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# The Impact of Cognitive-Behavioral Therapies for Nightmares and Prazosin on the Reduction of Post-Traumatic Nightmares, Sleep, and PTSD Symptoms: A Systematic Review and Meta-Analysis of Randomized and Non-Randomized Studies

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/64224>

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## Abstract

Post-traumatic nightmares (PTNMs) can be treatment resistant to conventional treatments for post-traumatic stress disorder (PTSD). New cognitive and behavioral treatments (CBTs) for nightmares (NM) and pharmacological treatments, such as Prazosin, have been developed to directly reduce PTNMs. *Objectives:* The first objective was to evaluate the impact of CBTs for NM and Prazosin on the reduction of PTNMs in an adult population. A second aim was to explore the impact of these treatments in general PTSD symptoms and sleep. *Method:* A systematic search of English and French clinical studies on any CBTs and Prazosin treatments for PTNMs published from 1980 to 2012 was conducted in PsycINFO, MedLine, PILOTS, and ProQuest Dissertations and Theses. *Results:* The final sample was composed of 26 studies. The combined effect size (ES) for Prazosin was  $g = 1.30$ , 95% CI [0.61, 2.00], and for CBTs, it was  $g = 0.55$ , 95% CI [0.38, 0.72]. *Conclusions:* Prazosin had a large impact on PTNM reduction, while CBTs had a moderate impact. Specific NM treatments (Prazosin or CBTs) contribute to PTNM reduction and reduce PTSD and sleep symptoms. These findings are significant to the literature on PTSD and future studies should consider them. Several recommendations are proposed.

**Keywords:** CBT, meta-analysis, nightmare, Prazosin, trauma

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# 1. Introduction

## 1.1. PTSD and nightmares

Nightmares (NM) are one of the intrusion symptom clusters of post-traumatic stress disorder (PTSD) in the fifth edition *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [1]. The prevalence of frequent NM is 70% in individuals with PTSD compared to only 2–5% in the general population [2]. Post-traumatic nightmares (PTNMs) are different from “normal” dreams as they are recurrent frightening dreams of past traumatic events [3]. Their content may vary from an exact replay to only some components of the trauma, such as changes in time and place [3]. Another distinction is their role in PTSD. In the general population, sleep loss impacts daily functioning due to fatigue and cognitive difficulties [4], leading to poor quality of life [5]. However, in the particular PTSD context, the presence of NM seems to be related to PTSD prevalence and severity [6], and therefore, to contribute to the development of PTSD. They could even contribute to PTSD symptom maintenance [7].

PTSD used to be considered as an anxiety disorder in the fourth edition revised *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) [8]. Now, it is part of the trauma- and stressor-related disorders in the DSM-5 [1]. Several meta-analyses, systematic reviews, and guidelines underline that general trauma-focused cognitive and behavioral treatments (CBTs) (through exposure and cognitive restructuring) are superior, or equivalent, to other types of psychological treatments, such as eye movement desensitization and reprocessing (EMDR), psychodynamic psychotherapies, or supportive techniques (e.g., [9]). They also emphasize the efficacy of selective serotonin reuptake inhibitors (SSRIs) as a pharmacological treatment [10]. However, studies also reveal that CBTs and SSRIs do not effectively resolve all PTSD symptoms in individuals who no longer meet PTSD diagnosis criteria. In fact, NMs were found to be treatment resistant, and residual insomnia was also reported [11, 12].

## 1.2. Emergence of treatments directly targeting nightmares

One approach is to conceptualize NMs in two steps after a traumatic event. First, right after the trauma, NMs would be considered as trauma-induced and would be a PTSD symptom. Later, at a second stage, they would become a learned behavior distinct from PTSD symptoms. The idea is that the person, by fearing and avoiding NM content, cannot process the information related to the event and cannot incorporate it [13]. As these NMs disrupt sleep, it can be difficult for the victims to return to sleep and they may adopt unsuitable sleep hygiene, which could lead to insomnia [14]. Therefore, new psychological and pharmacological treatments are emerging and tested to directly reduce NMs.

Recently, the Standards of Practice Committee (SPC) of the American Academy of Sleep Medicine (AASM) commissioned a task force to assess the literature on the treatment of NM disorder in general. They presented their recommendations in a Best practice guide about pharmacotherapies and CBTs for NM for adults [15, 16]. Their classification was based on study designs from “level 1” (high-quality randomized clinical trials with narrow confidence intervals) to “level 4” (case series or poor case-control studies or poor cohort studies or case

reports). Their suggestions were made according to a level of recommendation from “level A” (treatment recommended—level 1 or 2) to “level C” (treatments that may be considered—level 3 or 4). Their recommendations concerned both psychological and pharmacological treatments.

Regarding the medications conclusions, Prazosin was given an “A level recommendation” compared to antidepressants, anxiolytics, anticonvulsants, and antipsychotics. Prazosin is an  $\alpha_1$ -adrenergic receptor antagonist, which was first introduced as a treatment for high blood pressure in 1970. It reduces the adrenergic response and has the advantage of crossing the blood-brain barrier. We know that stimulation of  $\alpha_1$  receptors induces the primitive fear response, disrupts rapid eye movement (REM) sleep, and increases non-REM sleep. We believe that Prazosin exerts its effect through a mechanism that blocks the primitive fear responses by antagonizing the  $\alpha_1$  receptors in the CNS and decreasing PTNMs [17].

In addition, the Best practice guide lists six specific CBTs for NMs: imagery rehearsal therapy (IRT) (Level A), systematic desensitization (Level B), lucid dreaming therapy (LDT) (Level C), exposure, relaxation, and rescripting therapy (ERRT) (Level B), sleep dynamic therapy (Level C), and self-exposure therapy (Level C). These CBTs conceptualize NMs as a learned behavior, but each treatment approaches them differently. The IRT rationale is to select a repetitive NM, to transform and write it into a new dream, and finally to rehearse it in imagination. The idea is to gain control over the NM. The ERRT model is to expose the person to his original nightmare content a little further than IRT. The participant has to write down his original NM and to identify traumatic themes that will be used when rescripting and rehearsing it. Going further than IRT, it also incorporates sleep hygiene education and modification, and relaxation for insomnia. Contrary to IRT and ERRT, LDT will train individuals to become aware that they are dreaming while they are actually dreaming and to change the scenario [18].

### 1.3. Objectives

The first objective of this chapter is to review and evaluate the impact of CBTs compared to Prazosin for NM reduction, after a traumatic event in an adult population. The secondary objective is to evaluate the impact of both types of interventions on other PTSD symptoms and sleep.

## 2. Method

### 2.1. Search strategy

Studies published from 1980 (with the introduction of PTSD in the DSM-III) to the end of December 2012 were identified by searching the electronic databases MedLine, PsycINFO, PILOTS, and ProQuest Dissertations and theses databases [19] to identify relevant studies evaluating the impact of CBT and Prazosin on PTNMs in an adult population. Each search was separately run using the following command in all fields: (treatment OR therapy OR Prazosin OR cognitive OR behav\* OR CBT) AND (nightmare\* OR dream\*) with the asterisk specifying

the plural and grammatical variations. We also scanned reference lists of relevant meta-analyses, systematic reviews, and reference lists of each study included in this meta-analysis.

## 2.2. Eligibility criteria

To be included in the meta-analysis, studies must have met the following criteria: (a) they reported quantitative treatment outcomes for NMs (such as frequencies or questionnaires' scores) occurring after a traumatic event; (b) at least one group received CBT or Prazosin treatment for NM; (c) the study either had a group protocol or was a case study of at least three participants; (d) the participants were 18 years old and above; (e) all the participants presented PTSD symptoms (evaluated by validated questionnaires or by a clinical and structured interview) and PTNM complaints; (f) the study was published between 1980 and 2012; and (g) the study was published in English or in French. Studies were excluded if they were (a) abstracts of posters and (b) did not report original results.

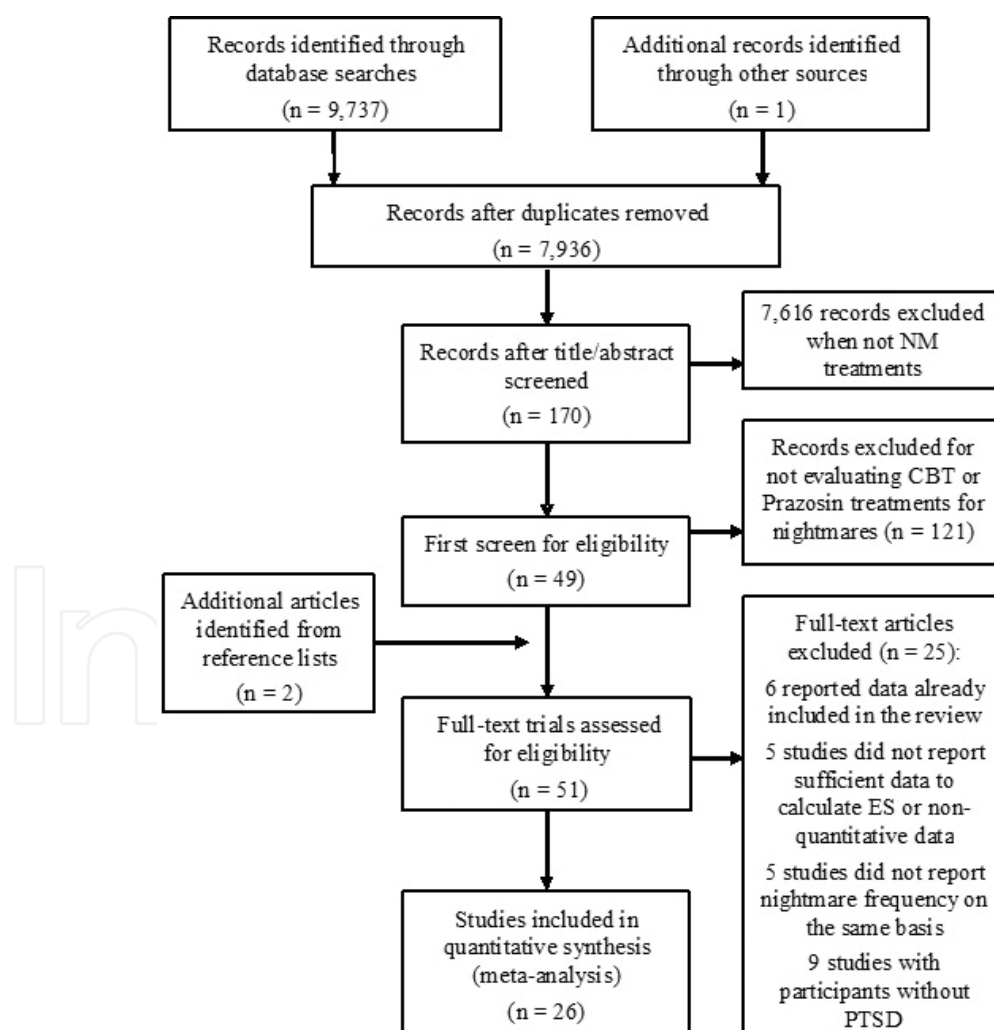
## 2.3. Data extraction

Information was extracted from each eligible record using a data extraction sheet adapted from previous meta-analyses [11, 20]. Data extracted were: (i) study identification (e.g., authors and publication date); (ii) study description (e.g., protocol sampling, assignment of participants, and research reports following CONSORT statement for randomized studies [21]); (iii) sample characteristics (i.e., sample size, gender, mean age and standard deviation, PTSD and acute stress disorder (ASD) diagnoses, records of PTSD treatments, trauma type, trauma date of occurrence, nightmare definition, nightmare frequency, nightmare intensity, nightmare content, explicit report of sleep difficulties other than nightmares, reports of comorbidity, and attrition rate); and (iv) the type of intervention for NMs at large was also reported (i.e., IRT, IRET, ERRT, LDT, relaxation, exposition, desensitization, EMDR, Prazosin, and any other CBTs for NMs). CBTs for NMs were defined as incorporating cognitive (new dream rehearsal, restructuration, etc.) and/or behavioral strategies (progressive muscle relaxation, gradual exposure, etc.), contrasting with other approaches, such as dream interpretation. We recorded the number of therapy sessions, duration, the therapy modality (i.e., individual psychotherapy, in groups, at distance with or without any contact), the presence of a therapy protocol, the therapist's training (psychologist, graduates in psychology, other medical professionals, other), and whether the CBT treatment also targeted PTSD and insomnia problems in addition to NMs. For Prazosin studies, trade names of Prazosin (Minipress, Vasoflex, Pressin, and Hypovase) were considered in the study screening and we extracted the average prescription (in mg/day), the timing of the prescription, the presence of a protocol for the prescription, and the presence of a washout period at follow-up. (v) In addition, the type of NMs, PTSD and insomnia outcome and measures were coded as either (a) clinic interview, (b) daily self-monitory, (c) EEG for NMs and insomnia, (d) validated questionnaires, (e) subscales from questionnaires, (f) isolated items from questionnaires or interviews, or (g) survey. And, finally, (vi) information was gathered to calculate the following three types of effect sizes: group comparison on post-treatment data (between-group analysis), pre- vs. post-treatment data for

groups receiving CBT or Prazosin (within group-group analysis), and pre- vs. post-treatment data for control groups.

## 2.4. Inter-rater agreement

In order to evaluate inter-rater reliability and to control for data extraction bias, each study was systematically checked by pairs of independent reviewers. Their results were compared and any disagreements were resolved by discussion. Before beginning the coding process, the rating instrument was tested with the four raters going through the coding form and checking one article testing CBT and one trial studying Prazosin together. Judges were students enrolled in a PhD program in psychology. The inter-rater reliability was good and varied from 58.3% to 100%. The strongest agreements were related to sampling method and treatment type while the lowest referred to attrition and female percentages, which may reveal inconsistencies in reporting. The final sample was composed of 26 studies published in English: 8 studies on Prazosin [22–29] and 18 studies on CBT for NM [6, 30–46] (**Figure 1**).



**Figure 1.** Search strategy flowchart.



## 2.5. Data analyses

The meta-analyses were performed using the random-effects model [47]. The analyses were conducted with *Comprehensive Meta-Analysis (Version 2)* [48]. Effect sizes (ES) were computed with Hedges'  $g$  between groups using mean and standard deviation (SD) [47] except for one study where they were obtained from  $t$  values [37]. When available, quantitative analyses were performed on the difference between the experimental and control groups at post-treatment (between-group); otherwise analyses were computed on pre- and post-data for the same group (within-group). As in the last case, the correlation coefficient  $r$  between pre- and post-test for each data is needed, and as this information was missing,  $r$  was set to 0 in order to be conservative and to give to these studies the smallest and the same weight, so there will be no bias in weighting [47]. However, we executed sensitivity analysis using a range of plausible correlations (0; 0.5 and 0.95) and the results did not significantly differ between each correlation. The direction of the ES was set as positive when NMs, PTSD symptoms, and sleep variables were improved at post-treatment or for the experimental compared to the control group at post-treatment. ES were not computed at follow-up due to disparities in reporting these data for CBT studies, and only one Prazosin study provided them.

For the NMs variable, effect sizes were calculated based on means and SD of weekly NM frequency for CBT studies; and on the CAPS-B2 final scores (item B2 on the *Clinician Administered PTSD Scale*) for Prazosin studies. The CAPS-B2 item sums up the frequency and the intensity (from 0 to 4) of recurrent distressing dreams related to the traumatic event (refer to Blake et al. [49] for a scale description). When these NMs were reported by month or by night, we computed their mean by the week. Effect sizes were also computed for PTSD symptoms. For CBTs, we considered any questionnaire evaluating the construct of PTSD symptoms intensity: *impact of event scale* (IES-R [50]), *PTSD Checklist—Civilian and Military Versions* (PCL [51]), *post-traumatic symptom scale* (PSS [52]), and *post-traumatic diagnostic scale* (PDS [53]). For Prazosin, we used the scores of the PCL and the CAPS. Finally, ES were calculated for sleep difficulties using (1) the CAPS-D1 (CAPS, item D1) final score (sum of the frequency and intensity) for Prazosin and (2) scores on the *Pittsburgh Sleep Quality Index* (PSQI) [54] for CBTs. Computations were also possible for the insomnia construct, as data Pertained only to CBT studies, using scores on the *Sleep Impairment Index* (SII [55]).

We used the data, if available, on an intent-to-treat basis (patients who were enrolled and randomly allocated to treatment), otherwise variables were selected on a completer basis. Also, as a few study designs did not implement immediate post-evaluation and rather evaluated the interventions at follow-up, we decided to include them in the analysis if follow-ups were less than three months after the end of the treatment. Each effect size (and the combined effect size) was calculated with 95% confidence intervals.

We tested for heterogeneity with the  $Q$  test and the proportion of true variance was assessed with the  $I^2$  index for each computed ES.  $Q$  tests were also used for contrast analyses. Also, due to problems of power in this meta-analysis (less than 20 studies) ( $n = 8$  for Prazosin;  $n = 18$  for CBT studies), we computed the 95% confidence intervals (95% CI) for the  $I^2$  index [56, 57]. Heterogeneity was detected when  $Q$  test was significant ( $p < 0.05$ ) or  $I^2$  index was higher than

50% [56]. In this case, sensitivity analyses and ES comparison across subgroups (subgroup analyses) were performed using the random effect model. Finally, to test for possible publication biases, funnel plots evaluating the association between the Hedges'  $g$  and the standard error were visually assessed [58]. In addition, Orwin fail-safe  $N$  tests [59] were computed to estimate the number of studies with no effect necessary to reduce the combined ES to a clinically nonsignificant value (0.2).

### 3. Results

#### 3.1. Characteristics of the studies

Three Prazosin and 10 CBT studies used between-group comparison and randomization to assign participants except for one Prazosin study. However, no randomized Studies specified when they fulfilled CONSORT criteria [21]. Their comparison groups were placebo treatment, waiting list, or no active treatment. All studies used a convenience population sample. Eight Prazosin and 13 CBT studies had immediate post-evaluation. Only one Prazosin and 11 CBT studies reported data at follow-up.

Author, year	Mean dosage achieved (mg/day)(SD)	Time of prescription (in weeks)	Procedure for dosage	Tapering mentioned
Boynton et al., 2009	2.30 (1.40)	8	Yes	–
Calohan et al., 2010	4.10 (2.20)	–	Yes	No
Peskind et al., 2003	2.30 (0.70)	8	Yes	No
Raskind et al., 2002	9.60 (0.90)	8	Yes	No
Raskind et al., 2003	9.50 (0.50)	9	Yes	Yes
Raskind et al., 2007	13.30 (3.00)	8	Yes	No
Taylor et al., 2008	3.10 (1.30)	3	Yes	Yes
Thompson et al., 2008	9.60 (6.00)	–	Yes	–

**Table 1.** Treatment characteristics for Prazosin studies.

There was a large variation in the total sample sizes from  $n = 9$  to  $n = 51$ , or a total of 181 participants for Prazosin studies; and a variation from  $n = 4$  to  $n = 278$  for CBTs, or a total of 1169 participants. We also observed a variation in female proportions: from 0% to 84.62% in Prazosin treatments, and from 0% to 100 % in CBTs. Mean ages varied from  $M = 26.69$  to  $M = 76.00$  for Prazosin, and  $M = 36.17$  to  $M = 59.42$  for CBTs. The attrition rates varied from 0% to 40% for Prazosin and from 0% to 53.85% for CBTs. The percentage of participants who did not finish the treatment did not differ by type of treatment (Prazosin or CBT) ( $p = 0.08$ ). The first most common trauma for both types of studies was combat experience, followed by



sexual assault and mixed trauma. No studies recorded medical comorbidities. To evaluate the impact of Prazosin on PTSD symptoms, only two studies reported global score for PTSD questionnaires. CBTs studies mainly used questionnaires related to PTSD symptom intensity (such as the PTSD Checklist Civilian Version). Finally, four Prazosin studies used the CAPS and more precisely its item D1 for sleep disturbance related to PTSD, and one study used the PSQI to evaluate sleep quality at large.

Author, year	Type of CBT	No. of sessions	Mean duration (min)	Delivery	Therapists	PTSD addressed	Insomnia addressed
Cook et al., 2010	IRT	6	90	GROUP	PSY and OTHER	No	No
Davis & Wright, 2005b	ERRT	3	120	GROUP	–	No	Yes
Davis & Wright, 2007	ERRT	3	120	IND/GROUP	–	No	Yes
Davis et al., 2011	ERRT	3	120	IND/GROUP	–	No	Yes
Forbes et al., 2001	IRT	6	90	GROUP	PSY	No	No
Germain & Nielsen, 2003	IRT	1	180	GROUP	–	No	No
Germain et al., 2012	IRT	8	45	IND	STU	No	Yes
Gerlinde C. Harb et al., 2009	IRT	7.5	–	IND	PSY and OTHER	No	Yes
Krakow, Johnston, et al., 2001	IRT	3	200	GROUP	OTHER	No	Yes
Krakow et al., 2000	IRT	3	140	GROUP	–	No	No
Krakow, Hollifield, et al., 2001	IRT	3	140	GROUP	OTHER	No	Yes
Lancee et al., 2010	IRT/IRT+ SH/IRT +SH+LDT	–	–	REMOTE	–	No	NA
Lu et al., 2009	IRT	6	90	GROUP	PSY and OTHER	No	–
Nappi et al., 2010	IRT	5	90	IND/GROUP	SPY and STU	No	No
Pruiksma, 2011	ERRT	3	105	IND/GROUP	SPY and STU	No	Yes

Author, year	Type of CBT	No. of sessions	Mean duration (min)	Delivery	Therapists	PTSD addressed	Insomnia addressed
Swanson et al., 2009	ERRT	10	90	GROUP	PSY	No	Yes
Thunker & Pietrowsky, 2012	IRT	8	50	–	–	No	No
Ulmer et al., 2011	IRT	6	60	IND	PSY	No	Yes

*Note.* ERRT: exposure, relaxation and rescripting therapy; IRT: imagery rehearsal therapy; LDT: lucid dreaming therapy; OTHER: other professions (e.g., nurse, physician); NA: not applicable; PSY: psychologist; SH: sleep hygiene; STU: graduate student in psychology; REMOTE: treatment administered remotely (e.g., mail, Internet, video).

**Table 2.** Characteristics of CBT studies.

**Tables 1 and 2**, respectively, present treatment characteristics for Prazosin and CBT studies. In **Table 1**, the mean dosage of Prazosin varies from  $M = 2.30$  to  $M = 13.30$  mg/day with a time of prescription ranging from three to nine weeks. All studies provided a procedure to initiate a stable Prazosin dosage but only two studies described a tapering process.

In **Table 2**, 13 studies looked at IRT efficacy, 5 at ERRT, 1 at IRT incorporating sleep hygiene (SH), and another at IRT incorporating SH and LDT. The mean number of sessions was 5 (from 1 session to 10 sessions), and they lasted from 45 to 140 minutes. They were mainly delivered in a group format by a psychologist. None of the therapies directly addressed PTSD, but half of them specifically addressed insomnia (since the ERRT protocol automatically incorporates the reduction of bad sleep habits).

Regarding NM definitions employed in each study, we noticed that all Prazosin studies used the DSM-IV-TR definition based on the CAPS-B2. It contrasts with CBT studies where they varied between articles, some applying the DSM-IV-TR definition, their own definition, or not providing one. Concerning NM frequency as an inclusion criterion, Prazosin studies employed the CAPS-B2 with a cutoff varying from three to six out of eight. For CBT studies, the criterion used most often was at least one NM per week in the last month or in the last six months. Finally, concerning NM content, as Prazosin studies referred to the CAPS-B2, NMs were related to trauma but it was not specified if they were a replica of the event or only trauma-related. In CBT studies, a few authors gave this information, as in Cook et al. [30] where NM were replica or in Forbes et al. [34] with only trauma-related NM.

### 3.2. Effect size summary on PTNMs

ES for Prazosin evaluated by the CAPS-B2 (weekly PTNMs in the last month) varied from a small effect (0.28) to a large effect (3.91) (see **Figure 2**). The combined ES was to  $g = 1.30$ , 95% CI [0.61, 2.00], which indicates a significant large effect ( $Z = 3.66$ ,  $p < 0.001$ ). There was signif-

icant heterogeneity in ES across samples ( $Q(6) = 21.38, p < 0.001$ ) and a significant 72% of the total variability among ES indicates that the inconsistency between studies is high ( $I^2 = 71.93$ , 95% CI [39.21, 87.04]).

Initially, ES was computed with one additional study [25]. After an outcome sensitivity analysis, homogeneity appeared to be affected by the result of this specific study, which also conflicted with the rest of the studies. We, therefore, decided to compute Prazosin combined ES without it.

Regarding subgroup analyses (group comparison and mean dosage subgroups), no significant differences were found. However, the small number of studies and, therefore, the loss of power could explain nonsignificant heterogeneity within each subgroup [56] while differences could be observed (e.g., “under 5 mg,” vs. “between 5 and 10 mg”).

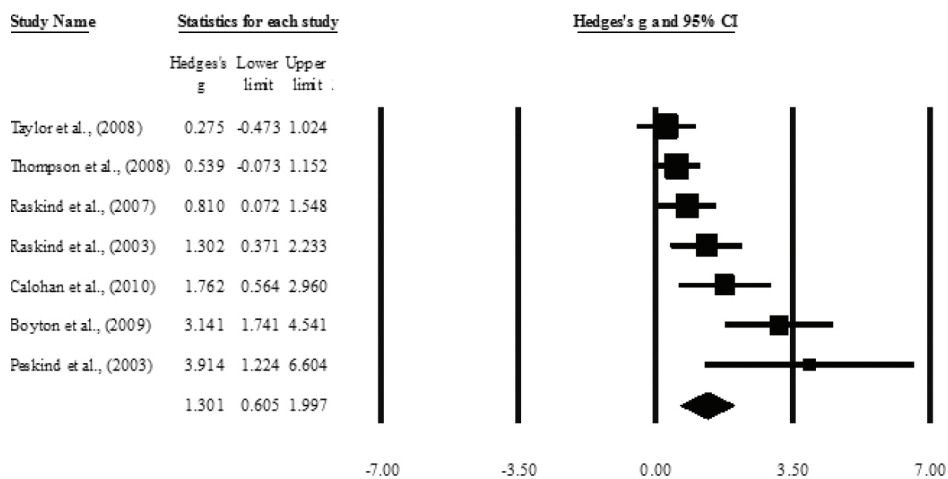
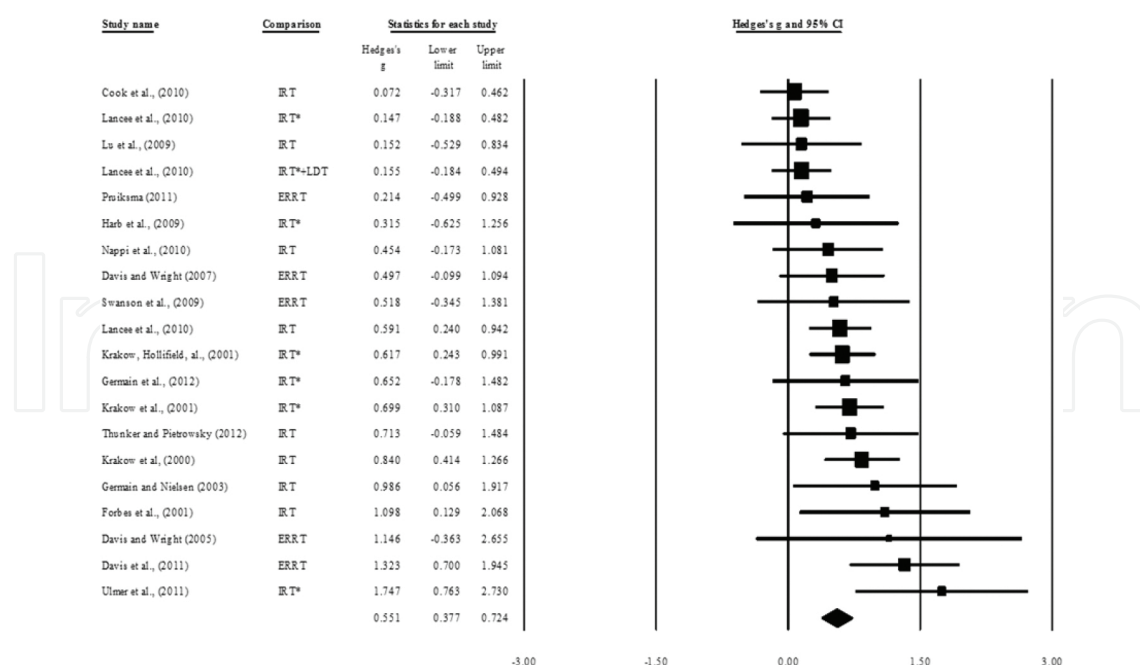


Figure 2. Results of meta-analysis for Prazosin studies using the CAPS-B2 and under the Random-effect model.

Figure 3 reports the ES summary for CBT studies on weekly PTNM frequency. We noticed ES varied from a small effect (0.07) to a large effect (1.75). The combined ES was  $g = 0.55$ , 95% CI [0.38, 0.72], which indicates a significant moderate effect size for CBTs on weekly PTNM frequency ( $Z = 6.21, p < 0.001$ ). There was significant heterogeneity in ES across samples ( $Q(19) = 35.26, p < 0.05$ ) with a moderate amount of observed heterogeneity (46%). The inconsistency between studies was moderately high ( $I^2 = 46.12$ ). Subgroup analyses did not reveal any statistical differences between studies. As mentioned before, this result may be due to loss of power rather than to homogeneity alone.

3.3. Secondary effect size summary

Concerning the PTSD symptoms, the ES for three studies varied from a small effect (0.27) to a large effect (0.88). Their combined ES was  $g = 0.58$ , 95% CI [0.12, 1.04] and was significant for CBT on PTSD symptoms ( $Z = 2.45, p < 0.05$ ). The analysis found homogeneity in ES across samples ( $Q(2) = 1.18, p = 0.55$ ). The amount of observed heterogeneity was null (0%), and therefore, there was no inconsistency between the studies ( $I^2 = 0.00$ ).



**Figure 3.** Results of meta-analysis for CBT studies on weekly NM frequency and under the Random-effect model.

For the PSQI variable, ES varied from a medium effect (0.71) to a large effect (0.98). The combined ES was  $g = 0.83$ , 95% CI [0.32, 1.35], which indicates a significant and large effect of Prazosin treatment on sleep quality ( $Z = 3.16$ ,  $p < 0.05$ ). There was nonsignificant heterogeneity in ES across samples ( $Q(1) = 0.30$ ,  $p = 0.58$ ). The amount of observed heterogeneity was null (0%), and therefore, there was no inconsistency between the studies ( $I^2 = 0.00$ ).

Regarding the CAPS-D1 variable, ES varied from a medium effect (0.48) to a large effect (1.74). The combined ES was  $g = 1.26$ , 95% CI [0.62, 1.89], indicating a significant large effect of Prazosin on PTSD sleep difficulties ( $Z = 3.88$ ,  $p < 0.001$ ). There was nonsignificant heterogeneity in ES across samples ( $Q(3) = 5.59$ ,  $p = 0.133$ ). The amount of observed heterogeneity was moderate (46%) and confirmed that inconsistency between studies was moderately large ( $I^2 = 46.36$ ).

The impact of CBTs on the intensity of PTSD symptoms varied from small ES (0.02) to large ES (1.46). The combined ES in 16 studies was  $g = 0.59$ , 95% CI [0.38, 0.80], which indicates a significant large effect ( $Z = 5.47$ ,  $p < 0.001$ ). There was significant heterogeneity between studies ( $Q(15) = 35.24$ ,  $p < 0.05$ ) and a significant 57% of the total of the variance among ES indicates that inconsistency between studies was moderately large ( $I^2 = 57.43$ ). Subgroup analyses did not reveal any statistical differences between them. Previously, the amount of the observed heterogeneity was higher (75%) and could be related to high heterogeneity across studies ( $I^2 = 74.68$ ). There was also a significant heterogeneity in ES across samples ( $Q(16) = 63.19$ ,  $p < 0.001$ ). ES varied from small ES (0.02) to large (5.70) and the combined ES across 17 studies was  $g = 0.69$ , 95% CI [0.42, 0.97], which indicated a significant moderate effect for CBTs ( $Z = 4.96$ ,  $p < 0.001$ ). Therefore, an outcome sensitivity analysis between studies was performed. Homogeneity was affected by the result of the Ulmer et al.'s study (2011) [46], which conflicts (5.70) with the rest of the studies and we therefore decided to compute the combined ES without this study.

Concerning the impact on PSQI outcome, ES varied from 0.07 to 4.63. The combined ES computed for 14 studies was  $g = 0.95$ , 95% CI [0.56, 1.34], which indicated a significant large CBT effect ( $Z = 4.78$ ,  $p < 0.001$ ). There was significant heterogeneity in ES across samples ( $Q(13) = 66.27$ ,  $p < 0.001$ ). The amount of observed heterogeneity was high (80%) and can be associated with true variance across studies ( $I^2 = 80.39$ ). Therefore, an outcome sensitivity analysis between studies was performed and no studies appeared to influence heterogeneity. No statistical differences between subgroup analyses were found, except for the subgroup insomnia, which was marginally significant with  $Q(1) = 3.39$ ,  $p = 0.07$ . It appeared that the addition of one sleep management component has a better effect on PSQI.

Another impact on sleep is insomnia where ES varied from 0.72 to 1.77. The combined ES, computed for six studies, was  $g = 1.06$ , 95% CI [0.78, 1.34], which represents a significant large effect of CBTs ( $Z = 7.41$ ,  $p < 0.001$ ). There was no significant heterogeneity in ES across samples ( $Q(5) = 2.69$ ,  $p = 0.75$ ). The amount of observed heterogeneity was null (0%), and therefore, there was no inconsistency between the studies ( $I^2 = 0.00$ ).

### 3.4. Publication bias

The shapes of the funnel plots of Prazosin outcomes (CAPS-B2, PTSD symptoms, and CAPS-D1) gave some indications of publication bias. The Orwin fail-safe test revealed that 27 studies for CAPS-B2, 6 studies for PTSD symptoms, and 20 studies for CAPS-D1 with a null effect should theoretically be added to the analysis to obtain a combined ES of 0.2. The funnel plots did not reveal any publication biases, and the Orwin fail-safe test results were large for CAPS-B2 and CAPS-D1. Therefore, the results from these two outcomes in this meta-analysis are valid and publication biases are negligible. However, caution is advised when interpreting the results for PTSD symptoms, given that six studies are sufficient to invalidate the analyses. Also, it was not possible to run publication bias analyses for PSQI, as we only had two studies.

The funnel plot shapes for CBTs indicated a limited effect of publication bias on the results. Also, Orwin fail-safe test results were 30 for weekly NM frequency, 30 for PTSD intensity, 43 for PSQI, and 26 for insomnia measure. As the funnel plots did not reveal any publication biases, and the Orwin fail-safe test results were large, we therefore concluded that CBT results from this meta-analysis are valid and publication biases are negligible.

## 4. Discussion

### 4.1. Search results

Fifty-one studies considered treatments specifically targeting PTNMs in an adult population, and 26 studies reported data and were, therefore, included in this meta-analysis. Out of eight Prazosin studies, only three reported data on PTSD symptoms, two on sleep difficulties (using the PSQI), and four on insomnia (using the CAPS-D1). Of the 18 CBTs, 17 reported data on PTSD symptoms, 14 on sleep difficulties with the PSQI, and 6 on insomnia (using the ISI and SII). We also noticed a tendency for ERRT, IRT, or Prazosin studies to be conducted by the same



research teams [27, 40, 60]. In fact, five out of eight teams working on Prazosin effect were from the University of Washington in Seattle. Of the 18 CBT studies for nightmares, 4 were issued from the University of Tulsa and 2 from the University of Philadelphia. Also, these studies were mostly published after 2000. This small number of studies is not surprising, as PTSD study in psychology and in PTNM research is quite new. It was only in 1980, PTSD was introduced in the DSM-III, and only in 1989 that Ross et al. [61] presented the hypothesis that “sleep disturbances are the hallmark of PTSD,” which opened the study of PTNMs. Also, PTNMs are conceptualized as one of the intrusive symptoms of PTSD [3], and therefore, as a secondary symptom of PTSD. In the dreaming field, they are seen as an adaptive function to emotionally adjust to trauma. This main discrepancy hinders their introduction in PTSD treatment and slows down and complicates their inclusion in research. Besides, recommendations concerning NM treatments were only published in 2010 [15], and the first reported open-label study of Prazosin for PTNM treatment was conducted in 2000 [62].

#### 4.2. Treatment efficacy

Looking at the positive results of the impact of Prazosin ( $g = 1.30$ ) and CBTs ( $g = 0.55$ ) on PTNM reduction, we found that treatments specifically targeting NMs are efficient. It was not possible to directly compare CBTs for NMs to Prazosin, but considering the large ES for Prazosin, we may conclude its efficacy is superior to CBTs for NMs in the reduction of PTNMs at post-treatment. However, several considerations on the overall efficacy of each treatment need to be examined and caution in confirming the superiority of Prazosin over CBT is advised.

First of all, only one study [36] has compared both treatments with a placebo group at short and long terms. Prazosin demonstrated slightly better results than CBTs. However, authors reported that their results did not differ at the four-month follow-up assessment.

Another consideration is that most medications have side effects that may force participants to withdraw from one treatment [63]. From a few Prazosin studies, we know researchers sometimes had to stop its administration due to adverse effects, such as dizziness [22], nausea and headache [23], and fainting and nasal congestion [64]. Nevertheless, attrition rates did not statistically differ from Prazosin treatment (0–40.00%) to CBT (0–54.31%). Also, CBT can also present side effects as costs, stigma, etc., but no information was provided. This aspect should therefore be considered in the future for both types of treatments.

Also, the majority of Prazosin studies did not report data at follow-up. It seems the authors' first objectives were to determine the optimal dose to be NM free. It is therefore impossible to evaluate the rate of relapse after stopping this treatment, whereas CBTs reported data at follow-up. In Raskind et al. [26], the authors mentioned that Prazosin effect did not persist after its cessation in a few patients, who returned to their initial NM frequency. This observation reminds us of the broader issue of medications benefits compared to psychological treatments in PTSD [63].

Another concern is related to the characteristics of the studies, which could have influenced the computed combined ES for both types of treatments. First, we noticed large variations in the sample sizes, with a total of 181 participants for Prazosin (from  $n = 9$  to  $n = 51$ ) and 1169



participants for CBTs (from  $n = 4$  to  $n = 278$ ). In addition, the evaluation of NMs varied between the two types of treatments (CAPS-B2 versus self-reported questionnaires). Moreover, Prazosin effect seems to vary according to its mean dosage, as the effect of a “small” dosage (“under 5 mg,”  $g = 1.57$ ) was equivalent or even more efficient than a higher dosage (“between 5 and 10 mg,”  $g = 1.30$ ; “over 10 mg,”  $g = 0.81$ ) (without reaching a statistically significant difference). On the other hand, some CBT studies did not favor immediate postevaluation and only reported data at follow-up (e.g., [30]).

When analyzing the efficacy of CBTs for NMs, we noticed that variations in their formats (individual compared to group format) or in the type of treatment (ERRT compared to IRT) could influence their impact. For example, even if subgroup analyses did not show any statistical differences, subgroup ES for individual CBT was higher ( $g = 0.87$ ) than the other types of formats. Also, treatment efficacy varied according to the type of CBT, with a slightly higher ES subgroup for ERRT ( $g = 0.70$ ) over IRT ( $g = 0.56$ ). To date, only a few studies have looked at the therapeutic ingredients for these two CBTs, and it would be interesting to directly compare them in the future.

Finally, to attain our second objective, we underlined that the efficacy of these two treatments was not limited to PTNMs and extended to other symptoms. Their impacts were positive and equivalent for PTSD symptoms ( $g = 0.58$  for Prazosin;  $g = 0.59$  for CBTs), for the PSQI ( $g = 0.83$  for Prazosin;  $g = 0.95$  for CBTs), and for sleep in general ( $g = 1.25$  for Prazosin;  $g = 1.06$  for CBTs). No subgroup analysis achieved statistical significance except for the subgroup looking at the efficacy of incorporating a sleep management component, which was marginally statistically significant for the PSQI. This result means therapists or researchers should therefore consider adding this component to IRT or to enhance it in ERRT.

As mentioned before, caution is advised in interpreting these results as discrepancies remained with the type of questionnaires selected. Nevertheless, these secondary effects of treatments specifically targeting NMs are interesting. Even if previous ESs are moderate or high, they are similar to those published in Belleville et al. [20]. The author pointed out that CBT for insomnia had a moderate impact on anxiety in individuals who presented insomnia, with or without a comorbid anxiety disorder. In the case of PTSD, it is therefore important to evaluate the impact of Prazosin and CBTs for NMs on PTSD.

#### 4.3. Implication of results

The large ESs obtained for Prazosin and CBTs demonstrate to clinicians the relevance of using specific NM treatments. From a research point of view, these positive results emphasize the idea that PTNM could become an independent disorder rather than a PTSD symptom that should disappear with conventional CBT or medications. Therefore, it requires a specific treatment, and studies in the PTSD field should focus more on sleep. Moreover, a limited update of the literature search was performed since December 2012, four articles [65–68] were published, as well as new meta-analysis and systematic reviews [69, 70], and still support the present results.

Prazosin, as a medication and because it is linked to PTSD biology and to the neurobiological, correlates between PTSD symptoms and sleep and presents several advantages compared to psychological treatments. First, it seems to offer the possibility of treating nightmares without considering their content compared to CBTs for NM. It represents an interesting option for some patients, for example, when therapy is not available (e.g., soldiers who are still on duty) [63]. It can also have a positive impact on the other PTSD symptoms; and finally, its low cost makes it a promising pharmacological option. However, it seems to take most of the time eight weeks prescription to obtain positive result while observing only one CBT session can be sufficient to train a patient to get rid of his nightmares. Moreover, no standard for Prazosin administration and duration exists.

On the other hand, psychological treatments help to deal with frightening content of NM. It is theoretically believed that CBTs for NM repair the normal sleep process which has been disrupted by NM. In fact, one sleep function is to select, classify, and consolidate information and the emotions lived during the day in the long-term memory [71]. When this process is interrupted by NM because of a strong emotion, the integration of new memories is impeded. In PTSD, individuals live negative emotions during PTNM, and the incorporation of the information related to the traumatic event fails [72, 73]. Compared to Prazosin, the main advantages of ERRT and IRT are easy and rapid learning (sometimes in one session), of how to eliminate NM. But their main disadvantage is that no standards have been proposed to deliver them, and research needs to be conducted for different types of trauma, different types of NM content, and different participant characteristics (such as gender).

#### 4.4. Strength and limitations

Studies may not be exactly the same or perfect. Disparities remained as the two treatments diverge clinically and methodologically, and therefore, heterogeneity had to be expected. However, analyses reflected that no bias could be detected. Nevertheless, caution should be exercised in the interpretation of the efficacy of Prazosin for PTSD symptoms. First, it was not possible to directly compare Prazosin against CBTs for PTNMs. Also, no information was provided on therapeutic maintenance. We observed variations in CBTs format and Prazosin administration. Methodological limits were detected due to a lack of questionnaire standardization to evaluate PTNMs; and NM definitions or NM content were not reported. Finally, variations in the population (sex and age) and in sample sizes were also observed.

There are some limitations including experimental and quasi experimental studies in this meta-analysis as in the latter case, the treatment and control groups may not be comparable at baseline. However, several strategies were used to increase the validity of our results: (1) reviewing each study to carefully interpret our results; (2) grouping outcome by type of questionnaire evaluating the same construct; (3) ES analyses within subgroups was a way of investigating variations; and (4) deciding upon inclusion criteria ahead of the review process and reporting them in a protocol. In spite of all these precautions, a larger *N*, more particularly for Prazosin, would have increased the statistical power of our analysis and would have helped us to highlight interesting results within subgroup analyses. Therefore, the combined ES reported are valid. Also, the “file drawer problem” criticism can be ignored for CBT studies

and should be interpreted with caution for Prazosin studies, more particularly for the PTSD symptom variable [47].

Finally, systematic reviews and meta-analysis have previously been published on these new psychological treatments and on Prazosin (e.g., [17, 74–78]). The main advantages of the present study are, compared to the previous ones, to have screened studies written in English and French and to have considered randomized and nonrandomized studies. Also, if looked at all types of nightmares, treatments not only considered imagery rehearsal treatments, in an adult population with PTSD evaluated by validated questionnaires or structured interviews. At last, this study combined both a meta-analysis and a systematic review on CBT for nightmares and Prazosin, which allowed discussing their respective impacts and advantages.

#### 4.5. Further studies

Despite the contribution of this study, future trials should consider some of the weaknesses observed in this meta-analysis when NM is in a PTSD context. First, efforts should be made to standardize the methodology used by including a control group, reporting outcomes at follow-ups, and giving NM definition or content.

Also, the different methods used to evaluate NM frequency in this meta-analysis emphasized that standardization was needed for questionnaire administration, NM definition, and treatment format. In fact, we observed that all Prazosin studies used the CAPS, a retrospective measure to evaluate NM, while CBTs used both self-reported retrospective and prospective measures like home daily logs. More precisely, all Prazosin studies evaluated NM using the CAPS-B2 item, compared to CBTs, which retrieved items evaluating NM from various retrospective questionnaires or home sleep logs. Only two studies, by the same author [36, 79], included objective sleep measurements (polysomnography, PSG). To date, prospective daily logs are considered the gold standard for the measurement of NM frequency [80], as self-reports underestimate current NM frequency [81]. Therefore, results could differ according to the method of measurement used and caution is advised in evaluating to Prazosin impact.

Only a few studies specified NM definition. Even if most studies adhered to a frequency cutoff of one weekly nightmare minimum or an average of two or more NM per week, it is not clear what participants understood by NM. In Prazosin studies, the CAPS-B2 item refers to the frequency and the intensity of recurrent distressing dreams related to the traumatic event. Therefore, we could wonder if the impact of Prazosin was on NM frequency or on NM distress. This could influence the interpretation of results. In addition, we could not retrieve information regarding NM content. As we know, PTNMs may be trauma-related or replicative trauma [3]. Therefore, it would have been interesting to have access to this information in order to evaluate which kind of PTNM contents was targeted and by which CBT. In fact, each treatment has its own rationale and degree of exposure to the selected NM. Therefore, this information would be an indicator of which PTNM contents favor each treatment and could help to refine guidelines.

Disparities were also observed in sample characteristics, with women being less represented than men, more particularly in Prazosin studies; and with combat experience and sexual

assaults being the main considered trauma. Research in the PTSD field is closely linked to war history but it is also important to consider other types of trauma. We could wonder, for instance, if one of the CBTs for NM would be more adapted according to the type of trauma (i.e., PTNM content being different in each case). This will help to generalize the results and to provide guidelines to clinicians in choosing which treatment to apply in a specific situation.

Recommendations on treatment delivery should be proposed (mean dosage, no. of sessions, and NM content) in order to help clinicians and to allow comparison between studies. This meta-analysis raises the possibility to directly treat PTNMs, as a symptom of PTSD, but clinical aspects should be examined. Can we combine any treatment for PTSD with any treatment for PTNMs? Which treatment should be prioritized in complicated PTSD? Could we add Prazosin at any moment in the treatment? Which treatment for PTNMs will be more appropriate in function of individual characteristics (such as gender or type of trauma)? Could we incorporate specific NM treatments in a conventional CBT for PTSD? Many avenues are opened to those who want to participate in standard PTSD treatment improvement.

Finally, secondary measures, such as PTSD scores and sleep, should be recorded.

## 5. Conclusions

We know CBTs and SSRIs do not effectively resolve all PTSD symptoms, as nightmares were found to be treatment resistant and residual insomnia was reported. From the positive results of this meta-analysis, we know specific NM treatments (Prazosin or CBTs) contribute to NM reduction. These treatments also demonstrate PTSD and sleep symptom reduction. The overall conclusion of this meta-analysis is that treating NM with Prazosin or CBTs directly is interesting and can be a way to improve conventional CBTs for PTSD. However, no consensus or guidelines are available to treat PTNMs. From these outcomes, clinicians can conclude that NM can affect the efficacy of first-line PTSD treatments, and new treatments are developed to solve this problem, while in sleep research PTSD outcomes should be reported.

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