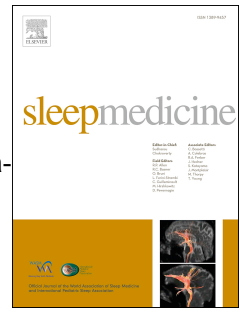

Sleep Management in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis

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Sleep Management in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis

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Abstract

Objective:
Post-traumatic stress disorder (PTSD) can lead to many negative secondary outcomes for patients, including sleep disturbances. The objective of this meta-analysis is (1) to evaluate the effect of interventions for adults with PTSD on sleep outcomes, PTSD outcomes, and adverse events, and (2) to evaluate the differential effectiveness of interventions aiming to improve sleep compared to those that do not.

Methods:
Eight databases were searched for relevant randomized controlled trials (RCTs) in PTSD from January 1980 to October 2019. Two independent reviewers screened 7176 records, assessed 2139 full-text articles, and included 89 studies in 153 publications for this review. Sleep, PTSD, and adverse event outcomes were abstracted and meta-analyses were performed using the Hartung-Knapp-Sidik-Jonkman method for random effects.

Results:
Interventions improved sleep outcomes (standardized mean difference [SMD] -0.56; confidence interval [CI] -0.75 to -0.37; 49 RCTs) and PTSD symptoms (SMD -0.48; CI -0.67 to -0.29; 44 RCTs) across studies. Adverse events were not related to interventions overall (RR 1.17; CI 0.91 to 1.49; 15 RCTs). Interventions targeting sleep improved sleep outcomes more than interventions that did not target sleep (p=0.03). Improvement in PTSD symptoms did not differ between intervention types.

Conclusions:
Interventions for patients with PTSD significantly improve sleep outcomes, especially interventions that specifically target sleep. Treatments for adults with PTSD directed towards sleep improvement may benefit patients who suffer from both ailments.

Keywords: PTSD; sleep; meta-analysis; systematic review

Introduction

While many people experience traumatic events and recover without long term effects, some develop posttraumatic stress disorder (PTSD). PTSD is a condition that develops after exposure to a traumatic event and is characterized by four symptom clusters: re-experiencing, avoidance, negative cognitions and mood, and hyper-arousal.[1] These symptoms can lead to many negative individual and social outcomes, such as psychiatric comorbidity, high medical costs, poor work performances, familial discord, crime, and suicide risk.[2-6] Some patients experience symptoms for an extended period, while others experience symptoms that resolve and reappear over time.[1]

Among patients with PTSD, sleep disturbances are extremely common. These disturbances, including generalized arousal that interferes with sleep and distressing dreams (i.e. nightmares), are prominent diagnostic criteria for the disorder.[1] In the Millennium Cohort Study, clinically significant insomnia was found in 92% of active duty personnel with PTSD, compared to 28% of those without PTSD.[7] A study of veterans with PTSD found that those with poor or average sleep quality had higher anxiety than those with good sleep quality.[8] Common symptoms by symptom cluster include: distressing dreams or nightmares (re-experiencing), insomnia (hyperarousal), and resisting sleep due to anxiety or to avoid nightmares (avoidance). These relationships between sleep and PTSD, suggest that sleep itself may be a target for therapeutic intervention for patients with PTSD and heightened anxiety.

Addressing the sleep issues in PTSD with effective treatments can allow for greater functioning in patients. PTSD patients with fewer sleep difficulties are more likely to be high functioning.[9] In addition, nightmares and their associated chronic sleep disruption may affect the

efficacy of first-line PTSD treatments.[10] Recovery from PTSD may be accelerated by targeting the treatment of sleep conditions.[11]

Treatment of sleep disturbances in patients with PTSD is often primarily pharmacological- and psychotherapy-focused, although other behavioral sleep interventions show efficacy as well.[12] While many PTSD patients use pharmacological treatments to manage their sleep disturbances, these treatments have side effects like daytime fatigue, nausea, and diarrhea, so it is important to compare the efficacy and safety of pharmacological vs. nonpharmacological treatment risk.[13] No existing reviews specifically examine treatments for sleep disturbances in patients with PTSD or analyze sleep outcomes in studies of non-sleep treatments for PTSD.

To address this gap in the literature, we conducted a systematic review that evaluated the effectiveness and safety of interventions aimed at improving sleep or other PTSD symptoms on sleep outcomes in adults with PTSD. Our primary objective was to examine the effects of interventions for PTSD patients on sleep outcomes, PTSD symptoms, and adverse events. Our secondary objective was to examine the variation in effects by intervention target (e.g., sleep-targeted vs. non-targeted-focused interventions).

Methods

The systematic review was registered in PROSPERO, an international registry for systematic reviews (PROSPERO #CRD42018102200).

Sources and Search Strategy

In October 2019, we searched the research databases PubMed (biomedical literature), PsycINFO (psychological literature), EMBASE (pharmacological research), CINAHL (nursing literature), PILOTS (Published International Literature on Traumatic Stress), AMED (Allied and Complementary Medicine Database), Cochrane CENTRAL, as well as the trial registries Clinicaltrials.gov and the International Clinical Trials Registry Platform for RCTs in PTSD from 1980 to present. In addition, we reference-mined included studies and pertinent systematic reviews and consulted with content experts. The search strategy, described in the Supplementary Material, was developed by the Evidence-based Practice Center librarian, informed by content experts and existing systematic reviews on the topic.

Eligibility criteria and inclusion screening

Titles and abstracts of retrieved citations were screened for inclusion through eligibility criteria by two independent reviewers. Conflicts were reconciled between these reviewers, with the advice of a third reviewer in the event that a conflict could not be resolved. Full-text publications of included citations were screened by two independent reviewers in a similar manner.

The inclusion and exclusion criteria we applied to the retrieved publications can be summarized using a "PICOTSS" framework (participants, interventions, comparators, outcomes, timing, settings, and study design):

- Participants: Studies of male and female participants, 18 years of age or older with PTSD, were eligible for inclusion. Participants had to have a current clinical diagnosis of PTSD according to DSM or ICD diagnostic criteria, or screen positive for PTSD using a validated measure with symptoms that are compatible with a PTSD diagnosis (e.g., duration of the disturbance is more than one month). Patients with comorbidities were allowed.
- Interventions: RCTs evaluating treatments aimed at improving PTSD symptoms (as described by authors) in adults diagnosed with PTSD were eligible for inclusion. Treatments were categorized as pharmacological (i.e. PTSD symptom medication, sleep symptom medication), psychological (e.g., cognitive behavioral therapy), behavioral (e.g., sleep hygiene interventions), complementary medicine (e.g., meditation), or other (e.g., eye movement desensitization, biofeedback).
- Comparators: Studies were not limited by comparator and studies may compare against no treatment, waiting list, placebo, treatment as usual, or active comparators.
- Outcomes: Studies had to report on sleep outcomes to be eligible. This may include measures of insomnia, nightmares, sleep improvement (e.g., onset, maintenance, quality, duration), or other sleep measures (e.g., pre-sleep arousal). Studies exclusively reporting on sleep apnea without other sleep outcomes relevant to PTSD were excluded. Studies had to report post-intervention outcome results for the intervention and the control group. Studies that commented on sleep ("no effect on sleep") but did not provide numerical results were excluded.
- Timing: Studies could involve any treatment duration and any follow-up period.

- Setting: Studies were not limited by setting.
- Study design: Parallel and cross-over RCTs, individual and cluster randomized studies were eligible.
- Other limiters: Studies had to have results published in an English language publication to be eligible.

Data extraction

The project team designed a data extraction form in an online database designed for systematic reviews. Reviewers pilot tested the form to ensure agreement of interpretation. The form included detailed instructions and decision rules for reviewers to facilitate a standardized data collection process. Data were abstracted by one reviewer and checked by a second experienced reviewer. Any discrepancies were resolved through discussion. Publications reporting on the same study population were consolidated so that individual studies entered the analyses only once.

Information extracted from individual studies included:

- Study Information: ID, year
- Participants: gender, age, trauma type (category of traumatic events/ context of trauma- e.g., sexual abuse or assault, physical abuse or assault, emotional abuse or psychological maltreatment, neglect, serious accident, illness, or medical procedure, natural or manmade disasters; war, terrorism or political violence excluding military servicemembers; military trauma /combat, traumatic grief or separation, other), diagnostic criterion
- Interventions: category (sleep symptom medication, PTSD symptom medication, sleep psychotherapy [treatments focused on improving thoughts and behavior to

enhance sleep], PTSD psychotherapy [treatments focused on improving thoughts and behavior to reduce PTSD symptoms], behavioral/sleep hygiene [actions that patients can take to improve health outside of psychotherapy], combined medication and psychotherapy, complementary and alternative medicine, other), description of the intervention (content and duration), sleep explicitly targeted in study as described by authors or through the presence of primary hypotheses or outcomes that focus on sleep (yes, unclear, no), co-interventions

- Comparators: type and description of comparator
- Outcomes: Sleep outcomes (e.g., onset, maintenance, nightmares), PTSD symptoms (by any measure designated by authors to measure PTSD severity), and adverse events associated with the intervention
- Timing: time-points of latest outcome assessment post-intervention
- Study design: type of RCT and unit of analysis (randomized at patient, provider, or site level), inclusion and exclusion criteria, sample size, reported power calculation, items relevant to risk of bias assessment

Intervention category and target for medication and psychotherapy interventions were often the same (e.g., PTSD or sleep), but not always. We coded intervention category according to the pre-study indication of the intervention (e.g., cognitive processing therapy for PTSD), and intervention targeted according to condition targeted in the primary hypotheses or outcomes evaluated in a particular study (e.g., evaluating cognitive processing therapy to improve sleep).

Risk of Bias

Two reviewers assessed the risk of bias of included studies using the Cochrane Risk of Bias tool.[14] Specifically, the reviewers assessed risks of bias related to the following domains:

- Selection bias and confounding (random sequence generation and allocation concealment): We evaluated for selection bias, which refers to systematic differences between baseline characteristics of the groups that are being compared. The risk is low in randomized controlled trials where the trial investigator randomly assigns participants to the intervention and control group if the random sequence was correctly generated and allocation concealment was maintained.
- Performance bias (blinding of participants and providers): We evaluated whether the knowledge of the allocated intervention could have influenced the outcome. In a placebo trial, patients and their healthcare providers do not know whether they received the treatment or a placebo, and thus that knowledge cannot influence their behavior. Accordingly, the risk of performance bias is low. However, if people know that they are under observation, they may change their behavior (Hawthorne effect), in which case the risk of performance bias is high.
- Detection bias (blinding of outcome assessors): We evaluated whether the outcome assessor or the method of outcome assessment could have been influenced by the participants and modified due to knowledge of the allocated intervention. In studies where participants / outcome assessors were blind to the intervention allocation (placebo condition), detection bias was determined to be low risk.
- Attrition bias (completeness of reporting outcome data): We evaluated incomplete outcome data and imbalances in follow-up data and selective dropout that are likely to be associated with the intervention. Attrition bias is suspected when there

are systematic differences between treatment groups in withdrawals from the study. Studies with no missing data and loss to follow up and studies reporting intention to treat data were considered low risk of bias.

- Reporting Bias (selective outcome reporting): We evaluated whether published reports included all expected outcomes, noting whether the study protocol was available and all of the study's prespecified (primary and secondary) outcomes that are of interest for our review have been reported.
- Other sources of bias: We also captured any additional aspects or study flaws that reviewers noticed and that could potentially affect the validity of the reported results.

We also rated the methodological quality of studies used in sensitivity analyses as good, fair or poor according to a previously established framework,[15] and detailed below:

- Good: Comparable groups are initially assembled and maintained throughout the study with at least 80 percent follow up; reliable, valid measurement is used and applied equally to all groups; interventions are clearly described; all important outcomes are considered; appropriate attention is given to confounders in analysis; intention-to-treat analysis is used.
- Fair: One or more of the following issues is found in the study: some though not major differences between groups exist at follow up; measurement instruments are acceptable but not ideal, though are generally applied equally; some but not all important outcomes are considered; some but not all potential confounders are accounted for in analyses. Intention-to-treat analysis must be done.

- Poor: One or more of the following "fatal flaws" is found in the study: initially assembled groups are not comparable or maintained throughout the study; unreliable or invalid measurements are used or applied unequally across groups; key confounders are given little to no attention in analyses; intention-to-treat analysis is not used.

Data synthesis

Study results for the outcomes of interest (based on those most widely used throughout the studies reviewed) were converted to effect sizes and we documented the point estimate of standardized mean differences (SMD) for continuous outcomes and relative risks (RR) for categorical outcomes together with the 95 percent confidence interval (CI). When sufficiently comparable studies were available, we performed meta-analysis to pool results across included studies for each of the outcomes of interest and presented forest plots for these meta-analyses. We used the Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis.[16-19] Heterogeneity between studies was measured with I^2. The analyses differentiated passive comparators and active comparators. For the overall analysis, we selected one sleep, one PTSD, and one adverse event outcome per study. Preference was given to integrated sleep outcome measures such as total scores on the Pittsburgh Sleep Quality Index (PSQI) rather than individual measures such as the frequency of nightmares. Further analyses were by outcome domain such as insomnia, sleep quality, and nightmares. For adverse events, we grouped clusters of symptoms by organ system, as follows:

- Gastrointestinal/metabolic-nutritional system: nausea, diarrhea, gastroenteritis, abdominal pain, and constipation

- Neurological/nervous system: headache, dry mouth, dizziness, numbness, fatigue, lethargy, asthenia, sweating, tremor, pain, restlessness, thirst, and forgetfulness
- Cardiovascular system: vascular disorders, palpitations, heart complaints, and syncope, blood pressure changes
- Skin/musculoskeletal system: skin and appendages disorders, joint pain, muscle pain/ aches, rash, skin and integumentary system, musculoskeletal and connective tissue system disorders, skin and subcutaneous system disorders, muscle spasms, muscle or joint stiffness, allergic skin reactions, pruritis, exanthema, photosensitivity, and swelling
- Psychiatric system: psychiatric symptoms, substance abuse, suicidal or homicidal ideation
- Respiratory/infectious system: cold symptoms, flu, upper respiratory tract infection (URTI), infections and infestations, sinusitis, bronchitis, common cold, respiratory, thoracic and mediastinal disorders, cough, and herpes labialis
- Sexual/reproductive system: sexual difficulties, sexual dysfunction, and anorgasmia.
- Other organ systems: diseases of liver and bile duct, ear and labyrinth disorders, eye disorders, renal and urinary disorders, reproductive system and breast disorders, urinary problems, blurred vision, and frequent urination

We conducted subgroup analyses and meta-regressions to address the sub-questions of this systematic review. We also conducted sensitivity analyses to assess the robustness of study results as data allowed. This involved excluding studies with high risk of bias and excluding clear outliers that may drive the summary result. Publication bias was assessed using the Begg

and the Egger tests.[20,21] If there was evidence of potential publication bias, we applied the trim and fill method for adjusted effect estimates.[22]

Quality of evidence

The quality of the body of evidence was assessed for major outcomes using the GRADE approach. We assessed the certainty of the body of evidence by considering the following domains to downgrade quality of evidence: study limitations (risk of bias), indirectness, inconsistency, imprecision, and reporting bias. We considered three criteria for upgrading the quality of evidence: large effect sizes, dose-response data, and residual confounding suggesting the opposite effect. We rated our assessments of certainty as very low, low, moderate or high.

Results

Study characteristics

We found 89 randomized controlled trials (RCTs)[23-111] reported in 155 publications[23-177] (Figure 1). Database searches and reference mining resulted in 7176 citations. In total, 2139 publications were selected for full-text dual review. Of these, 89 RCTs met the inclusion criteria and are included in this review (Table 1).

All RCTs randomized individual participants, rather than clusters of participants. Study size ranged from six participants [70] to 304 participants.[48] The majority of studies were conducted in outpatient settings.[23-27,30,32-38,41,42,44,45,47,51,53,59-61,63-66,69,70,72-87,89-96,98,100,102-104,106-111] Most of the studies contained both male and female participants, and their ages ranged from 18 to 80 years.

Half of the included studies addressed military trauma.[24,27,29,35,36,39,42,44,45,47-49,51,53,54,58,59,64-66,70,71,73,74,78,81-83,85,87,89,92,96,98,99,101,104-108,110,111] We also identified studies that reported on participants with trauma due to sexual abuse or assault, whether in civilians or military personnel.[23,38,43,57,90] Two studies reported on participants with trauma due to war,

terrorism or political violence, excluding servicemembers.[68,91] Three studies reported on participants with trauma due to natural or manmade disasters.[80,93,109] The remainder reported on mixed types of trauma, some other type of trauma, or did not specify.

In over third of the identified RCTs the treatment intervention was pharmacologic,[26,31,34,40,47,48,50,59,62,63,65,66,69-79,84,89,98,100,102,104,105,107] in nearly a third of RCTs the treatment intervention was psychotherapy,[23,24,29,35,38,43,46,51-54,57,60,61,67,81-83,86,87,90,92-95,106] in eleven RCTs the treatment intervention was complementary and alternative medicine,[32,36,39,41,44,45,55,80,99,108,109] in four RCTs the treatment intervention was behavioral,[27,85,88,96] and in two RCTs the treatments were combinations of multiple individual treatments.[33,42] In the fourteen remaining RCTs, other treatments that could not be categorized were examined.[25,28,30,37,49,56,58,64,68,91,97,103,110,111] The total length of treatment ranged from one hour[68] to 26 weeks.[48]

Study quality and risk of bias

Less than half of studies (n=34) obtained a "good" overall quality rating. Twenty studies were judged to be of fair quality. These were unclear in some aspects of the methods, and in two cases the completeness of outcome data was unclear.[47,77] Thirty-eight further studies were judged to be poor. This was primarily due to issues with completeness of reporting outcome data such as inadequate or lack of intention to treat (ITT) analysis and/ or less than 80 percent follow-up.

Most studies were judged to have a low risk of bias, but 13 were categorized as high risk, mainly due to poor blinding of participants and personnel, incomplete outcome data, and other sources of bias like small sample size.

Meta-analyses

Treatments significantly improved sleep across studies (standardized mean difference [SMD] -0.56; confidence interval [CI] -0.75 to -0.37; 49 RCTs; Figure 2). Interventions did not show a positive effect in nine studies.[26,67,70,72,74-76,79,110] There was evidence of considerable heterogeneity (I^2 = 80%). Evidence of publication bias was borderline but tests were not statistically significant (Begg p = 0.09, Egger p = 0.08). Excluding high risk of bias studies showed a similar effect estimate and heterogeneity was not reduced (SMD -0.55; CI -0.81 to -0.28; 30 RCTs; I^2 = 84%).

Interventions also improved PTSD symptoms across studies (SMD -0.48; CI -0.67 to -0.29; 44 RCTs, Figure 3). Positive effects were not seen in nine studies. Heterogeneity was considerable (I^2 = 78%). Tests for publication bias were not statistically significant but results were borderline (Begg p = 0.06, Egger p = 0.09). Sensitivity analysis excluding high risk of bias studies yielded a similar effect and heterogeneity remained considerable (SMD -0.43; CI -0.64 to -0.23; 28 RCTs; I^2 = 70%).

Adverse events were assessed and reported in 15 studies, and serious adverse events were reported in twelve of those studies. The number of patients experiencing an adverse event did not differ between intervention and control arms (RR 1.17; CI 0.91 to 1.49; 15 RCTs). There was no evidence of heterogeneity (I^2 = 0%) and there was no indication of publication bias (Begg p = 0.56, Egger p = 0.47).

Overall, meta-regression across studies indicated that effects on sleep differ between studies targeting sleep and those that do not (p = 0.03). The results for the studies targeting sleep directly showed clear improvements of sleep (SMD -0.78; CI -1.12 to -0.44; 24 RCTs; Figure 4). Heterogeneity in this subgroup was still considerable (I^2 = 81%) but there was no indication of

publication bias (Begg p = 1, Egger p = 0.75). Meta-regressions also indicated that sleep symptom psychotherapy interventions produced the largest improvements in sleep compared to PTSD medications (p=0.004) and other interventions (p = 0.02; all interventions other than sleep medication, PTSD medication, or PTSD symptom psychotherapy). Sleep medication, PTSD medication, and PTSD symptom psychotherapy did not create improvements in sleep that differed from sleep symptom psychotherapy. The studies that evaluated interventions not targeting sleep specifically also reported improved outcomes for sleep compared to a control group (SMD -0.36; CI -0.54 to -0.17; 25 RCTs; Figure 5); however, the effect is statistically significantly smaller than in interventions targeting sleep. The subgroup of studies evaluating interventions not specifically directed at sleep still shows heterogeneity (I^2 = 62%) but there was no evidence of publication bias (Begg p=0.15, Egger p=0.16). We did not detect differences in PTSD outcomes (targeting sleep: SMD -0.71; CI -1.12 to -0.29; 17 RCTs vs not targeting sleep: SMD -0.35; CI -0.54 to -0.16; 27 RCTs; p = 0.09) or adverse events (targeting sleep: RR 1.03; CI 0.74, 1.41; 6 RCTs vs not targeting sleep: RR 1.57; CI 1.01 to 2.45; p = 0.9).

Discussion

Treatments for patients with PTSD have positive effects on sleep, especially treatments described by authors as targeting sleep rather than PTSD. The effect size on sleep outcomes was medium (SMD 0.56; CI -0.75 to -0.37; 49 RCTs). We also found improvement on PTSD measures (SMD -0.48; CI -0.67 to -0.29; 44 RCTs). With few exceptions, observed adverse events were comparable between intervention and control groups.

We found positive effects on sleep across all interventions, including those that did not address sleep specifically. However, across studies, reported treatment effects were statistically significantly larger in studies that specifically targeted sleep, in particular sleep-focused psychotherapy (both cognitive behavioral therapy for insomnia [CBT-I] and imagery rehearsal therapy [IRT]). These differences in effects should be interpreted with caution as they are not based on direct, head-to-had comparisons, but indirect comparisons across studies. We did not identify other systematic differences on effects based on intervention features, but it is difficult to detect study level moderators in the presence of residual heterogeneity.[178]

Other reviews

There have been several reviews of various aspects of sleep disturbances in PTSD, however, there are few that are not limited by treatment type, population, or type of sleep symptom. We identified only one systematic review that restricted to robust study designs, i.e., RCTs.[179] The authors searched for RCTs published between 1985 and 2014 and found 14 RCTs of treatment for sleep disorders in patients with PTSD. They found that, although selective serotonin reuptake inhibitors were effective in improving PTSD global symptoms, they showed a variable and modest effect on sleep disorder symptoms. The first review of the efficacy of sleep medication in PTSD was published in 2006, searching papers published after 1980.[180]. The

authors concluded that open-label and case studies suggested efficacy for some antidepressants, anticonvulsants and atypical antipsychotics. The placebo-controlled studies showed promising results for olanzapine and prazosin.[180] A further review concluded that, from the treatments available, cognitive behavioral therapy (CBT) techniques appeared to be the most successful and likely have fewer drawbacks.[181] Finally, one review that searched for articles published between January 2011 to April 2012,[182] found that CBT was at least as effective as pharmacologic treatment in the short-term and more enduring in beneficial effects.

Implications

PTSD is a serious and debilitating disorder that can have a devastating impact on those affected by the disorder and their families, as well as broader societal consequences, including increased risk of mental and physical health morbidity, high medical costs, poor work performance, familial discord, crime, unemployment and suicide risk.[2-6]

Sleep disturbances, including insomnia, nightmares, and daytime sleepiness, are common reactions to stress and trauma, and are in fact, cardinal symptoms of PTSD. Importantly, sleep disturbances are not only symptoms of PTSD, but longitudinal evidence further demonstrates that sleep problems can predict the development of PTSD as well as other mental health disorders.[183-188] Therefore, there is increasing recognition of the need for empirically supported treatments that target sleep disturbances in those with PTSD, regardless of whether such disturbances are the primary disorder or comorbid with other conditions, such as PTSD.

Our results provide strong evidence that both general treatments focused on PTSD improvement and treatments specifically targeting sleep improve sleep. However, interventions that specifically target sleep symptoms may demonstrate a greater benefit on sleep than non-

sleep-targeted interventions. Our review is based on an unbiased sample of studies that reported on the outcome of sleep regardless of whether or not sleep was a primary outcome of the study.

We showed sleep improvements across all intervention types; however, interventions specifically targeting sleep tended to report larger effects on sleep than other interventions, in particular sleep-focused psychotherapy. This finding is important as it suggests that targeting sleep disturbances specifically may benefit treatment outcomes. Furthermore, given that sleep disturbances are often considered less stigmatizing symptoms than mental health symptoms and that many of the treatments for PTSD are poorly tolerated by patients (e.g., exposure therapy),[189] these findings suggest that prioritizing sleep treatment may foster treatment compliance and improve the therapeutic alliance.

Although this review identified several treatments with demonstrated efficacy, in terms of behavioral treatments, two treatments in particular, CBT-I and IRT for nightmares, have received the most robust support, and target two of the most common types of sleep disturbances experienced patients with PTSD. Unfortunately, there remain significant gaps between guidelines from scientific studies and current practices in the healthcare system. In particular, pharmacologic therapies (i.e., "sleep aids" and other medications) continue to be the front-line treatment for sleep disturbances in PTSD prescribed by many providers,[190] though the evidence from this review does not suggest superiority of pharmacologic treatments over behavioral ones.

Strengths and limitations

The studies represented in this review allow an unbiased effect of interventions in adults with PTSD on sleep outcomes. The review was purposefully restricted to RCTs, a robust study design that allows strong evidence statements. However, this review has several limitations: (1) non-RCT studies are excluded, which may be the only type of evidence for less common

interventions; (2) broad categories were used to distinguish interventions and it is possible that efficacy differences exist between more refined intervention subcategories (e.g. trauma-focused vs. standard psychotherapy); and (3) no intervention and comparator combination was replicated across studies, preventing the use of direct comparisons.

Conclusions

Sleep disturbances, including insomnia, nightmares, and daytime sleepiness, are common reactions to stress and trauma, and are cardinal symptoms of PTSD. In this comprehensive and systematic review of interventions for adults with PTSD in studies reporting sleep outcomes, we found an overall positive treatment effect on sleep. We showed sleep improvements across all intervention types; however, interventions specifically targeting sleep, in particular sleep-focused psychotherapy approaches, tended to report larger effects on sleep than other interventions. While based on indirect comparisons, this finding is important as it suggests that targeting sleep disturbances specifically may benefit treatment outcomes and prioritizing sleep treatment may improve the therapeutic alliance. The results of this systematic review demonstrate that sleep disturbances are key, modifiable symptoms that are highly salient in the context of PTSD, and are promising treatment targets.

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Figures

Figure 1. PRISMA Flow Diagram.

Figure 2. Sleep symptom change in PTSD patients by treatments vs. comparators, standardized mean differences (SMD); CI = confidence interval.

Figure 3. PTSD symptom change in PTSD patients by treatments vs. comparators, standardized mean differences (SMD); CI = confidence interval.

Figure 4. Sleep symptom change in PTSD patients by treatments targeting sleep vs. comparators, standardized mean differences (SMD); CI = confidence interval.

Figure 5. Sleep symptom change in PTSD patients by treatments not targeting sleep vs. comparators, standardized mean differences (SMD); CI = confidence interval.

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Table 1. Evidence Table

Study	N	Intervention Target	Intervention Category	Intervention Description	Comparator(s)	Sleep Outcomes	PTSD Outcomes	Adverse Events
Abramowitz, 2008[78]	33	Sleep	Sleep medication	Zolpidem	Hypnotherapy	Morning Questionnaire; CGI	PDS	NR
Ahmadi, 2015[101]	48	Sleep	Combined	Sleep medication (SSRI and 2nd generation neuroleptic) + EMDR	No intervention; REM desensitization	PSQI	Mississippi Scale for Combat Related PTSD	NR
Ahmadpanah, 2014[40]	100	Sleep	Sleep medication	Prazosin	Placebo; other sleep medication: hydroxyzine	Sleep duration/onset latency; PSQI	Mini International Neuropsychiatric Interview	Nausea; dry mouth; gastrointestinal issues; headaches
Akuchekian, 2004[59]	67	PTSD	PTSD medication	Topiramate	Placebo	CAPS	CAPS	Lightheadedness; dizzyness; sexual dysfunction; hospitalization; lack of efficacy
Barilla, 2018[35]	95	Sleep	Sleep psychotherapy	CBT-I	Tele-psychotherapy: CBT-I	Nightmare Distress Questionnaire; Nightmare Frequency Questionnaire; ISI	NR	NR
Bartzokis, 2005[71]	65	PTSD	PTSD medication	Risperidone	Placebo	CAPS	CAPS	None
Becker, 2007[75]	28	PTSD	PTSD medication	Bupropion	Placebo	PSQI	CAPS	Heart pounding; concentration problems; problems with achieving orgasm; erectile dysfunction; increased appetite
Beidel, 2011[82]	35	PTSD	PTSD psychotherapy	Trauma management therapy	Exposure therapy	CAPS	CAPS	NR
Beidel, 2019[111, 155]	43	PTSD	Other	Trauma management therapy + virtual reality exposure therapy	Psychoeducation + virtual reality exposure therapy	Sleep duration; nightmares	CAPS	NR
Belleville, 2018[38, 144]	42	PTSD	PTSD psychotherapy	CBT	Usual care	Nightmare Distress Questionnaire; nightmares; PSQI	Modified PTSD Symptom Scale	NR
Blanaru, 2012[41]	13	Sleep	CAM	Muscle relaxation therapy	Other CAM: music relaxation therapy	Mini Sleep Questionnaire; Technion Sleep Questionnaire	NR	NR

Study	N	Intervention Target	Intervention Category	Intervention Description	Comparator(s)	Sleep Outcomes	PTSD Outcomes	Adverse Events
Bormann, 2018[36]	173	PTSD	CAM	Mantram-repetition therapy	Psychotherapy: present-centered therapy	ISI	CAPS	None
Brooks, 1985[39]	18	PTSD	CAM	Transcendental meditation	Psychotherapy	Custom insomnia measure (desgined by Charles Figley MD)	Custom PTSD measure (desgined by Charles Figley MD)	NR
Cates, 2004[70]	6	Sleep	Sleep medication	Clonazepam	Placebo	Sleep diary; distressing dreams	NR	Drowsiness; muscle weakness; dizziness; confusio; nausea
Church, 2016[58]	18	PTSD	Other	Emotional freedom technique	Waitlist	ISI	PCL	Not specified
Classen, 2001[57]	52	PTSD	PTSD psychotherapy	Trauma-focused and present-focused group therapy	No intervention	Trauma Symptom Checklist	Trauma Symptom Checklist	NR
Connor, 2006[72]	18	PTSD	PTSD medication	Tiagabine	Placebo	PSQI; Davidson Trauma Scale	Short PTSD Rating Interview	Headache; dizziness; dry mouth; nausea; constipation; drowsiness; muscle twitching
Cook, 2010[81,129,153,165]	124	Sleep	Sleep psychotherapy	IRT	Sleep and nightmare management treatment	Nightmares; PSQI	CAPS	NR
Davidson, 2001[63,157,164]	208	PTSD	PTSD medication	Sertraline	Placebo	PSQI	CAPS	Insomnia; headache; diarrhea; nausea; drowsines; nervousness; fatigue; decreased appetite; dry mouth; vivid dreams
Difede, 2014[91,124,163]	25	PTSD	Other	Virtual reality exposure therapy + PTSD medication (cycloserine)	Virtual reality exposure therapy + placebo	CAPS	CAPS	NR
Donner, 2017[56]	42	Sleep	Other	Olfactory stimulation	Placebo	Nightmares	NR	NR

Study	N	Intervention Target	Intervention Category	Intervention Description	Comparator(s)	Sleep Outcomes	PTSD Outcomes	Adverse Events
El-Solh, 2017[110,146]	42	Sleep	Other	Continuous positive airway pressure	Mandibular advancement devices	PSQI; Epworth Sleepiness Scale	PCL	NR
Friedman, 2007[76]	169	PTSD	PTSD medication	Sertraline	Placebo	PSQI	CAPS	Diarrhea; headache; insomnia; somnolence; nausea; fatigue
Galovski, 2016[103]	108	Sleep	Other	Hypnosis	Symptom monitoring	PSQI; CAPS; ISI	CAPS	NR
Germain, 2014[131]	40	Sleep	Behavioral	Sleep hygeine	Information control	PSQI; ISI; PSQI Addendum for PTSD	PCL	NR
Gersons, 2000[61]	42	PTSD	PTSD psychotherapy	Brief eclectic psychotherapy	Waitlist	Sleeping problems	Structured Clinical Interview for DSM-III-R Axis I Disorders	NR
Gutner, 2013[90,166,168]	171	Sleep	PTSD psychotherapy	Cognitive processing therapy	Prolonged Exposure	PSQI; CAPS	NR	NR
Hall, 2019[27]	54	PTSD	Behavioral	Exercise training	Waitlist	PSQI	PCL	None
Hamner, 2009[79]	29	PTSD	PTSD medication	Divalproex	Placebo	PSQI	CAPS	Dizziness; fatigue; somnolence; dyspepsia; diarrhea
Harb, 2019[24,117,154,175]	108	Sleep	Sleep psychotherapy	CBT-I + IRT	Other psychotherapy: CBT-I	PSQI; nightmare frequency/distress	PCL	None
Igreja, 2004[68]	137	PTSD	Other	Testimony method	No intervention	Nocturnal Intrusions after Traumatic Experiences questionnaire	Self-Inventory for PTSD	NR
Jacobs-Rebhun, 2000[62]	69	Sleep	PTSD medication	Cyproheptadine	Placebo	PSQI; Nightmare questionnaire	CAPS	NR
Jetly, 2015[98]	19	Sleep	Sleep medication	Syntethic cannabinoid	Placebo	CAPS	NR	Dry mouth; headache
Jindani, 2015[55]	80	PTSD	CAM	Yoga	Waitlist	ISI	PCL	NR
Keane, 1989[54]	24	PTSD	PTSD psychotherapy	Implosive/flooding therapy	No intervention	Jackson Structured Interview	Jackson Structured Interview	NR
Kim, 2013[88]	22	PTSD	Behavioral	Mind-Body Intervention	No intervention	Sleep quality	PCL	NR
King, 2015[99]	29	Sleep	CAM	Auricular acupuncture	Usual care	PSQI; sleep diary; actigraphy	NR	Fall; wrist injury; suicidal ideation; alcohol-related events

Study	N	Intervention Target	Intervention Category	Intervention Description	Comparator(s)	Sleep Outcomes	PTSD Outcomes	Adverse Events
Kip, 2013[92]	57	PTSD	PTSD psychotherapy	Accelerated resolution therapy	Attention control	PSQI	PCL	Nightmares; flashbacks; falls; anxiety; anger
Krakow, 2001[43]	168	Sleep	PTSD psychotherapy	IRT	Waitlist	PSQI; nightmare frequency	CAPS	Negative imagery
Krytsal, 2016[104,116,126,133,170]	267	PTSD	PTSD medication	Risperidone	Placebo	PSQI; CAPS	NR	NR
Lang, 2017[53,156]	160	PTSD	PTSD psychotherapy	Acceptance and commitment therapy	Other psychtherapy: present-centered therapy	ISI	PCL	NR
Lang, 2019[32,119]	37	PTSD	CAM	Compassion meditation	Veteran Calm	PROMIS	PCL	None
Lange, 2001[52,161]	30	PTSD	PTSD psychotherapy	Online therapy: Interapy	Waitlist	SCL	NR	NR
Lange, 2003[67]	184	PTSD	PTSD psychotherapy	Online therapy: Interapy	Waitlist	SCL	NR	NR
Mack, 2014[51]	34	Sleep	PTSD psychotherapy	CBI-I + IRT	Waitlist	PSQI; PSQI Addendum for PTSD; sleep diary; nightmare frequency	PTSD Symptom Scale	NR
Margolies, 2013[87]	40	Sleep	Sleep psychotherapy	CBT-I	Waitlist	PSQI; ISI; sleep diary; actigraphy	PTSD Symptom Severity	NR
McCall, 2018[26,160]	20	Sleep	Sleep medication	Prazosin	Placebo	Sleep (vs control) Disturbing Dreams and Nightmare Severity Index	PCL	Fainting; weakness; falls; sucidial ideation and hospitalization
McHugh, 2014[94,169]	353	Sleep	PTSD psychotherapy	Seeking Safety	Health education	Insomnia/ nightmare frequency	Posttraumatic Stress Disorder Symptom Scale	NR
McRae, 2004[69]	37	PTSD	PTSD medication	Nefazodone	Other PTSD medication: sertraline	PSQI	CAPS	Headahce; drowsiness; insomnia; restlessness; delayed ejaculation; anorgasmia; fatigue; nightmares; dry mouth; dizziness; difficulty concentrating
Meltzer-Brody, 2000[50]	53	PTSD	PTSD medication	Fluoxetine	Placebo	Structured Interview for PTSD	Structured Interview for PTSD	NR

Study	N	Intervention Target	Intervention Category	Intervention Description	Comparator(s)	Sleep Outcomes	PTSD Outcomes	Adverse Events
Meng, 2012[109]	245	PTSD	CAM	Chinese herbs	Placebo	SCL	NR	Nausea; diarrhea; malaise
Mithoefer. 2018[42]	26	PTSD	Combined	3,4-methyl enedioxy methamphetamine + psychotherapy	3,4-methyl enedioxy methamphetamine (different dosages) + psychotherapy	PSQI	CAPS	Major depression; sucidial ideation; appendicitis; premature ventricular contractions
Nakamura, 2011[85]	63	Sleep	Behavioral	Mind-body bridging	Sleep education	Medical Outcomes Study Sleep Scale	PCL	NR
Neylan, 2006[74]	63	PTSD	PTSD medication	Guanfacine	Placebo	Sleep Quality Index	CAPS	Dry mouth; lightheadedness; somnolence
Ot'alora, 2018[33]	28	PTSD	Combined	3,4-methyl enedioxy methamphetamine + psychotherapy	3,4-methyl enedioxy methamphetamine (different dosages) + psychotherapy	PSQI	CAPS	Anxiety; dizziness; fatigue; headache; jaw clenching; low mood; muscle tension; difficulty concentrating; irritability; insomnia; lack of appetite; nausea; need more sleep; ruminations; depressed mood; obsessive rumination; panic attacks; restlessness
Peniston, 1986[49]	16	Sleep	Other	Electromyographic biofeedback-assisted desensitization	No intervention	Frequency of recurring nightmars/ flashbacks	NR	NR
Petrakis, 2016[102,127,130]	96	Sleep	Sleep medication	Prazosin	Placebo	PSQI; CAPS	CAPS	Fainting; falling; dizziness
Pollack, 2011[84]	54	Sleep	Sleep medication	Eszopiclone	Placebo	PSQI	CAPS	Unpleasant taste; sedation; headaches
Prisco, 2013[108]	35	Sleep	CAM	Group auricular acupuncture	CAM: sham group auricular acupuncutre; waitlist	Morin Sleep Diary; ISI; actigraph	NR	Discomfort
Pruiksma,	108	PTSD	PTSD psychotherapy	Group cognitive	Other	PCL	NR	NR

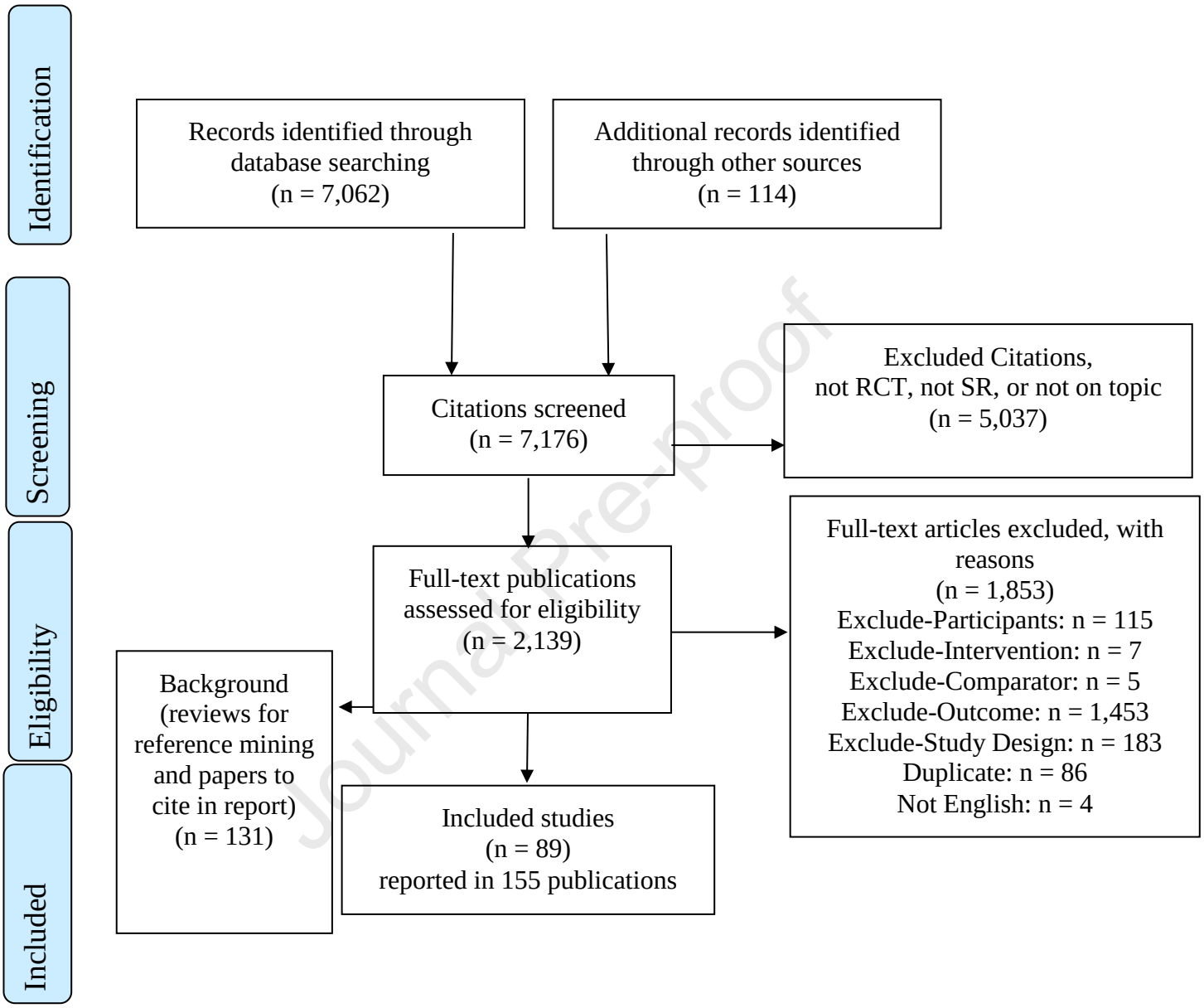
Study	N	Intervention Target	Intervention Category	Intervention Description	Comparator(s)	Sleep Outcomes	PTSD Outcomes	Adverse Events
2016[106,173]				processing therapy	psychotherapy: group present-centered therapy			
Ramaswamy, 2017[107,140]	59	PTSD	PTSD medication	Vilazodone	Placebo	CAPS; PSS	CAPS; PSS	Gastrointestinal events; sexual, and sleep-related events; headaches; irritability; suicidal ideation; self-mutilation
Raskind, 2003[66]	20	Sleep	Sleep medication	Prazosin	Placebo	CAPS	C APS	Orthostatic hypotension; dizziness
Raskind, 2007[73]	40	Sleep	Sleep medication	Prazosin	Placebo	CAPS; PSQI; Nightmare Frequency Questionnaire; PTSD Dream Rating Scale	CAPS	Dizziness
Raskind, 2013[89,159,145,174]	67	Sleep	Sleep medication	Prazosin	Placebo	CAPS; PSQI	CAPS	Lightheadedness; syncope; nasal congestion; lack of energy; palpitations; drowsiness; depression; muscle weakness; headache
Raskind, 2018[48,147]	304	Sleep	Sleep medication	Prazosin	Placebo	CAPS; PSQI	CAPS	Dizziness; lightheadedness; urinary incontinence; somnolence; nausaea; insomnia; diarrhea; dry mouth; suicidal ideation
Rasmusson, 2017[34,114]	112	PTSD	PTSD medication	Ganaxolone	Placebo	ISI	CAPS	Headache; somnolence
Rodgman, 2016[47,115]	16	Sleep	PTSD medication	Doxazosin	Placebo	PSQI	CAPS	Rashes; rhinitis; bloating
Rosenbaum, 2015[97,158]	81	PTSD	Other	Exercise intervention + usual care	Usual care	PSQI	PCL	None
Rosenberg, 2002[64]	12	PTSD	Other	Repetitive transcranial magnetic	Repetitive transcranial magnetic	Hamilton Rating Scale for Depression	Mississippi Scale of Combat Severity	None

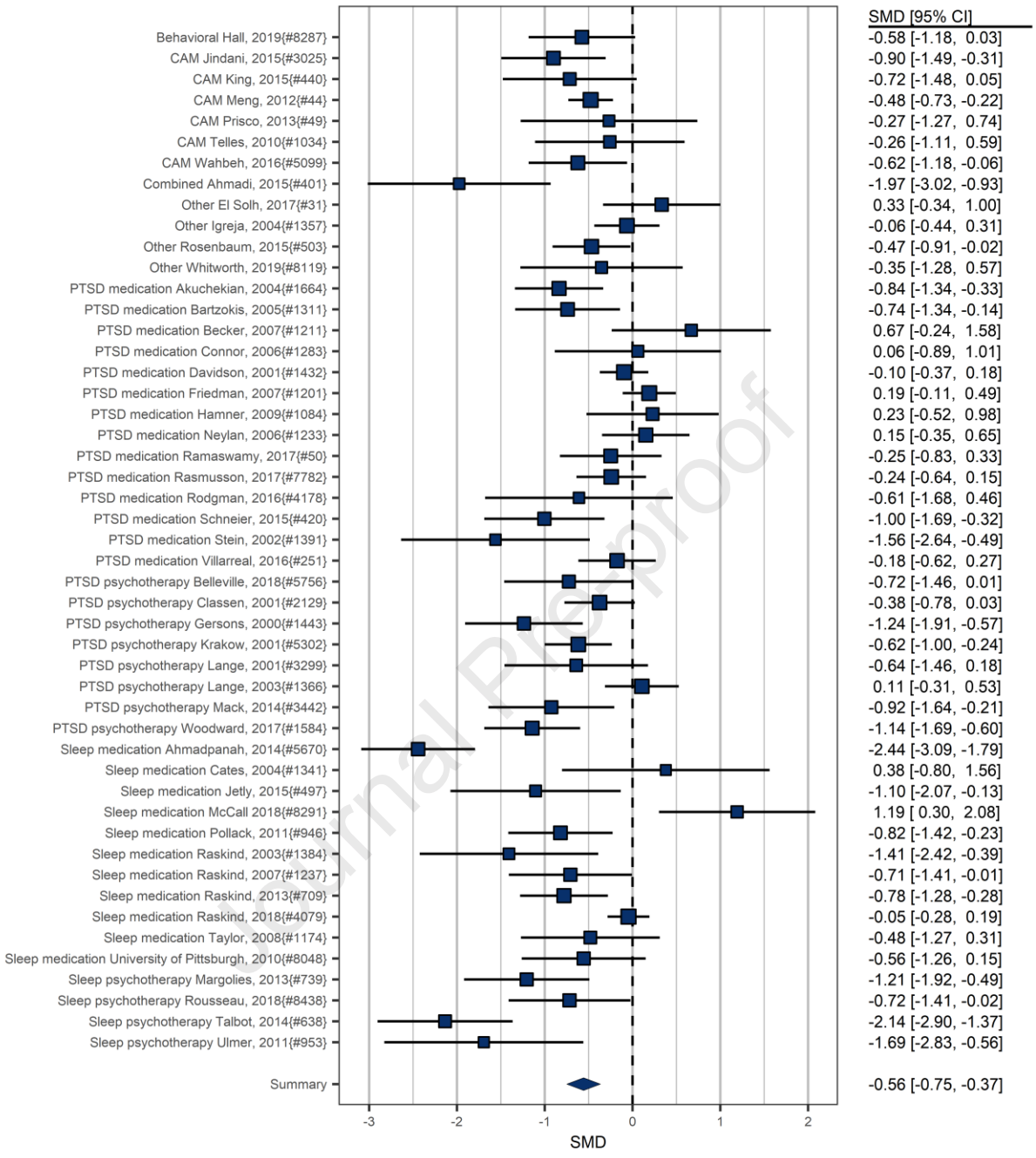
Study	N	Intervention Target	Intervention Category	Intervention Description	Comparator(s)	Sleep Outcomes	PTSD Outcomes	Adverse Events
				stimulation to left frontal cortex	stimulation to left frontal cortex (different frequency)			
Rousseau, 2018[23]	43	Sleep	Sleep psychotherapy	IRT	No intervention	PSQI; ISI; Nightmare Distress Questionnaire	NR	NR
Schafer, 2019[28,125]	48	Sleep	Other	Olfactory stimulation	Olfactory stimulation (alternative device); placebo	Sleep diary	NR	None
Schneier, 2015[100,113,141,162]	38	PTSD	PTSD medication	Mirtazapine + sertraline	PTSD medication: sertraline + placebo	PSQI	PCL	Nausea; headache; heartburn; vomiting; decreased appetite; dry mouth; constipation; diarrhea; flatulence; excessive sweating; skin problems; bruising easily; restlessness; tremor; nervousness; impaired coordination; insomnia; fatigue; somnolence; decreased libido; sexual dysfunction; urinary dysfunction; blurry vision; lightheadedness; forgetfulness; impaired concentration; apathy
Schnurr, 2015[46,123,128,156,167]	284	PTSD	PTSD psychotherapy	Present-centered therapy	Prolonged exposure	CAPS	NR	NR
Stein, 2002[65]	19	PTSD	PTSD medication	Olanzapine	Placebo	PSQI	CAPS	Somnolence

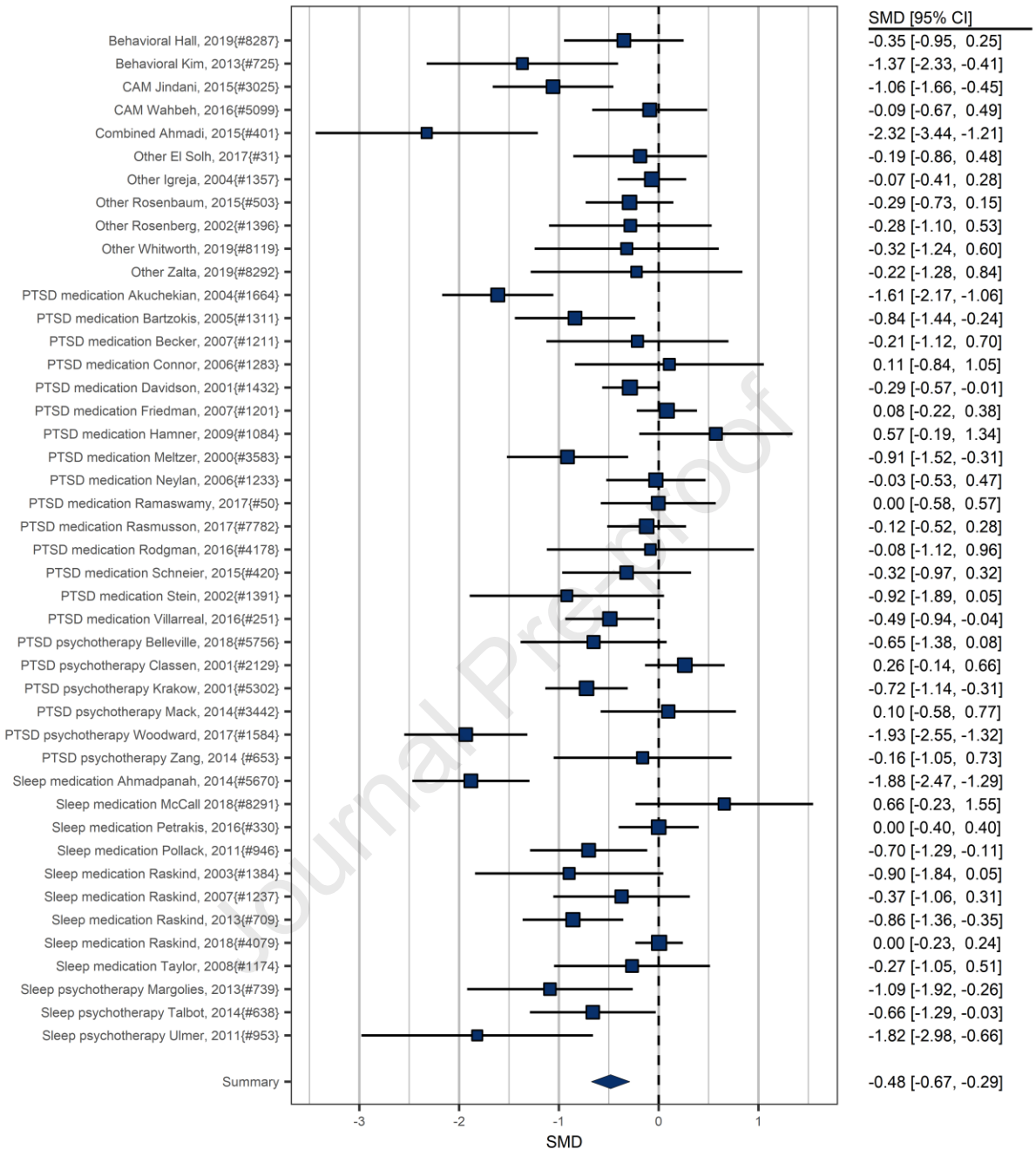
Study	N	Intervention Target	Intervention Category	Intervention Description	Comparator(s)	Sleep Outcomes	PTSD Outcomes	Adverse Events
Talbot, 2014[95,132,150]	45	Sleep	Sleep psychotherapy	CBT-I	Waitlist	ISI; CAPS; Epworth Sleepiness Scale; sleep diary; polysomnography; actigraphy	PCL	NR
Taylor, 2008[77,151]	26	Sleep	Sleep medication	Prazosin	Placebo	CAPS; PTSD Dream Rating Scale; Non-Nightmare Distressed Awakenings	PCL	Dizziness
Telles, 2010[80,112]	22	PTSD	CAM	Yoga	Waitlist	Disturbed sleep	NR	None
Thunker, 2012[86]	26	Sleep	Sleep psychotherapy	Nightmare therapy	Usual care	Nightmare frequency/anxiety	NR	NR
Ulmer, 2011[83]	22	Sleep	Sleep psychotherapy	CBT-I + IRT	Usual care	PSQI; sleep diary	PCL	NR
University of Pittsburgh, 2010[31,171]	50	Sleep	Sleep medication	Prazosin	Placebo; behavioral sleep intervention	ISI; PSQI; sleep diary; polysomnography	NR	Drowsiness
Villarreal, 2016[105,138,152]	80	PTSD	PTSD medication	Quetiapine	Placebo	PSQI	CAPS	Dry mouth; sedation; somnolence
Wahbeh, 2016[44]	102	PTSD	CAM	Mindfulness meditation	Other CAM: Mindfulness meditation + slow breathing; slow breathing; sitting quietly	PSQI	PCL	NR
Walters, 2019[29,148]	23	Sleep	Sleep psychotherapy	CBT-I + IRT	Supportive care therapy	PSQI; PSQI Addendum for PTSD; ISI; sleep diary	CAPS	NR
Watson, 1997[45]	90	PTSD	CAM	Relaxation + deep breathing + thermal biofeedback	Other CAM: relaxation + deep breathing; relaxation	Posttraumatic Stress Disorder Interview	Posttraumatic Stress Disorder Interview	NR
Whitworth, 2018[37]	30	PTSD	Other	Resistance training	Attention control	PTSD-related Sleep Disturbances; Sleep Quality	NR	NR
Whitworth, 2019[30]	22	Sleep	Other	Resistance training	Attention control	PSQI	Posttraumatic Diagnostic Scale	None
Woodward, 2017[60,172]	121	Sleep	PTSD psychotherapy	Trauma-focused cognitive therapy for PTSD	Waitlist; Other psychotherapy: intensive trauma-focused cognitive therapy for PTSD; emotion-focused supportive therapy	Hours of sleep; sleep quality; CAPS	PTSD severity	NR
Zalta, 2019[25,122]	15	PTSD	Other	Bright light treatment	Placebo bright light treatment	PSQI; wake after sleep onset; sleep time	PCL	NR
Zang, 2014[93]	30	PTSD	PTSD psychotherapy	Narrative exposure therapy	Waitlist; other psychotherapy: revised narrative	Sleep quality	Impact of Event Scale	NR

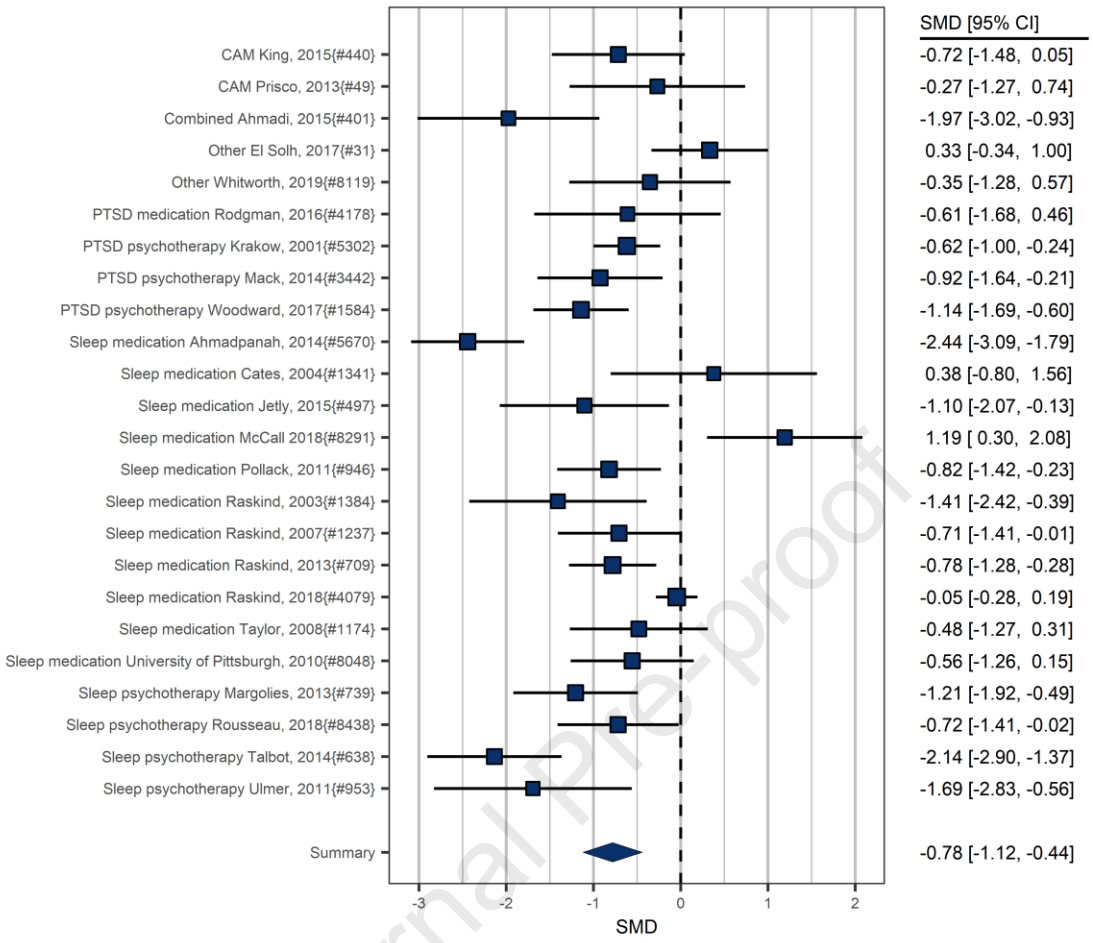
Study	N	Intervention Target	Intervention Category	Intervention Description	Comparator(s)	Sleep Outcomes	PTSD Outcomes	Adverse Events
					exposure therapy			

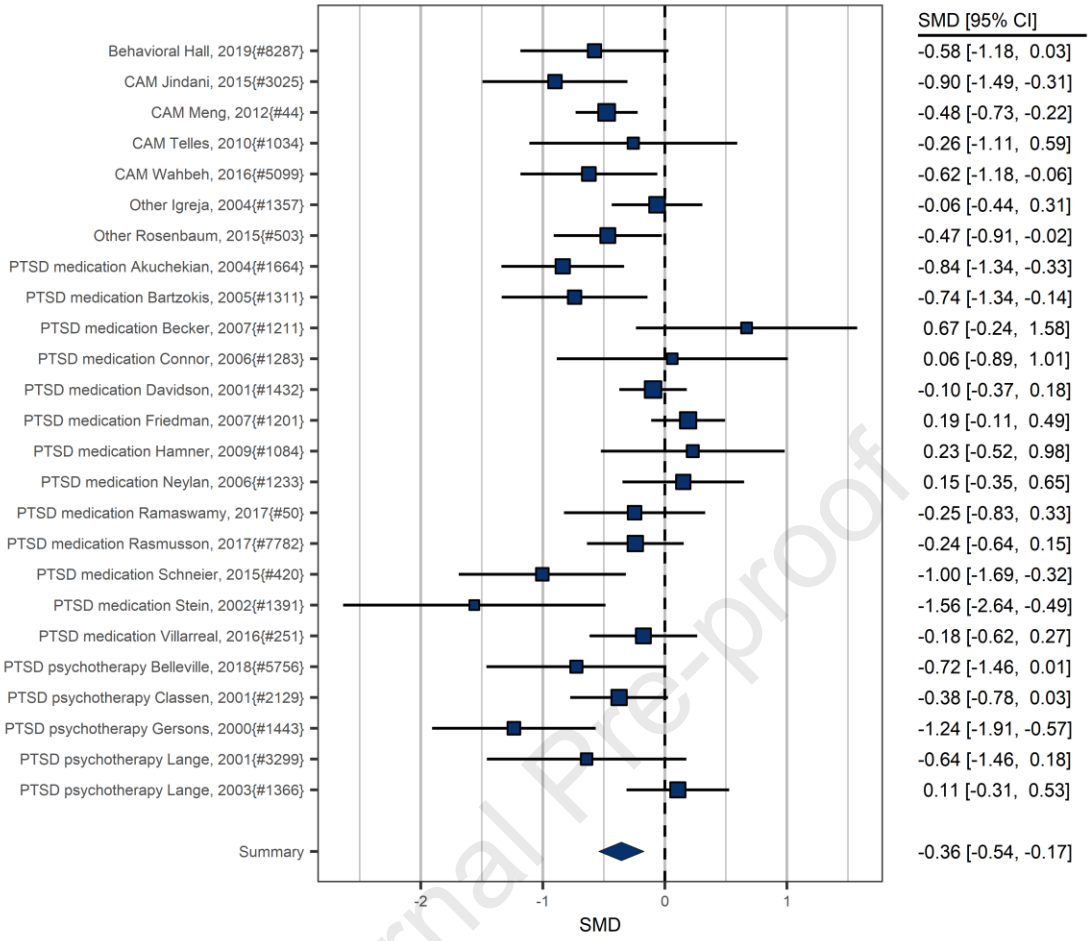
Note: Abbreviations: CAM: complementary and alternative medicine; CAPS: Clinician-Administered PTSD Scale; CBT: cognitive behavioral therapy; CBT-I: cognitive behavioral therapy for insomnia; IRT: imagery rehearsal therapy; ISI: Insomnia Severity Index; NR: not reported; PCL: PTSD Checklist: PSQI: Pittsburgh Sleep Quality Index; PTSD: posttraumatic stress disorder; SCL: Symptom Checklist.











Highlights

- Patients with PTSD often have difficulties with sleep
- Treatments for adults with PTSD improve both sleep outcomes and PTSD symptoms
- Interventions targeting sleep improved sleep more those with no sleep target
- PTSD outcomes did not differ between sleep- and non-sleep-targeted interventions