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RESEARCH ARTICLE

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Psychotherapeutic and pharmacological agents for post-traumatic stress disorder with sleep disorder: network meta-analysis

Cheng-Yang Huang[a], Yi-Fan Zhao[a], Zhi-Xin Zhang[a], Run-Ben Liu[a], Jia-Ling Liu[a], Xiao-Zheng Li[a], Jie Luo[a,b], Li Yue[c] and Chao Zhang[a]

[a]Center for Evidence-Based Medicine and Clinical Research, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, China; [b]Center for Neurological Diseases, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, China; [c]Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, China

ABSTRACT

Objective: The current guidelines and canonical norms of diagnosis or treatment for Post-traumatic stress disorder (PTSD) with sleep disorder are still conflicting and have not yet reached a consensus. This study aimed to unravel the most effective countermeasures between two categories (psychotherapy and pharmacotherapy) put forward by the National Institute for Health and Clinical Excellence (NICE) and World Federation of Societies of Biological Psychiatry (WFSBP) respectively to treat PTSD individuals co-exist with sleep disorders.

Methods: Four databases, including PubMed, EMBASE, Cochrane Library, and APA PsyNet, were searched from inception to February 02, 2023.

Results: Twenty articles with 24 Randomized controlled trials (RCTs) and a total number of 1,647 participants were included. As demonstrated in the network meta-analysis comparison results, CBT-I (standardized mean differences (SMD) =−1.51,95% confidence interval (CI):−2.55 to −0.47), CBT-I *plus* IRT (SMD=−1.71, 95%CI:−3.39, −0.03), prazosin (SMD=−0.87,95%CI:−1.59 to −0.16) and hydroxyzine (SMD=−1.06, 95%CI: −1.94 to −0.19) significantly reduced PTSD symptoms compared with placebo. In contrast to placebo, CBT-I (SMD=−5.61,95%CI:-8.82 to −2.40) significantly improved sleep quality. For nightmare severity, IRT (SMD=−0.65, 95%CI:-1.00 to −0.31), prazosin (SMD=−1.20,95%CI:−1.72 to −0.67) and hydroxyzine (SMD=−0.98,95%CI:-1.58 to −0.37) significantly reduced nightmare severity in comparison with placebo.

Conclusions: This study suggested that under most circumstances, psychotherapy namely CBT-I had a favorable profile, but pharmacotherapy with prazosin was effective in managing nightmare severity. The sole avail of CBT-I was recommended to improving sleep quality while CBT-I and CBT-I plus IRT showed excellent management of PTSD symptom severity. Exposure to CBT-I isrecommended for depression. The relevant clinical guidelines for the management of individuals with PTSD and sleep disorders may regard this as a reference.

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Post-traumatic stress disorder; sleep disorders; psychotherapy; pharmacotherapy; cognitive behavioral therapy for insomnia; prazosin

1. Introduction

Post-traumatic stress disorder (PTSD) is a mental health statue that arises from traumatic events featuring by intrusive memories of the incident, difficulty in interpersonal relationships, recurrent distress, avoidance of similar situations and flashbacks [1]. Diagnostic and Statistical Manual-5 (DSM-5) diagnosis PTSD by checking whether the client expose to one or more traumatic event(s), which is defined as one that involved death or threatened death, actual or threatened serious injury, or actual or threatened sexual violence [2]. Besides, PTSD is regarded as a multifaceted diagnosis that impacts multiple domains of functioning, including depression. Typically, the Clinician-Administered PTSD Scale (CAPS), DSM scale, PTSD

CONTACT Chao Zhang zhangchao0803@126.com Center for Evidence-Based Medicine and Clinical Research, Taihe Hospital, Hubei University of Medicine, Shiyan 442000, Hubei, China; Jie Luo taihehospital@yeah.net Center for Evidence-Based Medicine and Clinical Research, Taihe Hospital, Hubei University of Medicine, Shiyan 442000, Hubei, China; Li Yue 370665437@qq.com Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei 442000, China.

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Symptom Scale (PSS) and self-report PTSD checklist (PCL) areemployed as diagnostic criteria in clinical practice [3,4]. Meanwhile, sleep disorder is regarded as a primary complaint of a massive number of PTSD patients. Sleep disorder are conditions that result in changes in the way that you sleep. However, it can be qualitative and quantitative analyzed by sleep quality, nightmare severity, depression and total sleep time [5]. It can be concluded from recent studies that there exists great potential correlation between PTSD and sleep disorders. A research paper published in 2019 revealed that 2647 PTSD patients diagnosed by the DSM-5 criteria was reported 92% who underwent at least one sleep disturbance that affects sleep quality [6]. And another proved causality between PTSD and sleep disorder that once PTSD resolved sleep disorder subsided [7,8]. Ahmadi one of the lead authors previously mentioned endorse that insomnia (one of the sleep disorders) occurs 63% (95%CI: 45%~78%) in PTSD patients, also in the same way they suggest that check-up is required in managing insomnia with PTSD [7]. It's lamenting that those who have PTSD co-existing with sleep disorders will suffer a lot. As the symptoms limit the patients' capability to refresh from the botched symptom they originally have and the daily errands they encounter, this is a vicious cycle where inadequate sleep time impair the initially abnormal physio-logical balance of the organism, which may further increase the severity of PTSD [9].

Psychotherapeutic and pharmacological treatment regime are designated as the main countermeasures to tackle with the symptoms of PTSD [10]. As the evaluation of diagnostic criteria is mostly depending on mental illness [3,11], psychotherapeutic countermeasures are recommended for priority use according to the World Federation of Societies of Biological Psychiatry (WFSBP) guideline [12]. Former study identified that neurobiological mechanism regulate the relationship between sleep disorders and PTSD symptoms and it was downstream effect in this regulation system [13,14], as it can be seen that sleep is essential for healthy emotional regulation processes. As such, psychotherapy should be considered for PTSD patients with sleep disorders. Best intervention for PTSD patients with sleep disorders is cognitive behavioral therapy (CBT) that is recommended by National Institute for Health and Clinical Excellence (NICE) guideline, which include various forms listed as cognitive-behavioral therapy for insomnia (CBT-I), cognitive processing therapy (CPT), exposure therapy (ET), narrative exposure therapy (NET) Among them ET is a special countermeasure in treating the disease that it introduces individuals to increasing levels of the stress-related stimulus. They will begin to learn how to cope with these until their anxiety levels lower and, ideally, become non-existent when confronted with the stimuli [15,16]. While, the guideline also notes that the efficacy of how long it can be maintained remains largely dim [15]. In terms of pharmacotherapy, the best treatment for nightmares is prazosin as WFSBP referred [12]. Prazosin is a quinazoline derivative that acts as a competitive alpha1-antagonist, not only can it treat PTSD with nightmares but benign prostatic hyperplasia, hypertension as well [17]. Meanwhile, prazosin may be a promising agent for the PTSD treatment regime [18]. From the perspective of specificity, patients suffer from PTSD co-exist with sleep disorders are recommended in the combination therapy in which selective serotonin reuptake inhibitor (SSRIs) and psychotherapy was recommended [10]. Sleep quality, nightmare severity and total sleep time (TST) are included to measure the integrated therapeutic effects. Nonetheless, substantial evidence was putting forward in accordance with the long been known guidelines [10,12,15], the information to ensure the uniform standard of treatment for patients with PTSD and sleep disorders was scarce. Consequently, subjects with PTSD and sleep disorders are specific populations to whom more attention should be paid.

In this research detailed treatments (CBT-I, CPT, ET, NET) isn't mentioned into consideration, and, such an analysis is beyond the scope of our paper, which aims only to unveil that the certain population (people with PTSD) suffered specific symptom (sleep disorder) that which regime (psycho- or pharmaco-) is better in alleviating symptoms disease had caused. Furthermore, the study focused on the primary leading factor (PTSD) of the disease, and from the primary leading factor, explores the impact of treatment decisions on specific symptoms (sleep disorder). The research gap whether the different forms of treatment on earth were more beneficial still need joint effort to make it come out in the wash. Thus, to summarize the extant knowledge base and guide future-oriented research, this network meta-analysis (NMA) was performed. Compared with traditional meta-analysis, the restriction of pairwise comparisons of the two interventions was abolished. The NMA also compares myriad interventions by simultaneously synthesizing available direct and indirect evidence [19]. With regard to what has been considered above, we conducted the NMA to evaluate the general efficacy of psychotherapy and pharmacotherapy for sleep disorders among patients with PTSD and recommend the most practical countermeasures to treat this overwhelming malaise.

2. Methods

This systematic review and network meta-analysis was registered at PROSPERO at CRD42023415240. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension statement for NMA (PRISMA-NMA) [20].

2.1. Literature search

Four databases, including PubMed, EMBASE, the Cochrane Library, and American Psychological Association PsyNet, were systematically and comprehensively searched to retrieve relevant literature and references published before February 02, 2023. Supplementary Method 1 shows the literature search strategies and databases.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were used: (1) Participants: adults who had a concomitant diagnosis of PTSD on the basis of standard diagnostic criteria, including DSM-III, DSM-IV, DSM-IV-TR, DSM-5 and a significant sleep disorder as clearly defined by the scale or clinical. One thing in particular need for better description is that if PTSD is the principal etiology of sleep disorders, then other comorbidities are allowed; (2) Interventions: All types of interventions (psychotherapeutic/pharmacological) are included, psychotherapeutic (CBT, imagery rehearsal therapy (IRT), CBT-I, hypnosis and exposure) and pharmacological (hydroxyzine, mianserin, nabilone and prazosin). Exposure was designated as a psychotherapy that was developed to help people confront their fears and it might help break the pattern of evasion [21]; (3) Comparators: placebo or other psychotherapeutic/pharmacological interventions (head-to-head trial); (4) Outcomes: outcomes were separated into three classes PTSD related- (PTSD symptoms severity and depression), sleep related- (sleep quality, nightmare severity, total sleep time) and acceptability. PTSD symptoms severity was estimated by CAPS (Clinician-Administered PTSD Scale), PCL (PTSD Checklist), PCL-C (PTSD Checklist-Civilian Version), PSS (PTSD Symptom Scale), PDS (Posttraumatic Diagnostic Scale), PTSD score and Self-efficacy, while sleep related outcomes were estimated by PSQI (Pirrsburgh Sleep Qualify Index), IES (Impact of Event Scale), ISI (Insomnia Severity Index) and insomnia severity. Acceptability was defined as a multifaceted concept that reflects the extent to which people delivering or receiving an intervention; (5) Study design: randomized controlled trial (RCT). The analysis was restricted to studies conducted on humans in English.

Exclusion criteria were as follows: (1) reported cardiovascular disease, traumatic brain injury and other non-psychological conditions that may have a greater impact on the patient's mental state; (2) sleep disorders not caused by PTSD while incurred by other psychiatric disorders (e.g. TBI, other neurocognitive disorders, and substance use disorders); (3) no available data in the original research or the data could not be converted; (4) prevention of relapse trials; (5) cross-linking experiment; and (6) duplicate studies.

2.3. Data extraction and quality assessment

Information was integrated into the data extraction by two independent authors (CYH and YFZ) and, proofread by a final investigator (CZ). With regard to the selection of scales for symptom remission in PTSD, the CAPS score is the gold standard in the process of evaluation [3], for self-reported PTSD, the Davidson Trauma Scale served as the gold standard [22]. As for the selection of scales for relieving symptoms of insomnia, the Pittsburgh Sleep Quality Index (PSQI) score is the gold standard in the scale evaluated [23]. If the gold-standard scale was not adopted in this study, other optimal scales were employed under careful consideration. The difference between pre- and post-change was selected for comparison, if the included survey was unable to contain this segment of data, the final measurement will be recruited [24]. If relevant data were not reported within the article, the most recent data were calculated based on the related data reported in the original articles. On the quality appraisal of included study, two reviewers (CYH and YFZ) independently assessed the overall quality of the included studies under the criterion reported in the new edition of the Cochrane Handbook for Systematic Reviews of Interventions [24].

2.4. Statistical analysis

Continuous and dichotomous outcomes were denoted as relative ratios (RR) with their corresponding 95% confidence intervals (CI) and standardized mean differences (SMD) with their corresponding 95%CI [25]. The chi-square test was applied to assessing heterogeneity, in which the level of significance was set to $p < 0.1$, I^2 values ≥40% were interpreted as indicating significant heterogeneity, in which circumstances a random-effects model was used to conduct meta-analysis, whereas for I^2 values <40%, a fixed-effect model was used instead

[26]. According to the underlying assumption of transitivity within the network, conflicts may exists between pairwise comparisons and the distribution of effect modifiers [27]. When a closed loop was considered present, the 'loop inconsistency' method was used for test the inconsistency [28]. Thiswas noticeable when the treatment effects around a loop did not fit the consistency equations. The surface under the cumulative ranking curve (SUCRA) with regard to summarizing probabilities, was used to provide summary and pooled statistics for cumulative ranking. According to this definition, SUCRA values mirror the effectiveness of an intervention; therefore, a rank plot with larger SUCRA values indicates more effective interventions. Publication bias is analyzed by using funnel plots. Funnel plot is a scatter plot of the effect estimates from individual studies against some measure of each study's size or precision. Funnel plots was used to examine bias in the results of meta-analyses, whereas x-axis is comparison-specific pooled effect, while y-axis is standard error of SMD or standard error of logRR [29]. All statistical analyses were performed and accomplished using Stata version 15.0 (StataCorp LLC, College Station, TX, USA) and R version 4.0.5 (Vienna, Austria), obtained copyright license.

3. Result

3.1. Study characteristics and quality assessment

The search yield 5,095 results. After the initial evaluation, 1,048 duplicates were removed and 4,026 studies were regarded as irrelevant (as determined by reading the titles and abstracts). 21 articles with 24 RCTs were determined by reading the full text. Ultimately, 20 studies were included in the NMA. Supplementary Figure 1 shows the work flow for the selection of studies.

A total of 1,647 participants from 20 articles with 24 RCTs [30–49] were included in this NMA. Baseline characteristics are summarized in Supplementary Table 1. The two categories of intervention were designated as psycho- [32–35,37–39,41,44–46,48,49] or pharmaco- [30,31,36,40,42,43,47]. The psychotherapy included in this NMA were CBT-I [35,39,41,46,48], CBT-I *plus* IRT [33], IRT [34,37,38,44,45], exposure [49], and hypnosis [32]. While, pharmacotherapy included prazosin [31,40,42,43,47], hydroxyzine [31], nabilone [36] and zolpidem [30]. With respect to the included studies, seven studies evaluated PTSD severity using CAPS scale [34,35,37,40,42,43,49] and 12 studies evaluated insomnia severity using the PSQI scale [31,33–35,37,38,42–45,48,49].

Information on the quality and bias risk assessment of all studies is summarized in Supplementary Figure 2 and Supplementary Figure 3.

3.2. Results of NMA and direct comparison

3.2.1. PTSD symptom severity

Sixteen studies [30,31,33–39,41–44,46,48,49], with 644 participants and 10 intervention categories were included in the NMA to assess PTSD symptoms. A network plot of PTSD symptom severity, including nine categories of active interventions (five psychological and four pharmacological interventions) and placebo, is presented in Figure 1A. No inconsistencies were found in the severity of PTSD symptoms (Supplementary Figure 4. According to the NMA results, the active psychological interventions, including CBT-I (SMD= −1.51, 95%CI: −2.55 to −0.47), CBT-I *plus* IRT (SMD= −1.71, 95%CI: −3.39 to −0.03), and the active pharmacological interventions, including prazosin (SMD= −0.87, 95%CI:-1.59 to −0.16), hydroxyzine (SMD= −1.06, 95%CI: −1.94 to −0.19), significantly reduced PTSD symptom severity compared with placebo, while zolpidem (SMD= 2.71, 95%CI: 0.56 to 4.86) showed significantly poor treatment compared with all types of interventions (Table 1). Comparisons of the effects of other active interventions on PTSD symptom severity are summarized in Table 1.

Regarding direct comparisons of PTSD symptom severity, the active psychological interventions CBT-I (SMD= −1.51, 95%CI: −2.15 to −0.88), CBT-I *plus* IRT (SMD= −1.21, 95%CI: −2.18 to −0.24), IRT (SMD= −0.56, 95%CI: −0.86 to −0.25) and the active pharmacological interventions nabilone (SMD= −1.10, 95%CI: −2.08 to −0.12) significantly reduced PTSD symptom severity compared with placebo, other direct comparisons were shown in Supplementary Table 2.

Figure 2 shows that, according to the SUCRA, CBT-I *plus* IRT (82.6%), CBT-I (81.9%) and hydroxyzine (66.6%) were the most effective interventions for managing PTSD symptoms scores, among which zolpidem (0.2%) was lower than placebo (18.6%).

3.2.2. Depression

Eleven studies [30,34,35,39,41–43,45,46,48,49] with 841 participants and 9 intervention categories were included in the NMA assessing depression. The network plot of the symptoms of depression, including eight categories of active interventions (five psychological and three pharmacological interventions) and a placebo, is showed in Figure 1B. No inconsistencies were found in depression (Supplementary Figure 5.

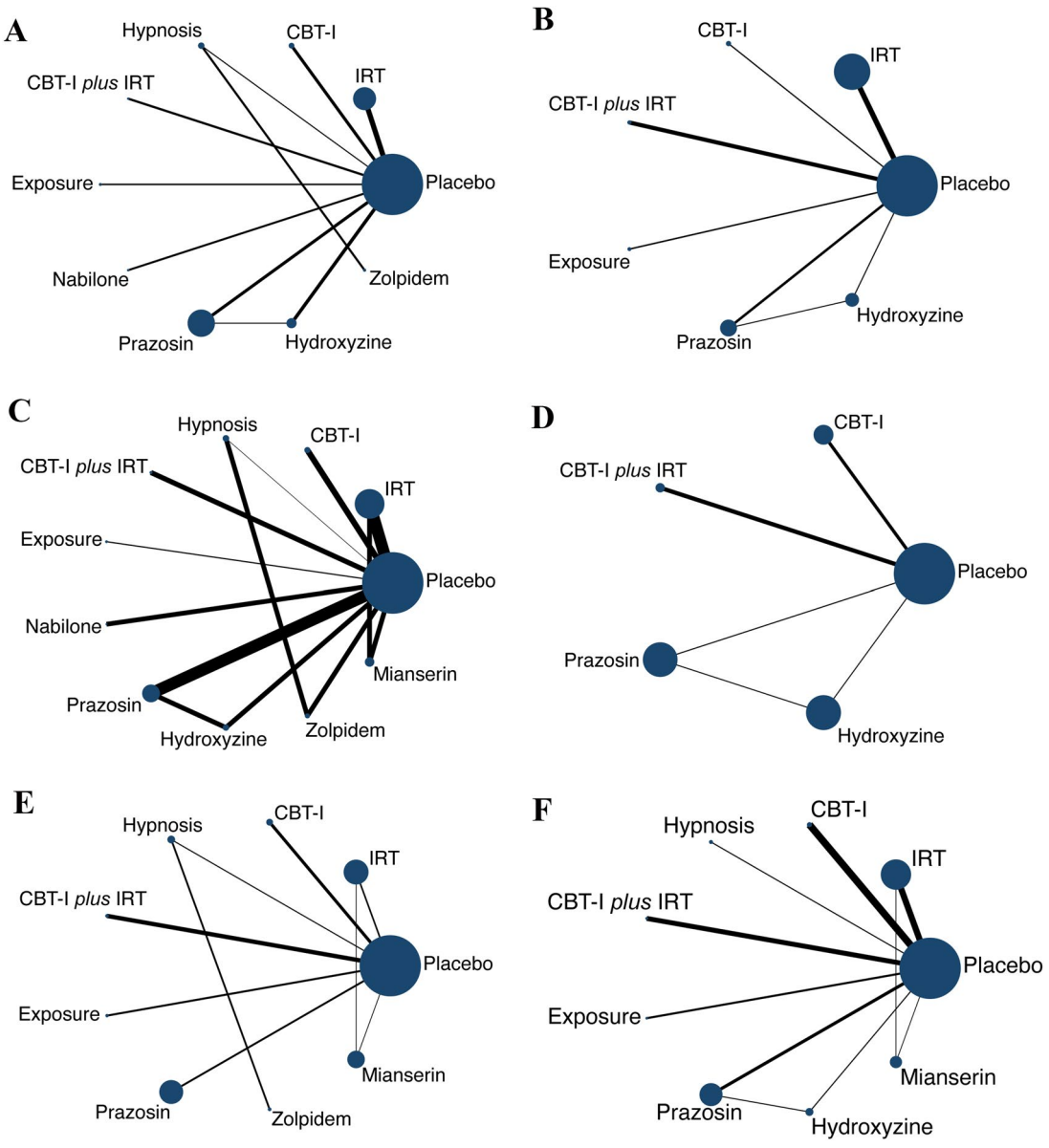

Figure 1. The evidence network of all outcomes.
Note: Panel (A) PTSD symptom severity; Panel (B) depression; Panel (C) sleep quality; Panel (D) nightmare severity; Panel (E) total sleep time and Panel (F) acceptability. Figure geometry explained as the size of the node corresponds to the number of trials that investigated the treatments. Directly comparable treatments were linked with a line, and the thickness of the line corresponded to the sum of the number of studies in each pairwise treatment comparison. IRT: Imagery Rehearsal Therapy, CBT-I: Cognitive-Behavioral Therapy for Insomnia.

In step with depression results, the active psychological interventions CBT-I (SMD = −1.51, 95%CI: −2.10 to −0.92) and exposure (SMD = −2.17, 95%CI: −3.20 to −1.14) significantly reduced depression compared with placebo, whereas pharmacological intervention zolpidem (SMD = 1.77, 95%CI: 0.59 to 2.94) significantly exacerbated depression (Table 1). A comparisons of the effects of active interventions on depression is summarized in Table 1.

Observing direct comparisons of depression, the active psychological interventions CBT-I (SMD= −1.51, 95%CI: −2.05 to −0.98) and exposure (SMD= −2.17, 95%CI: −3.13 to −1.21) significantly reduced depression compared with placebo, other direct comparisons were shown in Supplementary Table 3.

Figure 2 shows that in obedience to SUCRA, exposure (98.2%), CBT-I (88.7%) and CBT-I *plus* IRT (62.9%) were the most effective interventions for managing depression, among which prazosin (29.8%), IRT (24.5%) and zolpidem (0.1%) ranked lower than placebo (30.3%).

3.2.3. Sleep quality

Fifteen studies [31,33–35,37–39,41–46,48,49] with 1,210 participants and nine intervention categories were

Table 1. The results of network meta-analysis for PTSD symptoms severity and depression.

Placebo	−0.49 (-1.09, 0.12)	**−1.51 (-2.55, −0.47)**	−0.39 (-1.76, 0.97)	**−1.71 (-3.39, −0.03)**	−0.58 (-2.05, 0.89)	−1.10 (-2.69, 0.50)	**−0.87 (-1.59, −0.16)**	**−1.06 (-1.94, −0.19)**	**2.71 (0.56, 4.86)**	/
0.07 (-0.26, 0.41)	**IRT**	−1.03 (-2.23, 0.18)	0.09 (-1.40, 1.59)	−1.23 (-3.01, 0.56)	−0.09 (-1.68, 1.49)	−0.61 (-2.32, 1.09)	−0.39 (-1.33, 0.55)	−0.58 (-1.65, 0.49)	**3.20 (0.97, 5.43)**	/
−1.51 (-2.10, −0.92)	**−1.58 (-2.26, −0.90)**	**CBT-I**	1.12 (-0.60, 2.83)	−0.20 (-2.18, 1.77)	0.93 (-0.87, 2.73)	0.41 (-1.49, 2.31)	0.64 (-0.62, 1.90)	0.45 (-0.91, 1.81)	**4.22 (1.84, 6.60)**	/
−0.46 (-1.12, 0.19)	−0.53 (-1.27, 0.20)	**1.05 (0.17, 1.93)**	**Hypnosis**	−1.32 (-3.48, 0.85)	−0.19 (-2.19, 1.82)	−0.70 (-2.80, 1.40)	−0.48 (-2.02, 1.06)	−0.67 (-2.29, 0.95)	**3.10 (1.45, 4.76)**	/
−0.55 (-1.34, 0.23)	−0.62 (-1.47, 0.23)	0.96 (-0.02, 1.94)	−0.09 (-1.11, 0.93)	**CBT-I *plus* IRT**	1.13 (-1.10, 3.36)	0.62 (-1.70, 2.93)	0.84 (-0.99, 2.67)	0.65 (-1.25, 2.54)	**4.42 (1.70, 7.15)**	/
−2.17 (-3.20, −1.14)	**−2.24 (-3.32, −1.16)**	−0.66 (-1.85, 0.53)	**−1.71 (-2.92, −0.49)**	**−1.62 (-2.91, −0.33)**	**Exposure**	−0.52 (-2.68, 1.65)	−0.29 (-1.93, 1.34)	−0.48 (-2.19, 1.23)	**3.29 (0.69, 5.89)**	/
/	/	/	/	/	/	**Nabilone**	0.22 (-1.52, 1.97)	0.03 (-1.79, 1.85)	**3.81 (1.13, 6.48)**	/
0.01 (-0.46, 0.49)	−0.06 (-0.63, 0.52)	**1.52 (0.76, 2.29)**	0.48 (-0.33, 1.29)	0.57 (-0.34, 1.47)	**2.18 (1.05, 3.32)**	/	**Prazosin**	−0.19 (-1.13, 0.75)	**3.58 (1.32, 5.84)**	/
/	/	/	/	/	/	/	/	**Hydroxyzine**	**3.77 (1.46, 6.09)**	/
1.77 (0.59, 2.94)	**1.70 (0.47, 2.92)**	**3.28 (1.96, 4.60)**	**2.23 (1.25, 3.21)**	**2.32 (0.90, 3.73)**	**3.94 (2.37, 5.50)**	/	**1.75 (0.48, 3.02)**	/	**Zolpidem**	/
−0.32 (-0.73, 0.08)	−0.40 (-0.80, 0.01)	**1.18 (0.47, 1.90)**	0.14 (-0.63, 0.91)	0.23 (-0.65, 1.11)	**1.84 (0.74, 2.95)**	/	−0.34 (-0.96, 0.28)	/	**−2.09 (-3.34, −0.85)**	**Mianserin**

Note: The results of the upper right panel were derived from a network meta-analysis of PTSD symptom severity, and the results of the lower left panel were derived from a network meta-analysis of depression. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the lower-right-defining treatment and upper-left-defining treatment. A standardized mean difference of less than 0 favors lower-right defining treatment. Significant results are in bold and underlined and/indicates not available. IRT: imagery rehearsal therapy; CBT-I**:** cognitive-behavioral therapy for insomnia.

included in the NMA assessing sleep quality. The network plot of sleep quality, including eight categories of active interventions (five psychological and three pharmacological interventions) and a placebo, is presented in Figure 1C. No inconsistencies were observed in sleep quality Supplementary Figure 6. As determined by the NMA results, the active psychological intervention CBT-I (SMD= −5.61, 95%CI: −8.82 –-2.40) significantly improved sleep quality compared with placebo, while significant results were not observed in pharmacological interventions (Table 2). A comparison of the effects of active interventions on sleep quality is summarized in Table 2.

As mentioned by direct comparisons of sleep quality, the active psychological interventions IRT (SMD= −0.60, 95%CI: −1.11 to −0.09), CBT-I *plus* IRT (SMD= −1.55, 95%CI: −2.39 to −0.71), exposure (SMD= −2.41, 95%CI: −3.42 to −1.40) and the active pharmacological interventions hydroxyzine (SMD= −1.42, 95%CI: −1.97 to −0.89) significantly improved sleep quality compared with placebo, other direct comparisons were shown in Supplementary Table 4.

Figure 2 shows that in light of SUCRA, CBT-I (97.3%), exposure (67.5%) and CBT-I *plus* IRT (57.8%) were the most effective interventions for managing sleep quality. There were no active interventions ranked lower than placebo (22.9%).

3.2.4. Nightmare severity

Eleven studies [31,33,34,37,38,41,43,44,46,48,49] with 644 participants and 7 intervention categories were included in the NMA assessing nightmare severity. The network plot of nightmare severity, including six categories of active interventions (four psychological and two pharmacological interventions) and placebo, is shown in Figure 1D. No inconsistencies were found in nightmare severity Supplementary Figure 7. As explained by NMA results, the active psychological interventions IRT (SMD= −0.65, 95%CI: −1.00 to −0.31) and the active pharmacological interventions prazosin (SMD= −1.20, 95%CI: −1.72 to −0.67) and hydroxyzine (SMD= −0.98, 95%CI: −1.58 to −0.37) significantly reduced nightmare severity compared with placebo (Table 2). Comparisons of the effect of active interventions on nightmare severity are summarized in Table 2.

As stated in direct comparisons of nightmare severity, the active psychological interventions IRT

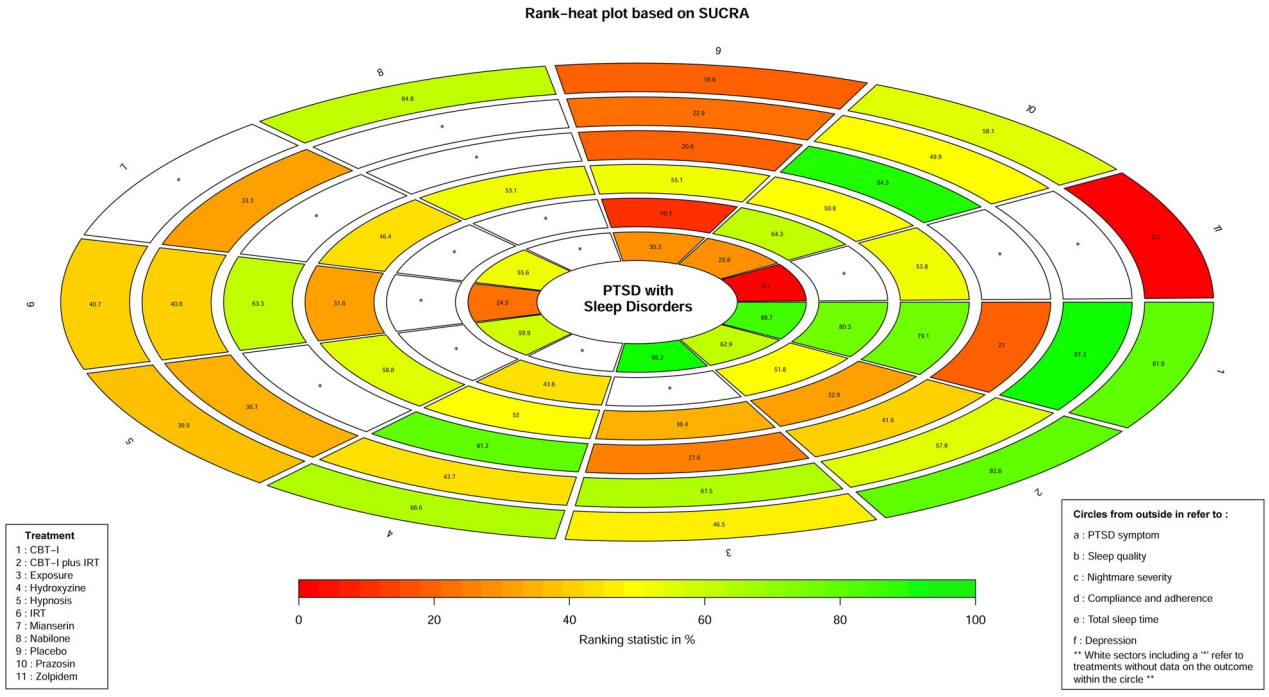

Figure 2. Rank−sheat plot based on SUCRA.
Note: Each sector is colored according to the SUCRA value for the corresponding treatment and outcome. The scale consists of the transformation of three colors red (0%), yellow (50%), and green (100%). Each color is associated with a different pattern. Uncolored sectors show that the underlying treatment was not included in the network meta-analysis for a particular outcome. SUCRA: Surface under cumulative ranking. SUCRA is a numeric representation of the overall ranking and presents a single number associated with each treatment. SUCRA values ranged from 0 to 100%. The higher the SUCRA value, and the closer to 100%, the higher the likelihood that a therapy is in the top rank or one of the top ranks; the closer to 0 the SUCRA vaslue, the more likely that a therapy is in the bottom rank or one of the bottom ranks.

Table 2. The results of network meta-analysis for sleep quality and nightmare severity.

	−0.61	**−5.61**	−0.31	−1.58	−2.41	−1.06	−0.80	−0.23
Placebo	(-2.18, 0.97)	**(-8.82, −2.40)**	(-4.33, 3.71)	(-4.52, 1.37)	(-6.52, 1.70)	(-3.21, 1.09)	(-3.83, 2.24)	(-3.17, 2.71)
−0.65		**−5.00**	0.30	−0.97	−1.80	−0.45	−0.19	0.38
(-1.00, −0.31)	**IRT**	**(-8.58, −1.43)**	(-4.02, 4.62)	(-4.31, 2.37)	(-6.20, 2.60)	(-3.12, 2.21)	(-3.61, 3.23)	(-2.56, 3.32)
0.06	0.71		**5.30**	4.03	3.20	**4.55**	**4.82**	**5.38**
(-0.80, 0.91)	(-0.21, 1.63)	**CBT-I**	**(0.16, 10.45)**	(-0.32, 8.39)	(-2.01, 8.41)	**(0.69, 8.41)**	**(0.40, 9.24)**	**(1.03, 9.73)**
/	/	/		−1.27	−2.10	−0.75	−0.49	0.08
			Hypnosis	(-6.25, 3.71)	(-7.85, 3.65)	(-5.31, 3.81)	(-5.53, 4.55)	(-4.90, 5.06)
−0.30	0.35	−0.36	/		−0.83	0.52	0.78	1.35
(-1.12, 0.52)	(-0.54, 1.25)	(-1.55, 0.83)		**CBT-I *plus* IRT**	(-5.89, 4.22)	(-3.13, 4.16)	(-3.45, 5.01)	(-2.81, 5.51)
−0.06	0.59	−0.12	/	0.24		1.35	1.62	2.18
(-1.01, 0.88)	(-0.41, 1.59)	(-1.39, 1.16)		(-1.01, 1.49)	**Exposure**	(-3.29, 5.99)	(-3.49, 6.72)	(-2.87, 7.23)
−1.20	−0.55	**−1.25**	/	−0.90	**−1.14**		0.26	0.83
(-1.72, −0.67)	(-1.17, 0.08)	**(-2.26, −0.25)**		(-1.87, 0.08)	**(-2.21, −0.06)**	**Prazosin**	(-2.77, 3.30)	(-2.81, 4.47)
−0.98	−0.32	−1.03	/	−0.68	−0.92	0.22		0.57
(-1.58, −0.37)	(-1.02, 0.37)	(-2.08, 0.02)		(-1.70, 0.34)	(-2.04, 0.21)	(-0.38, 0.82)	**Hydroxyzine**	(-3.66, 4.79)
/	/	/	/	/	/	/	/	
								Mianserin

Note: The results of the upper right panel were derived from network meta-analysis of sleep quality, and the results of the lower left panel were derived from network meta-analysis of nightmare severity. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the lower-right-defining treatment and upper-left-defining treatment. A standardized mean difference of less than 0 favors lower-right defining treatment. Significant results are in bold and underlined and/indicates not available. IRT: imagery rehearsal therapy; CBT-I**:** cognitive-behavioral therapy for insomnia.

(SMD= −0.65, 95%CI: −1.02 to −0.29) and the active pharmacological interventions prazosin (SMD= −1.08, 95%CI: −1.81 to −0.34) and hydroxyzine (SMD= −1.16, 95%CI: −1.68 to −0.64) significantly reduced nightmare severity compared with placebo, other direct comparisons were shown in Supplementary Table 5.

Figure 2 shows that, as claimed by SUCRA, prazosin (94.3%), hydroxyzine (81.2%) and IRT (63.3%) were the most effective interventions for managing nightmare severity, while there were no active interventions ranked lower than the placebo (20.6%).

3.2.5. Total sleep time

Six studies [30,31,39,46,48,49] with 271 participants and 5 intervention categories were included in the NMA assessing TST. The network plot of the TST,

Table 3. The results of network and direct meta-analysis for acceptability and total sleep time.

Placebo	1.40 (0.95, 2.05)	0.58 (0.26, 1.32)	0.93 (0.52, 1.67)	1.59 (0.47, 5.33)	1.40 (0.48, 4.07)	0.91 (0.02, 42.81)	1.05 (0.54, 2.06)	1.00 (0.06, 16.22)	0.91 (0.06, 14.58)	1.21 (0.08, 19.66)
/	**IRT**	0.42 (0.17, 1.03)	0.67 (0.33, 1.34)	1.14 (0.32, 4.02)	1.00 (0.32, 3.11)	0.65 (0.01, 31.21)	0.75 (0.35, 1.63)	0.71 (0.04, 11.91)	0.65 (0.04, 10.71)	0.87 (0.05, 14.07)
1.51 (0.17, 2.84)	/	**CBT-I**	1.60 (0.58, 4.39)	2.73 (0.63, 11.80)	2.40 (0.63, 9.25)	1.56 (0.03, 80.18)	1.80 (0.62, 5.22)	1.71 (0.09, 31.36)	1.56 (0.09, 28.21)	2.09 (0.11, 38.04)
/	/	/	**Hypnosis**	1.71 (0.44, 6.56)	1.50 (0.45, 5.08)	0.98 (0.02, 48.09)	1.13 (0.46, 2.76)	1.07 (0.06, 18.53)	0.98 (0.06, 15.66)	1.31 (0.08, 22.46)
0.81 (-0.61, 2.23)	/	−0.70 (-2.64, 1.25)	/	**CBT-I *plus* IRT**	0.88 (0.18, 4.43)	0.57 (0.01, 32.49)	0.66 (0.17, 2.65)	0.63 (0.03, 13.15)	0.57 (0.03, 11.83)	0.77 (0.04, 15.92)
/	/	/	/	/	**Exposure**	0.65 (0.01, 35.35)	0.75 (0.21, 2.65)	0.71 (0.04, 14.11)	0.65 (0.03, 12.70)	0.87 (0.04, 17.11)
/	/	/	/	/	/	**Nabilone**	1.16 (0.02, 57.70)	1.10 (0.01, 127.45)	1.00 (0.01, 115.30)	1.34 (0.01, 154.89)
1.08 (-0.38, 2.54)	/	−0.42 (-2.40, 1.55)	/	0.27 (-1.76, 2.31)	/	/	**Prazosin**	0.95 (0.06, 15.44)	0.87 (0.05, 15.05)	1.16 (0.07, 20.29)
0.66 (-0.79, 2.12)	/	−0.84 (-2.82, 1.13)	/	−0.15 (-2.18, 1.89)	/	/	−0.42 (-1.87, 1.04)	**Hydroxyzine**	0.91 (0.02, 46.74)	1.22 (0.02, 62.87)
/	/	/	/	/	/	/	/	/	**Zolpidem**	1.34 (0.03, 68.12)
/	/	/	/	/	/	/	/	/	/	**Mianserin**

Note: The results in the upper right were derived from a network meta-analysis of acceptability, and the results in the lower left were derived from a network meta-analysis of total sleep time. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the lower-right-defining treatment and upper-left-defining treatment. A relative risk greater than 1 favors the upper-left-defining treatment for the upper right section, while for the lower left section, a standardized mean difference lower than 0 favors the lower-right-defining treatment. Significant results are in bold and underlined and/indicates not available. IRT: imagery rehearsal therapy; CBT-I**:** cognitive-behavioral therapy for insomnia.

including four categories of active interventions (two psychological and two pharmacological interventions) and placebo, is presented in Figure 1E. No inconsistencies were observed in the TST Supplementary Figure 8. Conformable to the NMA results, the active psychological intervention CBT-I (SMD= 1.51, 95%CI: 0.17 to 2.84) significantly increased TST compared with placebo, while significant results were not observed in pharmacological interventions (Table 3). Comparisons of the effects of active interventions on the TST are summarized in Table 3.

In light of direct comparisons of TST, the active psychological interventions CBT-I *plus* IRT (SMD= 0.82, 95%CI: 0.09 to 1.56) and the active pharmacological interventions prazosin (SMD= 1.10, 95%CI: 0.58 to 1.62) and hydroxyzine (SMD= 0.64, 95%CI: 0.15 to 1.13) significantly increased TST compared with placebo, other direct comparisons were shown in Supplementary Table 6.

Figure 2 shows that, in pursuit of SUCRA, CBT-I (80.3%), prazosin (64.3%) and CBT-I *plus* IRT (51.8%) were the most effective interventions for managing TST, while there were no active interventions ranked lower than the placebo (10.1%).

3.2.6. Acceptability

Twenty studies [30–49] with 1,647 participants and 11 intervention categories were included in the NMA to assess acceptability. The network plot of acceptability [30,34,35,39,41–43,45,46,48,49], including ten categories of active interventions (five psychological and five pharmacological interventions) and placebo, is shown in Figure 1F. No inconsistencies were found in acceptability Supplementary Figure 9. Statistically speaking, there were no discrepancies between the NMA results and the direct comparisons (Table 3 and Supplementary Table 7).

Figure 2 showed that as seen in SUCRA, CBT-I (79.1%) and hypnosis (58.8%) were the most effective interventions for managing acceptability, including zolpidem (53.8%), nabilone (53.1%), hydroxyzine (52.0%), prazosin (50.8%), mianserin (46.4%), exposure, (36.4%), CBT-I *plus* IRT (32.9%) and IRT (31.6%) ranked lower than placebo (55.1%).

3.3. Publication bias

Publication bias was not found in any of the network funnel plots shown in Supplementary Figures 10–15.

4. Discussion

This NMA is the most up-to-date analysis of currently available data on psychotherapeutic and pharmacological treatment regimes for individuals with PTSD and

sleep disorders to identify the most effective regime for tackling this overwhelming distress. Twenty-four RCTs were pooled and included to consider the direct and indirect evidence, and a systematic review and NMA were performed to provide a basis for evidence-based medicine for clinicians and clinical researchers to choose more effective treatment to cope with PTSD individuals with sleep disorders. Based on these data, psychotherapy (CBT-I) was more advised than pharmacological therapy, which complied with the highly recommended treatments among guidelines put forward by the American Academy of Sleep Medicine that, under most circumstances, this is what clinicians should be aware of and adhereto the clinicians [50]. The present reviews focus on recent psychotherapy and pharmacotherapy for sleep disorder in PTSD, advocated that there exists a bidirectional relationship between sleep disorder and PTSD, it tends that there need effective interventions for PTSD patients have a comorbid sleep disorder, and targeted sleep interventions can ameliorate sleep symptoms and mitigate daytime PTSD symptoms [8]. Sertraline was suggested that it might improve sleep in PTSD compared to placebo, while due to the low certainty and the estimates they calculated are not robust enough to guide clinical decisions [51]. As the treatment plan remains to be developed in a more acceptable way to most PTSD-diagnosed patients, also before further develop an appropriate treatment plan for these patients evaluate the current statues of PTSD patients have a comorbidity of sleep disorder is important [52].

According to the collected data, CBT-I *plus* IRT and CBT-I may be the most appropriate countermeasures for tackling PTSD symptom severity. For sleep quality, CBT-I may be the most appropriate optionforthe regimes. As for nightmare severity, pharmacological therapy was more dominant in reducing the frequency of prazosin and hydroxyzine having a higher priority than other therapeutic procedures. In addition, CBT-I and hypnosis were recommended for acceptability, while there was no difference between all the included interventions and the placebo. With regard to TST, depression, and CBT-I following exposure, CBT-I was recommended for them respectively. It should be noted that all therapeutic regimes described above were recommended sequentially. The National Institute for Health and Care Excellence (NICE) guidelines consider CBT as the most effective psychological intervention when aimed at specific symptoms such as sleep disturbance, as well as improving overall PTSD symptoms [53]. This was largely consistent with what has been found in this NMA that psychotherapy was for high-priority in most cases except for a mental condition that develops following a traumatic event characterized. For this kind of intrusive thoughts, pharmacological therapy with prazosin was recommended, which was in accordance with the clinical guideline as World Federation of Societies of Biological Psychiatry (WFSBP) referred to prazosin as effective in treating nightmares in PTSD [12].

While there also exist a phenomenon that there exist large confidence intervals that border zero, appropriate explanations can be attributed as follow, the variance of the research results increases, the feasible interval widens and the credibility decreases. Therefore, the interpretation of the results needs to be more cautious, and follow-up large-sample high-quality RCTs are required to verify it.

The correlation between sleep disorder and PTSD has long been described in previous research, and it has been reportedthat insomnia is a prevailing clinical manifestation of PTSD, which develops after trauma related cases or analog trauma. To take things further, insomnia symptom antecede trauma is an extreme risk factor for the progression of PTSD [54,55]. In addition, there are similarities between the outcomes expressed by one study: a cohort of 15,204 military personnel found that pre-deployment insomnia was significantly associated with new-onset PTSD, depression, anxiety and those described by another study that pre-deployment insomnia was conducive to forecasting post-deployment PTSD and suicidal ideation in army soldiers [56,57]. Collectively, the present meta-analysis manifest there exist strong linkage between sleep and PTSD, as one meta-analysis mentioned PTSD patients have significantly lower sleep efficiency [58,59].

One particular phenomenon was observed in the NMA result of PTSD symptom severity: the potency of zolpidem was significantly poorer than with that of all other interventions. To date, there is no exist evidence or related clinical research exploring the potential or obscure relationship between zolpidem and PTSD. Zolpidem, commonly recognized as a Z-drug, is a non-benzodiazepine hypnotic that enhances the activity of gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor. In most cases, it is administered to treat disabling anxiety and insomnia [60,61]. According to this unique algorithm, NMA allows the synthesis of data from a network of RCTs and boosts the simultaneous comparison of many interventions [19,62]. Because of this, zolpidem was compounded in the potential comparisons and thus concluded that zolpidem was nevertheless worse than any other contained interventions. However, this conclusion may be somewhat limited by the scarcity of the literature. Therefore, further PTSD-zolpidem-related trials should be conducted in the future.

Exposure therapy is a psychotherapy developed to help people confront their fears and it might help break the pattern of evasion. In this procedure, individuals were exposed to the things they feared and avoided within a fairly safe and sound atmosphere created by psychologists. In relation to treatment efficacy, four functional dimensions were considered in which habituation, extinction, self-efficacy and emotional processing were integrated from the clinical practice guidelines for the treatment of PTSD [21]. As described in the consequence of this NMA, exposure was the most distinguished initiative to treat depression following the CBT-I. A clinical trial aimed at refugees revealed that there were no discrepancies between exposure and CBT, and that exposure led to a 54% reduction in depression and 57% reduction in CBT [63]. Contrary to this NMA that exposure in curtailing depression was more efficacious than CBT-I, with regard to this the possible explanation might attribute to the reason that head-to-head trials (CBT-I and exposure) has not been pulled off. Whereas for the facet of medical usage prazosin, zolpidem and mianserin was not suitable in the governance of depression in PTSD individuals, as the National Health and Medical Research Australian Guidelines suggested that sertraline, paroxetine or fluoxetine was suggested for those who is unwilling or unable to access psychological treatment [10].

CBT-I, a short-term therapy model that specifically addresses chronic insomnia is the most effective non-medical intervention for managing insomnia [64]. The results of this NMA according to sleep quality were in line with the idea that CBT-I is effective and has significantly improved sleep quality, yet, to some extent, dismantled insomnia severity. Hypnosis, prazosin, hydroxyzine and mianserin exhibited significantly unsatisfactory resuls as opposed to CBT-I. Other interventions, especially pharmacological interventions (prazosin, hydroxyzine and mianserin) were found to be more worse in controlling or healing sleep quality in contrast with CBT-I. Prazosin commonly utilized treatment for PTSD nightmares is an alpha-1-blocker that acts as an inverse agonist at alpha-1 adrenergic receptors, works to block noradrenergic stimulation of the alpha-1 adrenoreceptor [65]. A previous meta-analysis confirmed that prazosin has a statistically significant benefit on PTSD symptoms and sleep disturbances, as well as WFSBP recommended: prazosin is effective in treating nightmares in PTSD [12,66], which is consistent with the results of this NMA regarding nightmare severity that pharmacological treatments were in higher priority than psychotherapy, which indicated that prazosin and hydroxyzine tended to be more potent in relieving or improving nightmare severity. A relevant study also suggested that both prazosin and hydroxyzine can be regarded as pharmacological agent for treating sleep disorders and nightmares in populations who experienced PTSD, which also leads to reductions in PTSD symptoms [31]. On account of what has been talked over above, CBT-I and prazosin was recommended for patients who underwent PTSD with sleep quality impaired and nightmares, individually.

As can be seen from the TST outcome, the interventions were plausibly analogous when referring to the sleep duration prolonged by the two categories of treatments (psychotherapy and pharmacotherapy). In agreement with the composed data on TST, NMA results showed that psychotherapy (CBT-I) tended to show greater efficacy, while CBT-I *plus* IRT and pharmacological treatments (prazosin and hydroxyzine) did not display any disparities in contrast with placebo, while considering direct results the outcomes were diametrically opposite. NICE proposed CBT as an evidence-based targeting expedient in treating sleep disturbance and so long as the symptom of sleep disorder was alleviated, the sleep duration will also be increased, which indirectly boosted TST to some extent [53]. Howbeit, when it talks about pharmacotherapy prazosin and hydroxyzine, both kind of encaging interventions is hard to distinguish the efficacy of treating TST, as WFSBP advocated that prazosin was utilized in treating nightmares in PTSD [12], once the medication was taking effect it will sooner or later transfer into the outcome that the sleep duration will be increased. Hydroxyzine, an antihistamine with active ingredients of hydroxyzine hydrochloride, is mostly used to treat anxiety and difficulty in sleeping as counseled by the National Alliance on Mental Illness [67]. Considering the major points mentioned above and the unclear risk of bias of included trials, which could lead to errors that the conclusion of this outcome could not easily be confirmed. Therefore, more high quality RCTs investigating TST and PTSD employing different categories of intervention need to be conducted to further verify our findings and probe the potential between them. Based on the outcome of acceptability, there were no dissimilarities between placebo and the encompassed interventions, indicating that the encaged interventions pan out a seemingly virtuous conformance.

In comparison with a previously published meta-analysis [68], the NMA synthesized psychotherapy and pharmacotherapy to further rank the interventions with regard to their efficacy in treating PTSD and sleep related outcomes to evaluate their appropriateness. Notwithstanding the most comprehensive NMA [69]

appraised the efficacy and acceptability of both categories (psycho- and pharmaco-) of interventions on trauma related nightmares, concluding that IRT and prazosin should be considered as the inaugural choice of psychotherapy and pharmacotherapy separately, this study was partially consistent with the referred NMA in which IRT and prazosin were suggested. The distinctness of this NMA was that we comprehensively analyzed the above-mentioned outcomes related to sleep disorders (e.g. sleep quality and total sleep time) in which these efforts could be regarded as supplementary for the quoted NMA, while what this NMA had done was more encompassing and universal following stricter inclusion and exclusion criteria.

The strengths of this study were the availability of NMA for data processing, which enhances the scope of conventional paired analysis by concurrently dissecting direct and indirect evidence from different studies, even in the absence of a comparison between two interventions as head-to-head trials, estimating the relative potency of all the interventions considered and building a ranking order for them. In addition, our research may have a potential influence on the advancement of research in this field and clinical practice. Due to the paucity of related clinical guidelines, this NMA may help medical and health service personnel and scientists or researchers to buckle down to the regimes for treatment based on our research and further intensively inquiring following procedures in promising interventions such as CBT-I and inserting exposure into CBT-I. Furthermore, if the NICE guidelines are updated, our effort may be identified as more viable, as this NMA hands over comprehensive overviews of the current evidence-based approaches of psycho- and pharmaco- interventions being treated for individuals with PTSD.

Limitations should also be noted when presenting the results of this study. (1) The head-to-head studies were sparse, which led to the use of mostly indirect estimates for all comparisons between interventions which might directly imprecise estimates; (2) almost all the included studies reported continuity variables such as insomnia duration, nightmare frequency and total sleep time pre- and post- within each trail as well as their varied follow-up times, which might explain the high heterogeneity in this study; (3) among certain trials for several psycho- or pharmaco- intervention nodes (e.g. CBT-I, zolpidem, and nabilone) in this NMA were diminutive, however, the statistical power was limited. For these reasons, hierarchies namely SUCRA rankings were not processed and interpreted under the limelight.

5. Conclusion

In aggregate, the results from this study support the use of psychotherapy; specifically, CBT-I was more recommended than any other countermeasures in treating adults with PTSD co-existing with sleep disorders. Additionally, for PTSD related outcomes, CBT-I and CBT-I *plus* IRT were advised to treat PTSD symptom severity, whereas CBT-I and exposure were more compelling with respect to rehabilitating depression. Regarding sleep related outcomes, CBT-I could be available of for those who had problems in sleep quality; however, pharmacotherapy, namely prazosin was effective in coping with nightmare severity. Besides, CBT-I indicated an effect in improving TST, but data on this outcome were scarce and did not allow firm conclusions. Other included interventions (e.g. IRT, CBT-I *plus* IRT, nabilone, exposure, hydroxyzine and hypnosis) warranted further sampling in the steadily carried out high-quality RCTs. Additionally, future guidelines and daily errands in clinical decision-making on alternative interventions for PTSD individuals with sleep disorders should consider these disclosures. The relevant clinical guidelines for the management of individuals with PTSD and sleep disorders may regard this as a reference. It should be pointed out that for those who would like to interpret our results, there is a need to keep in mind the restricted available information.

Authors' contributions

Jie Luo, Li Yue and Chao Zhang conceptualized and coordinated the study. Cheng-Yang Huang and Yi-Fan Zhao developed the search strategy. Zhi-Xin Zhang, Run-Ben Liu, Cheng-Yang Huang and Yi-Fan Zhao screened citations and assessed studies for eligibility. Cheng-Yang Huang and Yi-Fan Zhao extracted data. Jie Luo and Li Yue performed quality assessments. Zhi-Xin Zhang, Chao Zhang and Cheng-Yang Huang performed statistical analyses. Jia-Ling Liu and Xiao-Zheng Li provided methodologic expertise in knowledge synthesis and resolved disagreements regarding study eligibility or quality assessments. Jie Luo, Li Yue and Chao Zhang critically reviewed the manuscript for important intellectual content. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Data availability statement

The data are available from the corresponding author upon reasonable request.

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