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CLINICAL REVIEW

Comparative efficacy of imagery rehearsal therapy and prazosin in the treatment of trauma-related nightmares in adults: A meta-analysis of randomized controlled trials

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SUMMARY

Pharmacological treatment with prazosin and psychological treatment with imagery rehearsal therapy (IRT) are the two main treatments of posttraumatic nightmares. The American Academy of Sleep Medicine task force recently listed IRT as the recommended treatment for trauma-related nightmares and changed the recommendation of prazosin to 'may be used'. This new recommendation was based on a single prazosin trial and not on a meta-analytic review of all available trials. The current meta-analysis aims to fill this gap in the literature. Eight studies on IRT and seven studies on prazosin ($N = 1.078$) were analyzed based on the random effects model. Relative to control groups, prazosin had a moderate to large effect on nightmare frequency ($g = 0.61$), posttraumatic stress symptoms ($g = 0.81$), and sleep quality ($g = 0.85$). IRT showed small to moderate effects on nightmare frequency ($g = 0.51$), posttraumatic symptoms ($g = 0.31$), and sleep quality ($g = 0.51$). No significant differences in effect were observed between prazosin and IRT on any of these outcomes (all p 's > 0.10). It is concluded that downgrading the recommendation of prazosin may be a premature decision and that the aggregated results in this meta-analysis clearly show efficacy of both treatments.

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Introduction

Nightmares are vividly realistic and well-remembered dreams that typically result in extreme dysphoric emotions [1]. These unpleasant dreams mostly occur during rapid eye movement sleep and often awaken the individual. In order to fulfil criteria for a nightmare disorder these dysphoric dreams need to cause clinically significant distress [2]. People can have nightmares with no identifiable origin (idiopathic nightmares) or as a consequence of a traumatic experience. Trauma-related nightmares are one of the

most common complaints of individuals with posttraumatic stress disorder (PTSD) [3,4].

There are currently two main treatment options for posttraumatic nightmares. First, prazosin is a pharmacological intervention that works as an alpha-adrenergic receptor antagonist. Prazosin crosses the blood–brain barrier, antagonizes the alpha receptors in the central nervous system (CNS), and blocks the stress response. It is thought that the high nocturnal CNS adrenergic activity that occurs in PTSD contributes to the disruption of normal rapid eye movement sleep. Therefore, agents that reduce CNS noradrenergic activity could be effective in treating posttraumatic arousal symptoms such as nightmares [5].

Second, imagery rehearsal therapy (IRT) is a cognitive-behavioral technique that teaches patients to change the content of a nightmare by creating a new and more positive ending. This new ending is then repeatedly rehearsed in imagination during the day [6]. It is thought that IRT alters the affective properties of the nightmare by changing its intrinsic meaning, for instance through a feeling of increased mastery of the nightmare content (e.g., [7]).

Effects of both prazosin [8–12] and IRT [13–16] have been demonstrated in several studies (but see [17,18]) and meta-analyses

Abbreviations: AASM, American Academy of Sleep Medicine; CAPS, Clinician administered PTSD scale; CI, Confidence interval; CNS, Central nervous system; ERRT, Exposure, relaxation, and rescripting therapy; IRT, Imagery rehearsal therapy; MINI, The Mini international neuropsychiatric interview; PTSD, Post-traumatic stress disorder; RCT, Randomized controlled trial; SCID, Structured clinical interview for DSM-IV.

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[19–22]. The most recent of these meta-analyses compared the short-term efficacy of prazosin to IRT. It was found that both treatments showed moderate effects on nightmare frequency (Hedges $g = 0.55–0.61$), posttraumatic symptoms ($g = 0.50–0.68$), and sleep quality ($g = 0.54–0.66$) [22]. No significant differences were observed between the two treatment modalities.

Since this latest meta-analysis a large-scale randomized controlled trial (RCT; $n = 304$) was published that found no significant treatment effects of prazosin on any of the measures [17]. The findings of this single study led an American Academy of Sleep Medicine (AASM) task force to change the recommendation for prazosin from 'recommended' to 'may be used for treatment' [23]. In our opinion, however, such a far-reaching decision should not be informed by a single trial, but by a meta-analytic review of the relevant outcome literature as a whole. To evaluate the AASM decision [23], we therefore performed a new meta-analysis based on all the available data, including the latest study of Raskind and colleagues [16].

We aimed to answer the following research question: Is IRT more efficacious than prazosin in treating trauma-related nightmares in adults? We hypothesized that in line with the AASM decision, IRT has greater positive effects on nightmare frequency, posttraumatic symptoms and sleep quality than prazosin. We focused on a sample with posttraumatic nightmares since posttraumatic nightmares are thought to elicit more effect load than idiopathic nightmares [24]. An additional issue is that prazosin is studied predominantly in posttraumatic samples and including idiopathic nightmares may have biased the results. Additionally, and in line with [22], we explored if sample type (civilian vs veteran) and delivery mode (group vs individual) were moderators of the treatment effects. In contrast to this earlier meta-analysis [22], we focused solely on studies that had rehearsal or re-scripting of nightmares as the major treatment component. This meant that we excluded studies that combined rehearsal or re-scripting with empirically supported stand-alone treatments of sleep disorders, such as cognitive behavioral therapy for insomnia (but allowed modules such as psycho-education or sleep hygiene).

Methods

Protocol and registration

The protocol of this meta-analysis was registered at PROSPERO and published on December 12, 2018 (CRD42018118116).

Eligibility criteria

To be included in this meta-analysis, primary studies had to: 1) employ a study design that randomly assigned participants to an experimental or a control group (with crossover designs accepted); 2) include an experimental group that received prazosin or IRT (or a similar treatment primarily directed toward nightmares that had rehearsal or re-scripting of nightmares as the major component, e.g., Exposure Relaxation and Rescripting Therapy [ERRT]); 3) include adult participants (age ≥ 18) with posttraumatic nightmare complaints; 4) report at least one of our dependent variables (i.e., nightmare frequency, sleep quality, or posttraumatic stress disorder symptoms); 5) include sufficient statistical information to calculate effect sizes; 6) be published in English. We excluded studies: 1) of which only an abstract was available; 2) that were reviews or editorials; 3) that investigated treatments that included other interventions in addition to IRT and were not directed at nightmares alone (e.g., IRT plus cognitive behavioral therapy for insomnia).

Search strategy

The search strategy was developed by DY, AvE, and JL. First, the bibliographic databases PsycINFO, Web of Science, Ovid MEDLINE, Cochrane Reviews, EMBASE, and Scopus were searched using the following search strings: (Imagery rescript* OR imagery modification OR exposure relaxation OR rescripting therapy OR ERRT OR imagery rehearsal* therap*), (prazosin* OR Furazolin* OR Minipress OR Pratsiol OR Vasoflex OR Lentopres OR Hypovase), nightmares/ OR (nightmare* OR (posttrauma* OR post-trauma* OR psycho-trauma* OR psycho-trauma* OR trauma) ADJ2 sleep*). English language and human participants were applied as search restrictions. Second, we examined the reference lists of all included publications and previous meta-analyses for additional publications that met our inclusion criteria [19,20,22]. The literature search was completed in November 2018. The search string used for each database can be found in [Supplemental File 1](#).

Study selection

Two reviewers (DY and JL) performed the eligibility assessment in a web-based tool specifically designed for this purpose (<http://rayyan.qcri.org>) [25]. An immediate agreement was reached for 93% of the potentially eligible studies ($\kappa = .80$). Disagreements were resolved through discussion between the reviewers. First, records were screened on title and abstract, and if a paper appeared eligible its full text was considered. If articles missed essential data, authors were contacted to retrieve the data.

Data extraction

A protocol was developed (DY) for coding and extracting the necessary information from each included study. The coding and extracting protocol can be found in [Supplemental File 2](#). The following information was coded and extracted: 1) study identification, i.e., author(s), title, year of publication, journal, country; 2) sample characteristics, i.e., sample size, percentage female, age (mean and SD), type of population, inclusion and exclusion criteria, type intervention, type of comparison; 3) treatment characteristics, i.e., type of intervention, number of treatment sessions, duration of treatment sessions, delivery mode, prazosin dosage; 4) methodological characteristics, i.e., study design, presence and duration of follow-up, intention-to-treat analysis, percentage of drop out, performed statistical analysis; 5) measures, i.e., screening measures, primary outcome measures, secondary outcome measures; 6) data for calculating effect sizes, i.e., mean and standard deviations for each measure at pretest, posttest, and follow-up; 7) quality characteristics (see 'risk of bias in individual studies' in the following section for a detailed description). Nightmare frequency was operationalized as the number of nights with nightmares per week. If this information was not provided, the number of nightmares per week [9,11,13,26] or a more general measure for nightmares [27] was coded and extracted. Two reviewers (DY and CS) independently coded and extracted data from all included studies to maximize data accuracy. Disagreements were resolved by jointly reviewing each discrepancy in the extracted data.

When articles [26,28] reported standard errors, the following formula was used to convert standard errors into standard deviations: $SD = SE \times \sqrt{N}$ [29]. Additionally, Raskind and colleagues [30] reported confidence intervals (CIs) for group means. Therefore, standard deviations were obtained based on the following formula [29]: $SD = \sqrt{N} \times (\text{upper limit} - \text{lower limit})/3.92$. When the sample sizes were small (e.g., less than 60 in each group), the number 3.92 was replaced with another number specific for the t-distribution [29]. Duplicate reports that described identical samples were

removed [13,31]. When multiple samples were compared within a single study, only the comparisons that were relevant for our research question were included in the statistical analyses.

Risk of bias in individual studies

The Cochrane Collaboration's tool for assessing the risk of bias was used to detect potential biases in the individual studies [32]. Two reviewers (DY and CS) independently assessed the studies and reached immediate agreement in 91% of the cases ($\kappa = .80$). Disagreements were resolved by discussion between the reviewers.

Risk of bias across studies

Publication bias was examined by inspecting the funnel plots for each of our outcome variables. In the absence of a publication bias, the largest studies are plotted near the average of the funnel plot, and smaller studies are scattered evenly on both sides of the average. Furthermore, publication bias was tested based on Egger's linear regression method (as implemented in Comprehensive Meta-Analysis, Version 3) [33]. In addition, Duval and Tweedie's trim and fill method was used to investigate biased effect size estimates [34].

Statistical analyses

The Comprehensive Meta-Analysis software program (Version 3, Biostat, Englewood, NJ, USA) was used to calculate individual and combined effect sizes. Meta-analyses were performed to compare prazosin to a control group (all studies had placebo as a control group) and IRT to a control group (five studies had wait-list as a control group) on three outcomes (nightmares, sleep quality, posttraumatic symptoms), resulting in six meta-analytic comparisons in total. Separate meta-analyses were conducted to compare the IRT to the prazosin studies and to assess the moderation effect of sample characteristics (civilians versus veterans). Sub-group analyses for different formats of treatment delivery (individual versus group) were only conducted for IRT studies. All calculations were based on the random effects model, which does not assume that included studies are identical or that effect sizes are the same across studies [35].

Treatment effect sizes were based on the first assessment following the treatment. Effect sizes were calculated based on intent-to-treat data if possible and otherwise on the completers sample. Effect sizes were calculated using Hedges' g , which is a variation of Cohen's d that corrects for bias due to small sample sizes [36]. The magnitude of Hedges' g can be interpreted as small (0.2–0.49, medium (0.50–0.79), or large (≥ 0.80).

Heterogeneity between studies was measured with the chi-square Q -statistic, which tests the null hypothesis that all the variation in effects is due to sampling error [33]. Heterogeneity was further examined with the I^2 index, which indicates the proportion of true variance relative to the observed variance. In general, I^2 values of 25%, 50%, and 75% represent small, moderate, and high levels of heterogeneity, respectively [37].

Results

Study selection

The search yielded 1186 citations. The reference list searches identified two more studies, bringing the total number of identified studies to 1188. After removing duplicates, 468 studies were screened based on their titles and abstracts; 419 studies were excluded at this stage. The full texts of the remaining 49 publications

were retrieved for further consideration. After reviewing and assessing these full texts, 15 studies remained for inclusion in the quantitative synthesis [8,9,11–13,17,18,26–28,30,38–41]. Fig. 1 summarizes the study selection process and the reasons for exclusion at the different stages.

Description of studies

All 15 studies included in the quantitative synthesis were RCTs published between 2001 and 2018. Of these, seven publications concerned prazosin [8,9,11,12,17,30,38] and eight concerned IRT [13,18,26–28,39–41]. Two of the prazosin RCTs employed a crossover design [11,35]. Table 1 shows the descriptive characteristics of the included studies. The number of participants included in the meta-analysis was 1078. The prazosin studies included 527 participants (275 in treatment groups and 275 in control groups; 20 participants were in a crossover design). The IRT studies included 551 participants (282 in treatment groups and 269 in control groups). Nine studies included civilian samples and the other six included military veterans. All 15 studies required the presence of trauma-related nightmares, with some studies including only patients with PTSD [8,11,12,17,18,30,38,39] and other studies including patients with self-reported trauma-related nightmares [9,13,26–28,40,41]. Fourteen studies explicitly mentioned the use of clinical interviews to assess PTSD (CAPS/SCID/MINI), one study used a screening questionnaire to assess PTSD [27].

In the prazosin studies the maximum medication dosages ranged from 3.1 mg [12] to 20 mg [17]. In all studies except [30], participants were instructed to take their medication at bedtime. Prazosin treatment duration ranged from seven weeks [12] to 26 wk [17]. Regarding the IRT studies, four employed standard IRT [13,18,26,39], three [28,40,41] employed ERRT, and one [27] employed imagery rescripting and reprocessing therapy. In three studies IRT was delivered in a group format, and in the remaining five studies IRT was delivered individually. The number of treatment sessions in IRT ranged from one to eight, and duration of the treatment sessions ranged from 50 min to three hours per session.

Not all studies reported relevant data on all outcomes. Fifteen studies reported data on nightmare frequency, 12 on posttraumatic stress symptoms, and 13 on sleep quality.

Synthesis of results

Nightmare frequency

Mixed-model analysis showed that the efficacy of IRT and prazosin was not significantly different for nightmare frequency, $Q [1] = 0.134, p = .71$ (see Table 2). IRT studies displayed a moderate effect size, Hedge's $g = 0.51, 95\% \text{ CI } [0.20, 0.81], p = .001$, with moderate heterogeneity, $Q [7] = 16.183, p < .001; I^2 = 67\%$. There was also a moderate effect size for the prazosin studies, Hedge's $g = 0.61, 95\% \text{ CI } [0.15, 1.07], p = .01$, with high heterogeneity, $Q [6] = 25.949, p < .001; I^2 = 77\%$. Omitting one study could decrease the heterogeneity to 57%; however, since this was the new Raskind study [17] we decided to leave it in. See Table 2 for the aggregated treatment outcomes and Fig. 2 for a graphical display of the outcomes per study. See Supplemental File 3 for all analyses' outcomes based on the fixed effect model.

Posttraumatic stress symptoms

Mixed-model analysis showed that the efficacy of IRT and prazosin did not significantly differ for posttraumatic stress symptoms, $Q [1] = 2.571, p = .11$ (see Table 2). IRT interventions demonstrated a small effect size, Hedge's $g = 0.31, 95\% \text{ CI } [0.03, 0.59], p = .031$, with small heterogeneity, $Q [4] = 6.383, p = .17; I^2 = 37\%$. Prazosin studies showed a large effect size, Hedge's $g = 0.81, 95\% \text{ CI } [0.26,$

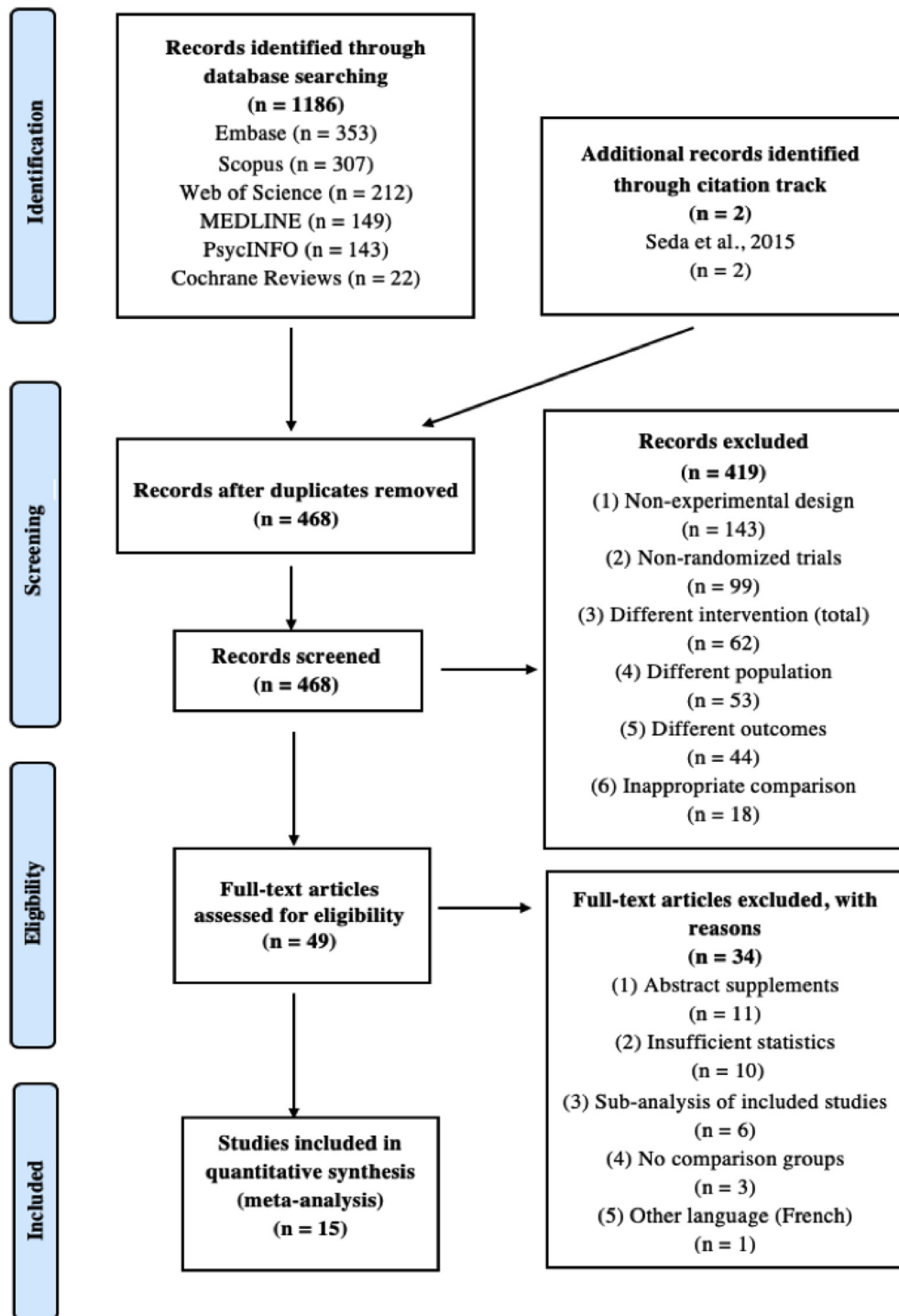


Fig. 1. PRISMA flow diagram indicating the number of publications identified and the number of publications that were assessed based on the eligibility criteria during the various stages of the review process.

1.35], $p < .01$, with high heterogeneity, $Q [6] = 38.353$, $p < .001$; $I^2 = 84\%$ (see Fig. 3).

Sleep quality

Mixed model analysis showed no significant difference between IRT and prazosin for sleep quality, $Q [1] = 0.834$, $p = .36$ (see Table 2). IRT interventions showed a moderate effect size, Hedge's $g = 0.51$, 95% CI [0.17, 0.85], $p < .01$, with moderate heterogeneity, $Q [5] = 13.203$, $p = .022$; $I^2 = 62\%$. Prazosin studies showed a large

effect size, Hedge's $g = 0.85$, 95% CI [0.19, 1.51], $p = .011$, with high heterogeneity, $Q [6] = 53.991$, $p < .001$; $I^2 = 89\%$ (see Fig. 4).

Subgroup analyses: sample and delivery mode

Mixed model analyses demonstrated that type of sample (civilian, $n = 506$, vs military, $n = 572$) was unrelated to changes in nightmare frequency, $Q [1] = 1.106$, $p = .29$, sleep quality, $Q [1] = 1.956$, $p = .16$, or posttraumatic stress symptoms, Q

Table 1
Study characteristics.

ID	Study	Treatment	Control	Enrolled N	Treatm. N	Cont. N	Female (%)	Mean Age	PTSD (%)
1	Krakow, 2001 [13]	IRT	WL	168	88	80	100	38	100
2	Davis, 2007 [28]	ERRT	WL	43	21	22	75	40	54
3	Cook, 2010 [18]	IRT	AC	124	61	63	0	60	100
4	Davis, 2011 [41]	ERRT	WL	47	24	23	82	47	70
5	Thünker, 2012 [26]	IRT	WL	26	14	12	27	38	100
6	Rahnama, 2016 [27]	IRRT	WL	30	15	15	NA	NA	NA
7	Pruiksma, 2018 [40]	ERRT	AC	70	37	33	70	42	100
8	Rousseau, 2018 [39]	IRT	WL	43	22	21	89	NA	100
9	Raskind, 2003 [38]	Prazosin	Placebo	10*	10	10	0	53	100
10	Raskind, 2007 [11]	Prazosin	Placebo	34	17	17	5	56	100
11	Taylor, 2008 [12]	Prazosin	Placebo	13*	13	13	85	49	100
12	Germain, 2012 [9]	Prazosin	Placebo	33	18	15	14	41	57
13	Raskind, 2013 [30]	Prazosin	Placebo	67	32	35	19	30	100
14	Ahmadpanah, 2014 [8]	Prazosin	Placebo	66	33	33	28	35	100
15	Raskind, 2018 [17]	Prazosin	Placebo	304	152	152	5	52	100

ID	Study	Symptom Criteria	Sample	Format	Dose/Sessions	Assessment	Duration
1	Krakow, 2001 [13]	TE, NM	Civ.	Group	2 × 180 min, 1 × 60 min	NFQ, PSQI, PSS, CAPS	3 or 6 mo
2	Davis, 2007 [28]	TE, NM	Civ.	Indiv.	3 × 120 min	TAA, SCID, PSQI, TRNS, MPSS-SR	1-week
3	Cook, 2010 [18]	NM, PTSD	Vet.	Group	6 × 90 min	NFQ, CAPS, NES, PSQI-A, PCL-M	4-week
4	Davis, 2011 [41]	TE, NM	Civ.	Group	3 × 180 min	TAA, CAPS, TRNS, PSQI, PTCSS	1-week
5	Thünker, 2012 [26]	NM, PTSD	Civ.	Indiv.	8 × 50 min	NFM, NMA, BDI	10-week
6	Rahnama, 2016 [27]	NM, SI	Civ.	Indiv.	7 × 90 min	DDNSI, ISI, BSSI	7-week
7	Pruiksma, 2018 [40]	NM, PTSD	Civ.	Indiv.	3 × 90 min	CAPS, TAA, TRNS, PSQI	1-week
8	Rousseau, 2018 [39]	NM, PTSD	Civ.	Indiv.	5 × 50 min	CAPS, SCID, PSQI, PSQI-A, NDQ	5-week
9	Raskind, 2003 [38]	NM, PTSD	Vet.	Indiv.	13.3 mg	NFQ, CAPS, PSQI, CGIC, PDRS	20-week
10	Raskind, 2007 [11]	NM, PTSD	Vet.	Indiv.	9.5 mg	CAPS, CGIC	8-week
11	Taylor, 2008 [12]	NM, PTSD	Civ.	Indiv.	3.1 mg	CAPS, PCL-C, CGIC, PDRS, SAFTEE	7-week
12	Germain, 2012 [9]	NM, SD	Vet.	Indiv.	8.9 mg	PSQI, PCL, BDI, BAI, SDS, PSG, CGI-I	8-week
13	Raskind, 2013 [30]	NM, PTSD	Vet.	Indiv.	15.6 mg	CAPS, PSQI, CGI	15-week
14	Ahmadpanah, 2014 [8]	PTSD, SD	Civ.	Indiv.	15 mg	PSQI, MINI	8-week
15	Raskind, 2018 [17]	NM, PTSD	Vet.	Indiv.	20 mg	CAPS, PSQI, CGIC	10-week

Note. Enrolled N, number of subjects enrolled in the study prior to treatment; N used in analysis, number of subjects included in the quantitative synthesis. * Both studies were randomized controlled trials with cross over design. We decided to include these studies with participants counting for both groups. AC, active condition; BAI, Beck anxiety inventory; BSSI Beck scale for suicidal ideation; BDI, Beck depression inventory; CGIC, clinical global impression of change; CGI-I, clinical global impressions improvement; CGI, clinical global impression; Civ., civilian; DDNSI, disturbing dreams and nightmare severity index; IRT, Imagery Rehearsal Therapy; ERRT, Exposure, Relaxation, and Rescripting Therapy; IRRT, Imagery Rescripting and Reprocessing Therapy; Indiv., individual; TE, traumatic event; NM, nightmares; PTSD, posttraumatic stress disorder; SI, suicidal ideation; SD, sleep disturbance; NDQ, nightmare distress questionnaire; NFM, number of nightmares per month; NMA, degree of anxiety during nightmare. NFQ, nightmare frequency questionnaire; MINI, the mini-international neuropsychiatric interview; PSQI, Pittsburgh sleep quality index; PSS, PTSD symptom scale; CAPS, clinician-administered PTSD scale; TAA, trauma assessment for adults; SCID, structured clinical interview for DSM-IV; TRNS, trauma-related nightmare survey; MPSS-SR, modified PTSD symptom scale self-report. NES, nightmare effects survey; PCL, PTSD checklist; PDRS, PTSD dream rating scale; PSG, polysomnogram; PTCSS, posttreatment clinical significance survey; PSQI-A, Pittsburgh sleep quality index addendum for PTSD; PCL-M, PTSD checklist-military version; SAFTEE, systematic assessment for treatment-emergent events; SDS, Sheehan disability scale. Vet., veteran; WL, waitlist.

Table 2
Effect sizes for IRT and prazosin interventions based on the random effects model.

Treatment Outcome	N _c	Hedge's <i>g</i>	95% CI		<i>p</i>	<i>I</i> ²
			Lower	Upper		
IRT						
Nightmare frequency	8	0.51	0.21	0.81	0.001	67%
Posttraumatic symptoms	5	0.31	0.03	0.59	0.031	37%
Sleep quality	6	0.51	0.17	0.85	0.003	62%
Prazosin						
Nightmare frequency	7	0.61	0.15	1.07	0.009	77%
Posttraumatic symptoms	7	0.81	0.26	1.35	0.004	84%
Sleep quality	7	0.85	0.19	1.51	0.011	89%

Note. N_c, number of comparisons. IRT, Imagery Rehearsal Therapy.

[1] = 0.175, *p* = .68. It must be noted that seven out of nine of the civilian studies were IRT studies.

Similarly, among the IRT studies, type of intervention (group, *n* = 339 vs individual, *n* = 212) was unrelated to changes in nightmare frequency, *Q* [1] = 0.002, *p* = .96, sleep quality, *Q*

[1] = 0.017, *p* = .90, or posttraumatic stress symptoms, *Q* [1] = 0.213, *p* = .64.

Also, among the IRT studies, larger effects were observed for the wait-list controlled studies (*n* = 357) versus the studies with an active control (*n* = 194). For nightmare frequency: *g* = 0.15 (active control) versus *g* = 0.68, *Q* [1] = 5.74, *p* = .017. For sleep quality: *g* = 0.24 (active control) versus *g* = 0.68, *Q* [1] = 2.58 *p* = .108. For posttraumatic symptoms: *g* = 0.08 (active control) versus *g* = 0.55, *Q* [1] = 4.69 *p* = .030.

Risk of bias in individual studies

Regarding selection bias, three IRT studies [26,27,41] showed high risk of bias in allocation concealment and none of the prazosin studies showed this bias. Four IRT [26–28,39] studies and two prazosin studies [12,38] showed a risk in the randomization sequence generation (i.e., randomization not adequately explained). Regarding performance bias, all IRT studies (and no prazosin studies) yielded either high or unclear risk of bias due to the fact that blinding of participants and personnel is not likely in psychotherapy. For attrition bias, three IRT studies [18,27,28] and

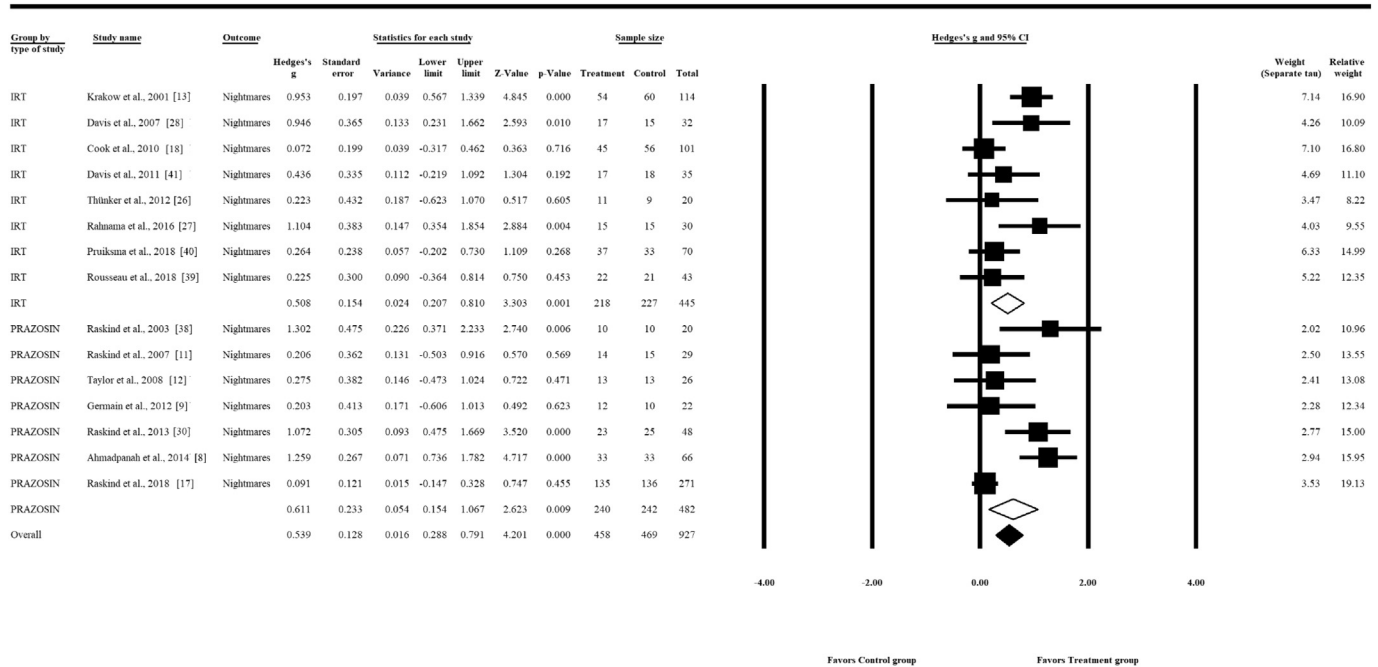


Fig. 2. Individual and combined effect sizes and 95% confidence intervals for Prazosin and IRT subjects on nightmares based on the random effects model.

two prazosin studies [8,38] showed a high risk of bias. For reporting bias, two IRT studies [26,27] and one prazosin [8] showed a high risk of bias. Overall, IRT studies showed more risk of bias than prazosin studies. An overview of risk of bias assessments in all included studies can be found in Supplemental File 4.

Risk of bias across studies

Visual inspection showed an asymmetry in the funnel plot that was confirmed by an Egger's test for nightmare frequency, $\beta_0 = 1.88$, 95% CI [-0.41, 4.17], $p = .05$, one-tailed, sleep quality,

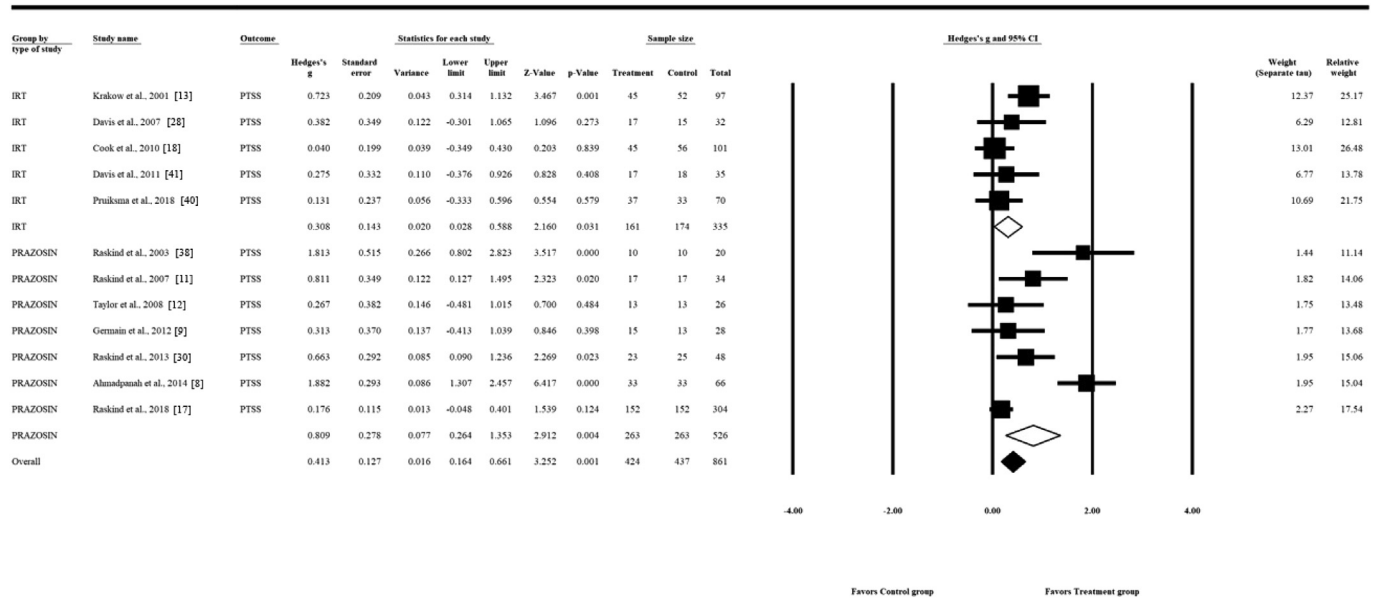


Fig. 3. Individual and combined effect sizes and 95% confidence intervals for Prazosin and IRT subjects on PTSS based on the random effects model.

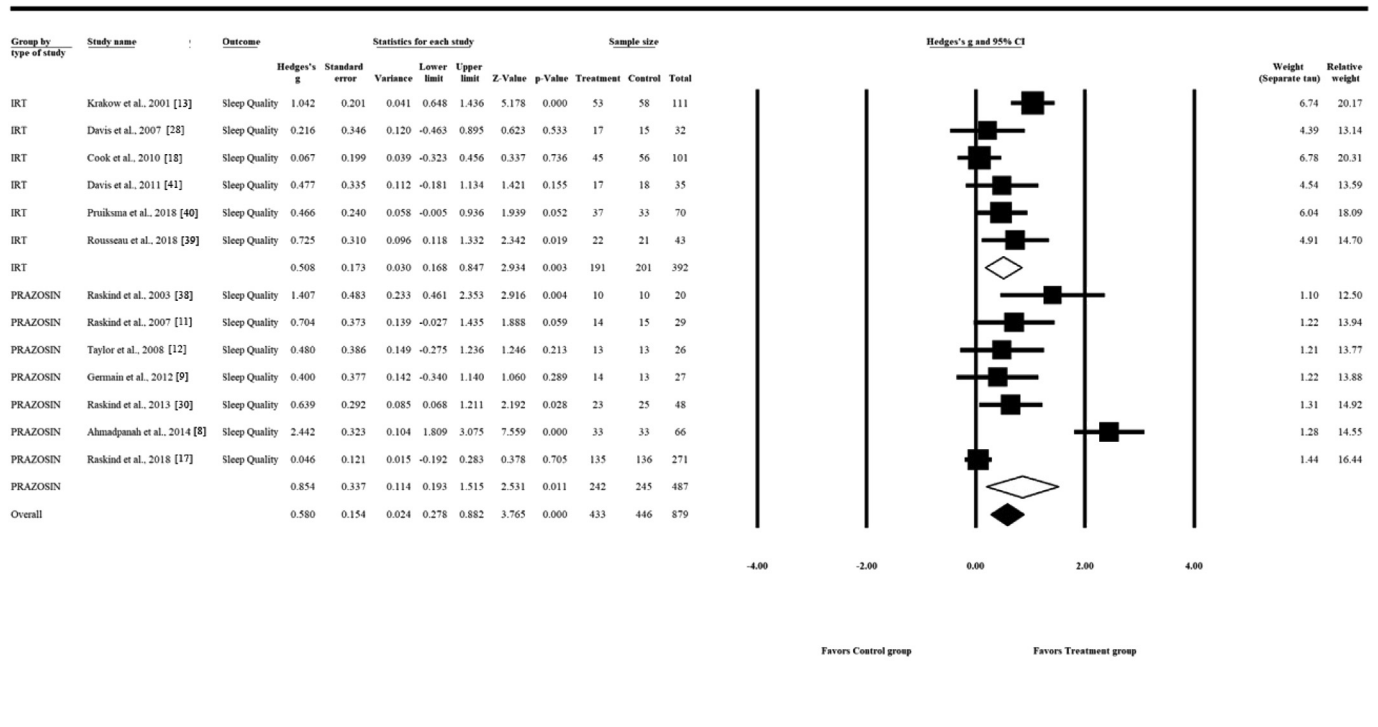


Fig. 4. Individual and combined effect sizes and 95% confidence intervals for Prazosin and IRT subjects on sleep quality based on the random effects model.

$\beta_0 = 3.06$, 95% CI [-0.22, 6.34], $p = .03$, one-tailed, and post-traumatic stress symptoms, $\beta_0 = 2.40$, 95% CI [-0.48, 5.29], $p = .04$, one-tailed. Since an asymmetric funnel indicates a relationship between treatment effect estimates and study size, this suggests the possible presence of publication bias [33]. Funnel plots can be found in [Supplemental File 5](#).

Discussion

This meta-analysis investigated the efficacy of IRT and prazosin in the treatment of posttraumatic nightmares in adults. The treatment effects of prazosin for posttraumatic nightmares were larger than expected. The results indicated that the treatments were not differentially effective in reducing nightmare frequency, with moderate effect sizes for prazosin ($g = 0.61$) and IRT ($g = 0.51$). The magnitude of the effect sizes for posttraumatic stress symptoms and sleep quality appeared larger for prazosin ($g = 0.85/0.81$) than for IRT ($g = 0.31/0.51$), but the differences between IRT and prazosin were not significant.

These effect sizes are in line with the effect sizes observed in the most recent previous meta-analysis on posttraumatic nightmares [22]. The effects are also in line with a meta-analysis of nightmare treatments that was not limited to PTSD-patients [20] and for meta-analyses focusing solely on IRT or Prazosin [19–21,42]. However, in a meta-analysis focusing exclusively on IRT [19], the effects on posttraumatic stress symptoms appeared to be larger than in the current meta-analysis.

The observation that the effects of prazosin and IRT do not significantly differ (with larger effect sizes for prazosin in all domains) does not support and is inconsistent with the recent decision of the AASM [23] to downgrade the recommendation for prazosin. It is true that this decision was informed by a large trial that employed a particularly strong methodology [16]. We nevertheless think that treatment recommendations should be based on evidence from all relevant studies that meet widely accepted

quality criteria, as is common in the development of treatment recommendations and guidelines.

Another important issue is that prazosin may have been investigated under more stringent conditions than IRT. For instance, the IRT studies showed more risk of bias than the prazosin studies, which all used double blinded placebo-controlled designs. In contrast, most IRT studies did not employ blinding procedures (except for blinded raters in some cases, e.g., [40,41]) and used a waitlist as a control group. These methodological choices are well defensible but could have major impact on the results. This is especially important in the light that the IRT studies [18,40] with active controls ($g = 0.16$) had smaller treatment effects than the wait-list controlled IRT studies ($g = 0.74$). With the limitation that only two studies used an active control, this observation strengthens the argument that it is premature to choose IRT over prazosin based on one very well-designed study.

The present study had limitations. First, the analysis showed considerable heterogeneity that appeared to be largely stemming from the Raskind study that lay at the basis of the AASM decision as well as this meta-analysis. For this reason, we used random effects instead of fixed effects models [35]. However, this led to a lower relative weight of the Raskind study (containing 304 of the 526 participants in the prazosin studies) in the random effects model compared to the fixed effects model (relative weight: 19.1 vs 68.5). This also influenced the aggregated effect sizes; for instance, the effects for Prazosin on nightmare frequency were $g = 0.63$ in the random effects model versus $g = 0.39$ in the fixed effects model (see [Table 2](#) and [Supplemental File 3](#)). Even though the random effects model is the preferred procedure, the large heterogeneity may therefore indicate that the effects of prazosin in the current meta-analysis are somewhat overestimated. Importantly, the effects sizes for prazosin in the fixed effects model were still significant and in the same range as the effect sizes for IRT.

Second, prazosin studies predominantly included veteran samples while IRT studies mostly included civilians. Although these

types of patients may show comparable symptom severity, they are highly different in other ways and may react differently to treatment. This may have confounded the response to the prazosin and IRT treatments.

A strength of this meta-analysis is that the included IRT studies only consisted of treatments that had IRT as their major component, and if they included other components these had to be focused on nightmares as well. Studies that combined nightmare treatment with for instance, cognitive behavioral treatment for insomnia (e.g., [43,44]) were excluded. These combined treatments seem to be more effective in reducing posttraumatic symptoms and this may be a reason why earlier meta-analyses observed larger effect sizes [19]. However, their inclusion would have blurred the central comparisons of the present meta-analysis.

In conclusion, we think that the AASM decision to downgrade the recommendation for prazosin is not justified by the existing research evidence. In line with earlier meta-analyses [19–22], the aggregated results in this meta-analysis clearly show the efficacy of both prazosin and IRT. A logical and useful next step would be randomized clinical trials that directly compare prazosin and IRT. If IRT continues to prove sufficiently effective, more scalable options such as internet-delivered IRT for posttraumatic nightmares should further be explored (e.g., [45]). Another important step would be to identify variables that predict differential response to each treatment. Promising leads are, for instance, the possible relationship of skin conductance to the efficacy of IRT [41] and the relationship of systolic blood pressure to the efficacy of prazosin [46]. There is also a need for more focus on the influence of differences in cultural context, study population, therapist training, and other variables that may enhance the effectiveness and generalizability of these treatments. Based on the currently available data however, clinicians seem to have both IRT and prazosin at their disposal as effective treatment formats. Essentially, this is good news for patients with trauma-related nightmares, who have a choice between two quite different empirically supported treatments.

Practice points

- Imagery rehearsal therapy and prazosin are effective for posttraumatic nightmares
- No differences in effect between imagery rehearsal therapy and prazosin were observed on any of the measures
- The decision to downgrade the recommendation for prazosin is not supported by this meta-analytic review

Research agenda

Future studies on the treatment of posttraumatic nightmares should aim to:

- Directly compare the effects of prazosin and imagery rehearsal therapy
- Investigate the additional value of cognitive behavioral treatment for insomnia to imagery rehearsal therapy
- Investigate the merits of combining prazosin and imagery rehearsal therapy

Conflicts of interest

All authors declare that they have no competing interests and did not receive financial support to perform this meta-analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.smrv.2019.101248>.

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