors and improved social interaction [94,95].

These reports may suggest that prazosin may be useful as a preventive agent to avoid the development of stress-related hyperarousal in circumstances where severe stress may be expected and may normalize maladaptive behaviors reminiscent of PTSD symptoms induced by exaggerated noradrenergic activation (and therefore by excessive α-1 adrenergic receptor-mediated postsynaptic signaling). Nonetheless, as discussed above, preclinical studies also demonstrate that the timing of prazosin administration may be crucial to impair fear extinction, to facilitate fear conditioning or, alternatively, to prevent reconsolidation of fear memory traces. These considerations may challenge the suggestion of administering prazosin before expected traumatic stress.

MATERIALS AND METHODS

Literature Search for the Systematic Review

Literature search was conducted in November, 2013. PubMed and Scopus databases were used to find studies for inclusion in the systematic review. The keywords employed for the search were: prazosin, post traumatic stress disorder, posttraumatic stress disorder and ptsd. In each search, keywords were used together with logical operators: “and”, “in”. Keywords used in the literature selection criteria are summarized in Table **1**.

Table 1. Keywords and logical operators used in the literature selection criteria.

prazosin	**and, in**	**Ptsd** Post traumatic stress disorder Posttraumatic stress disorder

The total number of articles retrieved by using PubMed and Scopus databases were two hundred and thirty four (n=234). The following criteria were adopted to select articles to introduct in the systematic review. Each study was required to meet all of the following criteria: a) diagnosis of

PTSD using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria (DSM-IV-TR) [96]; b) prazosin administration; c) randomized, placebo controlled trial. In this way, five (n=5) potentially relevant studies were obtained for the systematic review (Fig. **1**).

DDB and SM evaluated each abstract, and paper or pdf copies of any pertinent articles were obtained. All authors indipendently reviewed the publications and any disagreement in selecting the studies were determined by discussion.

Statistical Analysis

When appropriate, results of comparable studies were pooled using meta-analytical approach by means of Comprehensive Meta-Analysis Software version 2 [97]. Effect sizes (ES), with a 95% of Confidence Interval (CI), were calculated for each study included in the meta-analyses using Hedges'g unbiased approach [98]. The random effects model was used as a conservative approach to account for different sources of variation among studies. Q statistics and I-squared index were used to assess heterogeneity among study point estimates. To evaluate the influence of moderator variables on study outcomes, a meta-regression analysis was performed, using the method of moments approach.

The possibility of publication bias was examined applying the Egger's t test (with significant values based on 2-tailed p values) [99]. Fail-safe method and "trim and fill" method were also performed.

RESULTS AND DISCUSSION

Systematic Review Results

There are five published double blind, placebo controlled trials in literature that investigated the use of prazosin in PTSD [8, 100-103] (Table **2**).

Participants were different between the studies and were represented by war veterans [100,101,103], active duty soldiers [8] and civilians [102]. The authors used different scales to assess PTSD symptoms, but the common scale used in each study was represented by the Clinician-Administered PTSD Scale (CAPS). Maximum prazosin doses and studies durations varied between the studies. In the majority of patients, prazosin or placebo were added to an ongoing

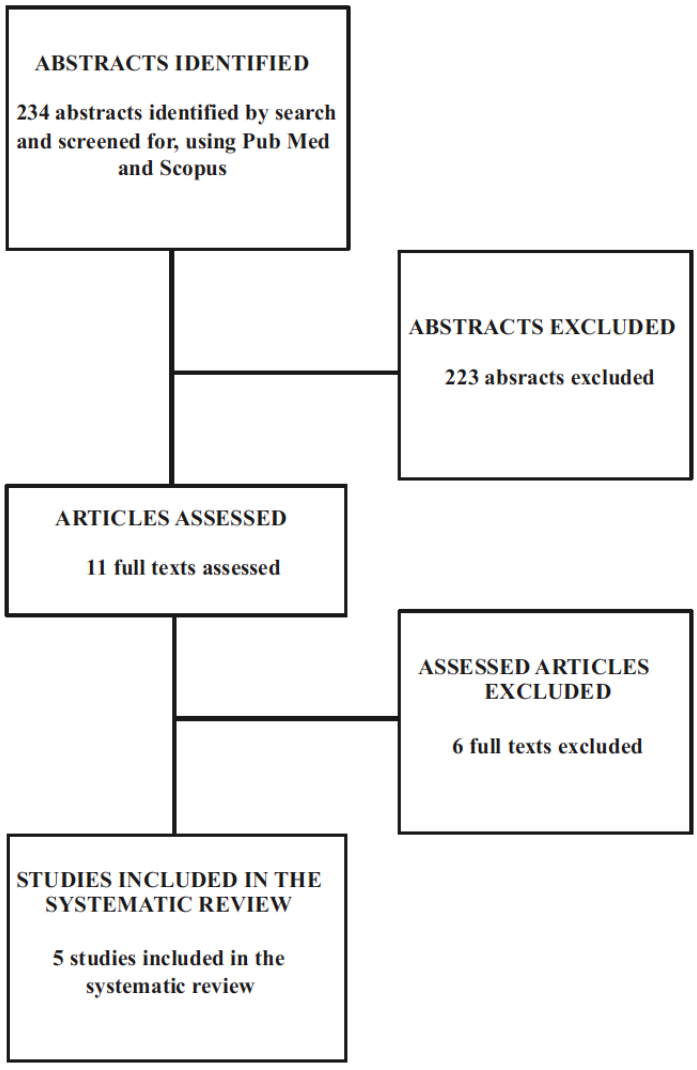

Fig. (1). Flow chart of the systematic review.

Table 2. Prazosin trials in PTSD.

Author	Study Design	Primary Outcome	Participants	Maximum Dose	Adverse Effects	Major Findings
Raskind *et al.* 2003 [100]	Randomized, double- blind, placebo- controlled; 20 wk with crossover at wk 10	CAPS, CGI-C	10 male Vietnam war veterans, age (y), 53±3	10 mg daily dose	Dizziness and mild orthostatic hypotension were reported as adverse events.	Prazosin was superior to placebo for recurrent distressing dreams item and the difficulty falling/staying asleep item of the Clinician-Administered PTSD Scale and change in overall PTSD severity and functional status according to the Clinical Global Impression of change.
Raskind *et al.* 2007 [101]	Randomized, double- blind, placebo- controlled; 8 wk	CAPS, CGI-C, PSQI	40 veterans (38 men), age (y), 56±9	15 mg daily dose	Dizziness and nasal congestion were adverse effects experienced with prazosin.	Prazosin was significantly superior to placebo for reducing trauma nightmares and improving sleep quality and global clinical status
Taylor *et al.* 2008 [102]	Randomized, double- blind, placebo- controlled; 7 wk with washout/ crossover after 3 wk	CAPS, CGI-I, NNDA, PCL-C, PDRS	13 civilians (2 men), age (y), 49±10	6 mg daily dose	Dizziness and orthostatic hypotension were similar between groups.	The use of prazosin was related to a clinical and a statistical increase in total sleep time, REM sleep time and mean REM preiod duration. Recurrent distressing dreams item of the CAPS and NNDA scales were both significantly improved. PTSD symptoms were significantly improved in the prazosin group.
Germain *et al.* 2012 [103]	Randomized, placebo comparison; 8 wk	CGI-I, ISI, PSQI, PSQI addendum for PTSD Pittsburgh Sleep Diary	50 veterans (45 men), age (y), 40.9±13.2	15 mg daily dose	Most common side effects in both the prazosin and placebo groups were drowsiness, physical tiredness, headaches, and dry mouth	Prazosin and BSI groups showed greater changes on mean weekly nightmare after treamtent
Raskind *et al.* 2013 [8]	Randomized, double- blind, placebo- controlled; 15 wk	CAPS nightmare item,PSQI	67 active-duty soldiers (57 men), age (y), 30.0 ± 6,6 (prazosin group) and 30.8 ± 6.5 (placebo group)	25 mg daily dose	Prazosin was well tolerated, and blood pressure changes did not differ between groups.	Prazosin was effective for trauma nightmares, sleep quality, global function, CAPS score, and the CAPS hyperarousal symptom cluster.

Adapted from: Kung S *et al.* [104]. ISI: Insomnia Severity Index; CAPS: Clinician-Administered PTSD Scale; CGI-I: Clinical Global Impression of Improvement; CGI-C: Clinical Global Impression of Change; NNDA: non-nightmare distressed awakening; PSQI: Pittsburg Sleep Quality Index; PCL-C: PTSD Checklist–Civilian; PDRS: PTSD Dream Rating Scale

psychopharmacological or psychotherapic treatment. Both therapies remained unchanged throughout the trials. In particular, patients who were taking other drugs for PTSD symptoms, didn't discontinue the treatment. Only in two studies [100,101] adverse effects experienced in the prazosin group were superior than in the placebo rpoup. In the other studies [8,102,103], adverse effects didn't differ between groups. One suicide ideation and one suicide attempt were reported for placebo group in Raskind *et al.* study [8].

Prazosin was reported to be significantly superior to placebo for reducing trauma nightmares [8, 100, 101, 102]. Sleep quality and overall PTSD symptoms severity significantly improved [100,101]. In contrast to previous studies, prazosin was not correlated to significant daytime PTSD symptoms reductions [102, 103]. The "distressing dreams" item of the CAPS was reduced in the prazosin group [100, 101, 102]. In Raskind *et al.* study [101], no significant improvement was seen on the Hamilton Rating Scale for Depression (HRSD). The use of prazosin was related to a clinical improvement and a statistical increase in total sleep, REM sleep time and mean REM period duration [102]. A reduction in difficulty falling or staying asleep, Clinical Global Impression of Improvement (CGI) and overall CAPS scores was found in the prazosin group [100]. Non-nightmare distressed awakenings (NNDA) scale were significantly improved [102]. Significantly improvements were reported in the prazosin group for difficulty falling or staying asleep, CGI and overall CAPS scores [100] and non-nightmare distressed awakenings (NNDA) scale scores [102]. A significant reduction in insomnia severity was observed in the prazosin and BSI groups than the placebo group [103].

Meta-Analysis Results

Data from the five studies descripted above were pooled together and different outcomes reported in at least three studies were analyzed.

As the five studies were all different in length, intermediate endpoints were not analysed. Only "end-of-the-study versus baseline" outcome or "end-of-the-study" scores (in case of not available or not comparable pre-treatment data) were considered for the meta-analysis.

The effects of the following moderators were tested for each outcome: study length, mean daily dose of prazosin, mean age of participants and percentage of males.

Analyzed Outcomes

Reduction in CAPS Distressing Dreams Item

It was reported in 4 studies [8,100,101,102]. The pooled effect size, using the random effects model was 1.07 (CI 0.73-1.41, p<0.001), favouring prazosin with respect to placebo. The heterogeneity was very low (Q=2.45 p=0.48; I-squared=0.00). The Egger's t test for publication bias was 1.19 (p=0.36), the Number of missing studies (fail-safe method) that would bring the p-value > 0.05 was 37. The estimate value did not change after Duval and Tweedie's trim and fill adjustment. None of the moderators significantly influenced the pooled effect size.

CGI-Change Difference from Baseline

It was reported in 4 studies [8,100,101,103]. The pooled effect size, using the random effects model was 0.99 (CI 0.73-1.41, p<0.001), favouring prazosin versus placebo. The estimated pooled effect, after Duval and Tweedie's trim and fill adjustment was 0.84. The heterogeneity was very low (Q=2.88 p=0.41; I-squared=0.00) and the number of missing studies (fail-safe method) that would bring p-value > 0.05 was 34. On the other end, the Egger's t test was significant (t=5.01, two tailed p=0.04), so the possibility of a publication bias could not be escluded. None of the moderators significantly influenced the pooled effect size.

Table 3. Results of the meta-analysis. Pooled effects sizes of outcomes for "prazosin versus placebo" comparison.

Outcome	No. of Studies	No. of Patients	Pooled Effect Size Hedges's g (95% CI)	Q for Heterogeneity	I-Squared	Egger's t Test for Publication Bias	Fail-Safe N
CAPS distressing dreams item – reduction from Baseline	4	130	1.01 (0.73; 1.41)[b]	2.45	0.00	1.2	37
CGI-Change from Baseline	4	130	0.99 (0.66; 1.34)[b]	2.88	0.00	5.0[a]	34
CAPS total score at end of the study	3	117	-1.96 (-4.50; 0.60)	58.47[b]	96.58	1.07	41
PSQI at end of the study	3	157	-1.92 (-4.20; 0.36)	53.24[b]	96.24	2.83	45

CAPS = Clinician Administered PTSD Scale; CGI-Change = Clinical Global Impression of Change; PSQI = Pittsburgh Sleep Quality Index; [a]p<0.05 [b]p<0.001

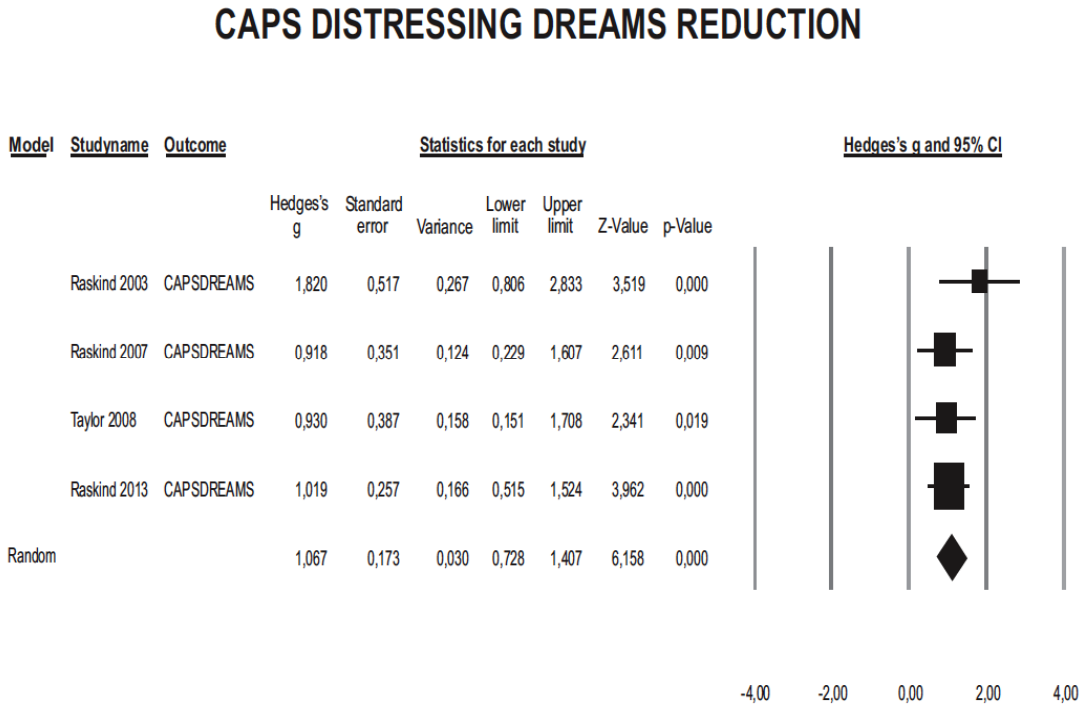

Fig. (2). Caps distressing dreams reduction.

CAPS Total Score at the End of the Study

It was reported in 3 studies [8,100,101]. The pooled effect size, using the random effects model was -1.96 (CI -4.50; 0.60, p=0.13), failing to reach the significance threshold. The estimated pooled effect, after Duval and Tweedie's trim and fill adjustment, did not change. The number of missing studies (fail-safe method) that would bring p-value > 0.05 was 41. The Egger's t test for publication bias was not significant (t=1.07, two tailed p=0.48). The heterogeneity was extremely high (Q=58.47 p<0.001; I-squared=96.58). A significant influence of the following moderators found on the pooled effect size: age of participants (beta=0.17, p<0.001), and percentage of males (beta=0.28, p<0.05), thus suggesting a higher efficacy of prazosin on younger participants and when more females were enrolled in the studies.

PSQI at the End of the Study

It was reported in 3 studies [8,101,102]. The pooled effect size, using the random effects model was -1.92 (CI -

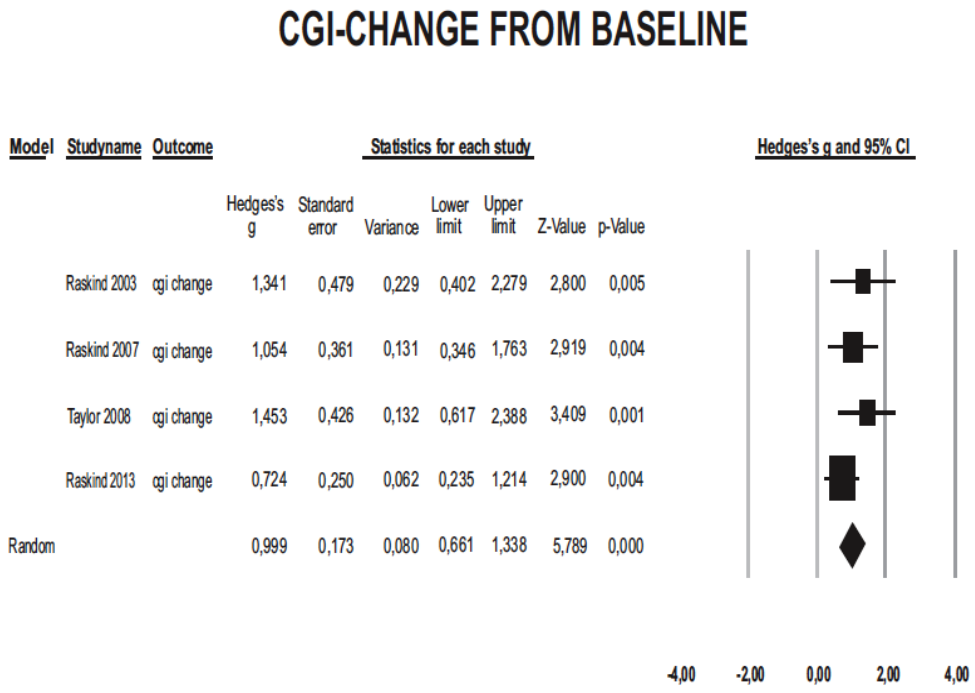

Fig. (3). CGI change.

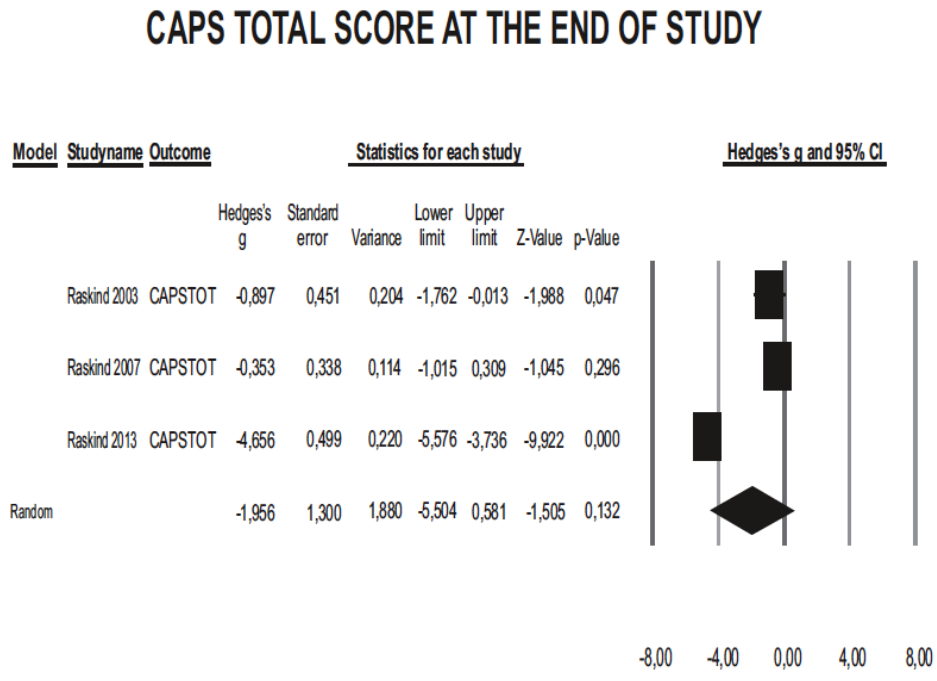

Fig. (4). Caps total score.

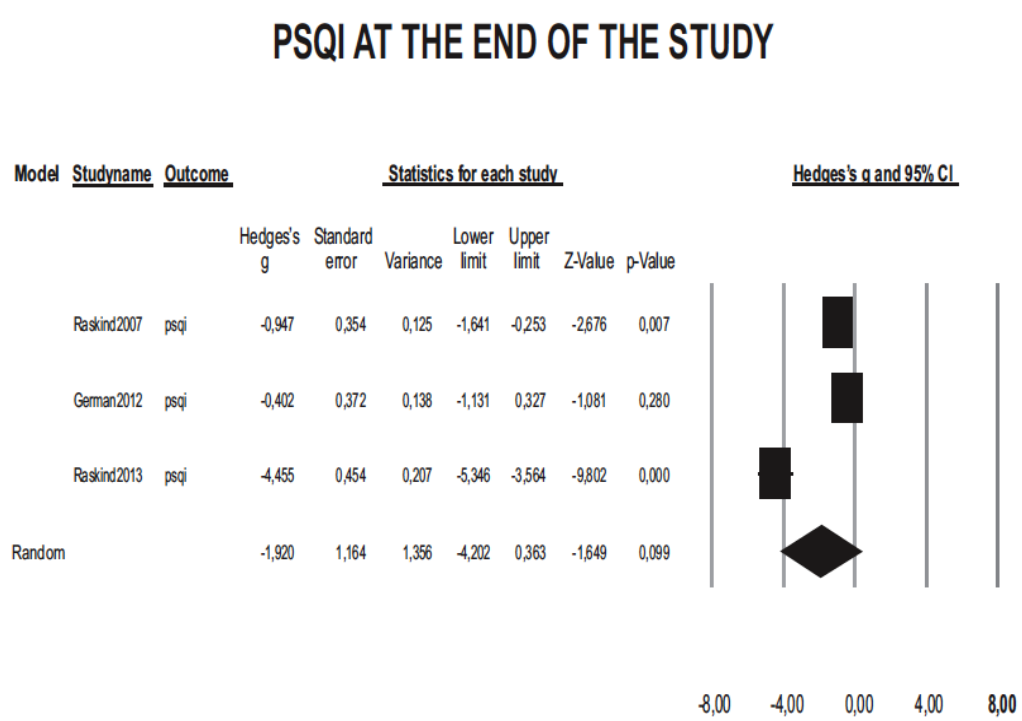

Fig. (5). PSQI at study end.

4.20; 0.36, p=0.10), and was therefore not significant. Duval and Tweedie's trim and fill adjustment did not changed the estimated effect. The number of missing studies (fail-safe method) that would bring p-value > 0.05 was 45 and the Egger's t test for publication bias was not significant (t=2.83, two tailed p=0.22). The heterogeneity was extremely high (Q=53.24 p<0.001; I-squared=96.24). None of the moderators significantly influenced the pooled effect size.

CONCLUSION

The noradrenergic system may be considered as having the leading role in memory formation, as well as in the pathophysiology of psychiatric disorders in which memory consolidation and recalling are disrupted, such as PTSD [81, 94]. Moreover, the modulation of this system may also be effective in treating sleep disturbances that are core symptoms of PTSD [8].

Evidence has emerged in recent years that the therapeutic action of prazosin (and generally of drugs acting on the noradrenergic system) in PTSD has much to deal with modifications in memory trace processing, including aversive learning and normalization of sleep disturbances associated with PTSD. Overall, the results of this systematic review and meta-analysis support the notion that prazosin, a selective α-1-adrenergic blocker, may be effective in the management of PTSD and was generally well tolerated in such patients. In particular, summarizing the meta-analysis results, prazosin was found significatively more efficacious than placebo in reducing CAPS distressing dreams items. The CGI-C also seemed to favour prazosin with respect to placebo, but results should be interpreted with caution due to the possibility of publication bias. The other two analyzed outcomes (CAPS total score and PSQI score at the end of the study) did not reach the statistical significance. On the other hand, important limitations of the meta-analysis were the small number of studies entered in the quantitative synthesis and the heterogeneity of measured outcomes, so other original studies on larger samples with longer follow-up are needed to better clarify the efficacy of prazosin in PTSD.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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