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The influence of sleep disturbances and sleep disorders on pain outcomes among veterans: A systematic scoping review

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SUMMARY

Chronic nonmalignant pain, sleep disturbances and sleep disorders are highly prevalent conditions among U.S. military veterans. Evidence summaries highlight the influence of sleep on pain outcomes in the general adult population but not for the military veteran population. This is a significant gap as U.S. military veterans are an exceedingly high-risk population for both chronic pain and sleep disturbances and/or disorders. We aimed to review the influence of sleep disturbances and sleep disorders on pain outcomes among veterans with chronic nonmalignant pain. A systematic scoping review was conducted using PubMed/Medline, EMBASE, Scopus, CINAHL, and PsycINFO. Twenty-six out of 1450 studies from initial search were included in this review resulting in a combined sample size of N = 923,434 participants. Sleep disturbances and sleep disorders were associated with worse pain outcomes among veterans with chronic pain. Treatment-induced sleep improvements ameliorated pain outcomes in veterans with sleep disorders and sleep disturbances. Research is indicated to address an overlooked pain treatment opportunity – that of sleep disturbance and sleep disorder management.

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Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Appendix A. Supplementary data

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Keywords

Sleep disturbance; Sleep disorder; Sleep; Chronic pain; Veteran

Chronic nonmalignant pain, defined as pain unrelated to cancer that persists or recurs for 3-months or more [1], is a highly prevalent condition in the adult population [2]. Approximately 20% (50 million people) of adults in the United States (U.S.) experienced chronic pain in 2016 [2], with earlier prevalence estimates ranging from 11% to 40% [3]. Chronic pain is associated with restriction of daily life activities [4], poor quality of life [5–7], impaired social relationships [5], low productivity [7], lost wages [8], increased healthcare expenditures [8], opioid use disorder [9], depression and anxiety [7], and a wide range of health consequences [10].

Adults with chronic pain frequently report sleep disturbances such as impaired sleep duration and/or quality [11,12]. Sleep disorders are also common in adults with chronic pain [13–15]. When co-occurring, chronic pain and disturbed sleep and/or sleep disorders lead to substantially more impairment, further impacting overall health and quality of life. The current evidence supports a reciprocal relationship, where pain disrupts sleep, and sleep disturbances and disorders lead to increased pain [16,17], however support for the latter relationship is more robust [17,18]. The mechanisms underlying the sleep and pain association remain unclear. Given the complexity of the sleep and pain interaction, and based on findings from a growing, albeit relatively under-developed scientific literature it is reasonable to hypothesize that several biopsychosocial mediators explain the observed relationship between sleep and pain (Fig. 1).

Veterans, defined as adults discharged from previous active service in the U.S. military forces [19], are uniquely vulnerable to both pain and sleep disorders. A comparative study found that veterans experience higher pain prevalence and greater pain severity than the general population; 65.5% of U.S. veterans reported the presence of pain over a prior three month period and 9.1% rated the pain as severe [20]. The etiology of painful conditions is unique among veterans, who are likely to suffer traumatic combat and training-related injuries, which are typified by chronic pain [21,22]. Musculoskeletal back and joint pain have been consistently reported as the most prevalent chronic pain diagnoses in veterans across different conflict cohorts [23–25]. Likewise, sleep disturbances and sleep disorders are common among veterans as deployment-related activities are associated with irregular sleep schedules, long and rotating shifts, unsafe sleep environments, psychological and physical trauma, and combat-related nightmares, all of which can chronically impact sleep [26]. The total prevalence of diagnosed sleep disorders among veterans seeking healthcare at Veteran Administration (VA) showed a six-fold relative increase from 2000 to 2010 (estimated prevalence of 6% in 2010), with higher rates of sleep disorders observed among veterans with comorbid chronic conditions [27].

In the veteran population, the sleep–pain relationship is further complicated by the high prevalence of mental health comorbidities, such as post-traumatic stress disorder (PTSD) [28], which predispose veterans to both sleep disorders [27] and increased pain [28,29]. Mental health comorbidities coupled with the high prevalence of chronic pain escalates

veterans' risk for opioid misuse and abuse [30] that further contribute to sleep disturbances and sleep disorders [31]. It is thereby important to understand the unique relationship between sleep and pain among the veteran population. The complex interaction between pain and associated chronic conditions, such as sleep disorders, is of high priority within the VA research agenda as is evidenced by VA's dedicated Center of Innovation, PRIME (Pain research, Informatics, Multi-morbidities, and Education) [32].

Although extensive literature has been published on the association between sleep and pain [12,16,17,33], no study to date has summarized the evidence on the influence of disturbed and/or disordered sleep on pain outcomes in veterans. Thus, the primary aim of this systematic scoping review was to answer the question: "What is the influence of sleep disturbances and sleep disorders on chronic pain outcomes among military veterans?" For the purposes of this review, sleep disturbance was defined as a symptom characterized by decreased sleep duration and/or poor sleep quality. Sleep disturbances are not a synonym of sleep disorders, although sleep disturbances may occur as a consequence of a sleep disorder(s). Sleep disorders are pathological changes to one or more dimensions of the complex sleep-wake experience as defined by standard international disease classification systems. Secondary objectives were 1) to investigate how sleep disturbance is defined in the context of chronic pain, and 2) identify gaps in the evidence to guide future research.

This review is limited to studies investigating people with chronic nonmalignant, or noncancer pain (e.g., musculoskeletal and neuropathic disorders) as this cluster of pain conditions is believed to have shared neuropathophysiological mechanisms, which differs from the mechanisms of malignant, or cancer-related pain conditions [34]. Chronic nonmalignant pain is a broad category, and although there is no unanimously agreed upon pain classification system, pain disorders in this category are often further classified based on etiology (e.g., trauma, inflammation), system involved (e.g., musculoskeletal, cutaneous), region affected (e.g., cervical, back), and causal mechanisms (e.g., nociceptive, neuropathic) [35]. This approach for defining and categorizing chronic pain is consistent with clinical diagnostic criteria [36] and was used in this review to permit consideration of a wide range of studies consistent with the purpose of a systematic scoping review.

Methods

Design

A systematic scoping review methodology was employed as this method is ideal for a broad exploration of a topic area. Scoping methods are particularly useful for aggregating evidence that is complex and heterogeneous, and thus not amenable to traditional systematic reviews methods [37] that answer narrowly-circumscribed questions with a priori delimited intervention(s), comparator(s), and often a single, specific outcome(s) for which summary estimation is supported [38]. A scoping methodology may be used for surveying the state of the evidence to determine if a traditional systematic review is feasible. For lines of research that are relatively new, scoping review methods provide critical insight to the state of scientific development on a phenomenon of interest [37]. This study was conducted in accordance with the Joanna Briggs Institute guidelines for systematic scoping reviews [37]

and conforms to the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guideline [38].

Eligibility criteria

Studies included were 1) primary research, 2) on adults (≥18 y), 3) who were military veterans (worldwide), and 4) diagnosed with obstructive sleep apnea (OSA), insomnia or hypersomnia disorders – the three most prevalent sleep disorders among veterans [27], or with sleep disturbance symptoms such as poor sleep quality and/or decreased sleep duration. To be included, primary studies sampled participants with 1) documented or presumed chronic nonmalignant pain, or assessed chronic nonmalignant pain as the endpoint and 2) reported the association between sleep disorder diagnosis or sleep disturbance and a pain outcome. Inclusion criteria were not established for any specific pain domain(s) as such criteria would limit the usefulness of this scoping review which aimed to summarize the state of the science in a broad and integrated manner. Thus, we assess the influence of sleep disturbances and sleep disorders on a variety of pain outcomes including severity/intensity, prevalence and frequency, pain-related disability, and pain interference on relevant aspects of one's life.

Exclusion criteria were: 1) non primary research papers (e.g., case series, opinion papers), 2) sleep disorders other than OSA, insomnia or hypersomnia, 3) active military or non-veteran individuals, and 4) pain of acute or malignant origin. Secondary data analyses that did not evaluate different sleep and/or pain variables than those reported in the primary study were excluded. If a conference abstract and equivalent journal manuscript were retrieved, the manuscript was used unless otherwise specified.

Search strategy

A systematic literature search was conducted with keywords such as "sleep", "pain", and "veteran" across the following databases from inception to March 18, 2020: PubMed/Medline, EMBASE, Scopus, CINAHL, and PsycINFO (see Appendix 1S). Ancestry search of relevant selected articles was performed to identify any potential references missed in the original database searches. Eligible gray literature sources such as conference abstracts and dissertations were included if indexed by one of the five databases and retrieved upon search. A biomedical librarian provided search process oversight.

Screening

Titles and abstracts were screened by the lead author (BS) using an investigator-developed checklist. Full texts of selected articles were further assessed for eligibility using a detailed checklist. A second reviewer was consulted (AMS) if uncertain regarding study eligibility. DistillerSR (Evidence Partners, Ottawa, Canada) was used to manage the screening procedures.

Data extraction and quality assessment

The lead investigator (BS) abstracted and double-entered data into an electronic database. In cases where data were missing or unclear, the corresponding author of the published source was contacted (up to three times). Clarification requests were sent to authors of 17 of the

included studies; 13 provided additional information [39–51], and four did not respond or were unable to assist with the request [52–55].

The level of evidence and the methodological quality of included publications were independently assessed by two reviewers (BS and MM) using the Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) Research Evidence Appraisal system [56]. The JHNEBP system classifies evidence by level as follows: I) experimental studies, randomized controlled trial (RCT), II) quasi-experimental studies, III) nonexperimental studies, IV) opinion and consensus statements, or V) experiential and non-research evidence. Methodological quality ratings range from high to low quality or major flaws based on appropriateness of sample size for proposed design, adequate control, generalizability of results, consistency of results and recommendations in the context of scientific evidence, and definitiveness of conclusions [56].

Data synthesis

Due to the diversity of pain outcomes measured across studies and the heterogeneity of study designs, association results were not quantitatively summarized. Thus, study results are narratively synthesized [57]. Association results were reported by type of sleep problem (sleep disorder *or* sleep disturbance) based on underlying study design: observational (i.e., without treating pain or sleep) or experimental, quasi-experimental, and observational studies of treated samples (pain or sleep treatment). The direction and magnitude of the effects on pain outcomes, when available, were further described in the context of good or improved sleep as differentiated from poor or worsened sleep. Pooled descriptive estimates were computed where appropriate for age and sample size.

Results

Study selection

A total of 1450 records were retrieved through initial electronic database search. Upon removal of duplicates, 1094 publications remained. After title/abstract level screening, 147 studies received full-text assessment. Two papers were manually added in lieu of equivalent abstracts retrieved from database searching. Most studies were excluded for assessing sleep and pain variables independently (45.3%) and assessing samples other than veterans (26.6%). No eligible review papers were identified. A final sample of 26 publications were selected for analysis (manuscripts [n = 20], abstracts [n = 5], and dissertations [n = 1]; Fig. 2).

Study characteristics

Across studies, a total of 923,434 participants were included with median sample size of 154 (range 7–858,226); 84.6% of studies reported samples below 700 participants (22/26) (Table 1). Only studies of U.S. veterans met all inclusion criteria; therefore, this set of evidence addresses U.S. veterans. Studies were predominantly prospective (69.2%, 18/26), cross-sectional (53.8%, 14/26), and observational in design (80.8%, 21/26). There were three observational studies of treated samples (14.3%, 3/21) – two of prazosin-treated sleep disturbance [58,59] and one of continuous positive airway pressure (CPAP)-treated OSA

[60], and one qualitative study [61]. Pain was the primary outcome in 88.5% of studies (23/26); most studies assessed multiple outcomes. Studies were published between 2006 and 2020, with the majority published in the last 5 y (76.9%, 20/26).

Evidence quality appraisal

Studies were classified as level 1 (3.8% [1/26]), level 2 (11.5% [3/26]), and level 3 (84.6% [22/26]). The quality of evidence was high (19.2% [5/26]), good (38.5% [10/26]), and low/major flaws (42.3% [11/26]; Table 1S). Studies were downgraded for reasons such as insufficient control and/or small sample size for study design.

Subject characteristics

A pooled mean was computed [62] for studies reporting mean and standard deviations for age (69.2% [18/26]), which resulted in an average age of 53.3 ± 12.9 y (range of means 29.4–68 y). Eight studies were not included in this summary due to absence of reported standard deviations [41,48,50,54], reporting age categories only [44,61], reporting median ages for independent subgroups [49], or no report of participants' ages [46]. Subjects were predominantly male (82.1%) and white/Caucasian; two studies did not report a sex ratio [46,54], and only one study exclusively included female veterans [42] (Table 1). Veteran cohorts were reported in 38.5% (10/26) of studies; studied cohorts were Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and/or Operation New Dawn (OND) (26.9% [7/26]), mixed cohorts (7.7% [2/26]), and Gulf War veterans (3.8% [1/26]).

Sleep disturbances and sleep disorders

Fifteen studies assessed adults with sleep disturbances (57.7% [15/26]), and eleven studies assessed adults with sleep disorders (42.3% [11/26]; Table 2S). Sleep disturbances were most often measured using the Pittsburg Sleep Quality Index (PSQI) (40% [6/15]), the Insomnia Severity Index (ISI) (20% [3/15]), and the PROMIS Sleep Disturbance instrument (20% [3/15]). Sleep disorder diagnoses were established by medical chart review of codes from standard classification systems such as International Classification of Diseases (ICD)-9, ICD-10, and International Classification of Sleep Disorders-2 (45.4% [5/11]), polysomnography testing (PSG; 18.2% [2/11]), and subjective diagnostic criteria – e.g., pre-specified ISI cutoffs – (36.4% [4/11]). The most common sleep disorder diagnoses in this review were insomnia (54.5% [6/11]) and OSA (27.3% [3/11]). Of the five studies assessing samples with sleep disordered breathing (SDB), three established OSA diagnosis based on medical chart reviews of standard ICD diagnostic codes (Table 2S). One study defined OSA based on the presence of at least 5 obstructive respiratory events (apneas or hypopneas) per hour of sleep as summarized by the apnea hypopnea index (AHI; higher scores indicate greater OSA severity) from a full-night diagnostic PSG [60]. Lastly, SDB diagnosis was established based on PSG-derived AHI scores; however, no threshold criteria was defined (AHI mean ± SD: 19 ± 25) [40]. No other clinical criteria (e.g., daytime sleepiness, loud snoring) was accounted for with the diagnosis of OSA.

Pain outcomes

The most frequently assessed pain outcomes were self-reported pain severity/intensity (73.1% [19/26]), self-reported pain interference (38.5% [10/26]), self-reported pain-related disability (7.7% [2/26]), and likelihood/odds of a chronic pain diagnosis (7.7% [2/26]; Table 3S). Chronic pain duration at study onset was reported in ten studies (38.5% [10/26]) in which pain lasted for three months or more in 40% (4/10), and for six months or more in 60% (6/10). Multidimensional pain assessments were conducted in 42.3% of studies (11/26). When authors specified the type of chronic pain (50% [13/26]), musculoskeletal pain (38.5% [10/26]) or posttraumatic headaches (11.5% [3/26]) were the most common types (Table 3S). In instances where chronic pain was presumed but not diagnosed, the pain assessed was described as “current pain” (see Table 3S).

Influence of sleep disturbances and sleep disorders on pain outcomes

Observational studies (without sleep or pain treatment)

Veterans with sleep disorders.: Among studies assessing the influence of diagnosed sleep disorders on chronic pain outcomes, nine used an observational/non-experimental design (81.8% [9/11]; Tables 2 & 2S) [42,44,46–48,51,54,55,61]. Overall, the presence of a sleep disorder and/or worsening of sleep disorder-related symptoms resulted in worse pain outcomes across all nine studies (N = 920,417; Fig. 3).

Insomnia was associated with greater pain interference on sleep [42], increased odds of headache diagnosis [44], and greater pain-related disability [47]. Having insomnia was associated with almost a two-fold increase in the odds of being diagnosed with headache (aOR: 1.97 [1.81–2.15]; $p < 0.001$), and significantly increased odds of having persistent headache (aOR: 1.19 [1.02–1.39]; $p < 0.001$), even after controlling for characteristics such as traumatic brain injury (TBI) and PTSD [44]. Women veterans with insomnia reported greater pain interference on sleep than those without insomnia ($p < 0.001$) [42]. Older veterans with an insomnia diagnosis reported greater low-back pain disability [47] ($p < 0.01$). Compared to those without insomnia, veterans with insomnia were more likely to report a headache diagnosis, and experience greater chronic pain-related disability and interference.

Among veterans with insomnia and chronic pain, self-reported sleep quality and disturbances [51] and greater insomnia symptom severity [55] were associated with worse pain severity [55] and pain interference [51,55]. One study identified that insomnia partially mediated the relationship between PTSD and pain severity and pain interference [55]. Conversely, improved sleep through cognitive behavioral therapy for insomnia (CBT-I) in a qualitative study resulted in increased perceived functionality and quality of life in veterans with insomnia and chronic pain (Fig. 4) [61]. These findings suggest a positive association between insomnia severity and pain outcomes in veterans with insomnia, such that more severe insomnia symptoms result in greater pain severity and interference.

Veterans with OSA were more likely to report moderate/severe pain intensity compared to those without the diagnosis (aOR = 1.28; 95% CI = 1.27–1.30) [54]. Taylor et al. [46] showed that OSA strongly predicted lower back pain (LBP) diagnosis (aOR 8.99; 95% CI =

7.07–11.35) and identified that OSA partially mediated the effect of PTSD on LBP [46]. Cunningham et al. [48] reported greater self-reported pain sensitivity among veterans with a diagnosed sleep disorder (t [9401] = 12.9; $p < 0.001$), wherein OSA and insomnia were the most common sleep diagnoses (31% and 22%, respectively; email communication, August 2019) [48]. Thus, having OSA significantly increased the odds of veterans reporting a chronic pain diagnosis and greater pain intensity and sensitivity.

Veterans with sleep disturbances.: Ten studies used an observational design to assess the influence of sleep disturbances on pain outcomes (66.6% [10/15]; Table 2 and 2S) [41,43,45,49,50,52,53,63–65]. Among veterans reporting disturbed sleep, worse pain responses were observed across seven studies (combined n = 2109; Fig. 3). Two studies (combined n = 211) did not find any influence of sleep disturbances on pain [52,53] (Table 2).

Poor sleep – defined by decreased quality and increased disturbance – as measured by the PSQI, was associated with higher chronic pain severity [41,49,63] and pain interference [49], and greater overall pain when assessed by a multidimensional scale [50]. Insomnia symptom severity, as measured by the ISI, was also associated with higher pain severity [43] and more overall pain when assessed by a multidimensional scale [50]. Though investigators did not qualify this sample as one with insomnia, by reported sample ISI (15.11 ± 6.32) and given the established threshold for clinically significant insomnia of ISI > 15 [66], this is in fact a sleep disordered sample. Disturbed sleep, when assessed by the PROMIS-sleep disturbance scale, was associated with greater chronic pain severity and interference [65], and with greater pain severity and catastrophizing as measured by a single item from the Patient Health Questionnaire-8 [64]. In a secondary analysis of data from a randomized trial, decreased self-reported sleep disturbance from baseline to three months predicted reduced pain intensity and interference at 12 months ($\beta = 0.29$, $p < 0.001$) [45].

Self-reported sleep disturbances were significantly associated with worse pain outcomes even after controlling for factors such as PTSD [43,49,63], anxiety [45,49,63,64], depression [42,62,65], and analgesic [43,64] and sleep medication [43] use. One study did not find disturbed sleep, measured by higher PSQI global scores, to be linked with pain severity and pain interference [53]. Within a small sample (n = 10), sleep disturbances failed to moderate the relationship between PTSD and chronic pain [52]. Overall, sleep disturbances were associated with intensified pain responses in the majority of studies reviewed.

Experimental, quasi-experimental, and observational studies of treated samples (pain or sleep treatment)

Veterans with sleep disorders.: Among studies assessing the influence of diagnosed sleep disorders on pain outcomes, two studies (18.2% [2/11]) evaluated samples with SDB treated with CPAP (Table 2 and 2S, Fig. 4) [40,60]. In a randomized, sham-controlled pilot trial (n = 18) of veterans with Gulf War Illness and SDB (mean apnea hypopnea index [AHI] 19 ± 25), Amin et al. [40] observed a 34% reduction in pain severity among those using CPAP (at least 5 h/night for 3 wk), compared to a sham-control group after 3-wk of treatment ($p < 0.001$). Although the authors suggest this is not a sleep apnea sample, 88.8% of participants

would qualify as at least mild OSA (AHI ≥ 5). A retrospective case-control study of veterans with OSA on chronic opioid treatment found that CPAP treatment did not decrease pain severity, nor was opioid consumption reduced from baseline to 12-months follow-up [60]. However, the authors did report higher pain intensity among veterans who were non-adherent to CPAP (adherence criteria: ≥ 4 h/24 h for ≥ 70% days over 30 days) at baseline ($p < 0.05$) and at 12-month follow-up ($p = 0.05$) [60]. Findings from these studies suggest that CPAP treatment improves pain outcomes in veterans with SDB.

Veterans with sleep disturbances.: Of studies assessing the influence of sleep disturbances on pain outcomes, five evaluated treated samples (33.3% [5/15]; Table 2 and 2S) [39,58,59,67,68]. Across all five studies (total n = 203), treatment-induced improvements on sleep disturbance were associated with improved pain outcomes (see Fig. 4). In a single-arm feasibility trial of multimodal CBT-I among veterans with sleep disturbance (n = 7), Eakman et al. [39] observed non-significant trends towards reduced pain interference when comparing pretest to post-intervention scores (Cohen's $d = 0.45$).

In an open, single arm pilot trial, morning bright light therapy (MBLT) resulted in significantly ($p < 0.05$) reduced pain intensity, pain-related behavior, and pain sensitivity following 13 days of daily (1 h/day) treatment [67]. In a secondary analysis, Burns et al. [68] assessed whether MBLT could affect pain volatility based on daily electronic diary data. In the study, MBLT was related to decreased mean pain severity ($p < 0.001$) and interference ($p < 0.05$), and reductions in the volatility of pain intensity ($p < 0.001$), but not in the volatility of pain interference.

In an observational study, Ruff et al. [59] investigated the effects of treating sleep with oral prazosin on headache frequency and severity in a sample of veterans with TBI and posttraumatic headache (n = 74). A significant reduction in pain intensity and interference at the end of the 9-wk intervention period ($p < 0.001$), and 6-month follow-up ($p < 0.001$) was identified. In a secondary analysis, Ruff et al. [58] assessed veterans (n = 63) with the triad of headaches, PTSD, and neurological deficits and found reductions in daytime sleepiness significantly correlated with decreased headache severity and frequency [58]. Together, these studies suggest that treating sleep disturbances with non-pharmacological [67,68] and pharmacological [58,59] interventions resulted in improved pain outcomes.

Sleep disturbance definitions

Among studies assessing samples with disturbed sleep, only one study (6.6%) provided a conceptual definition of sleep disturbances (Table 4S). However, the term sleep disturbance was used as a synonym for insomnia [39,43] and other sleep disorders such as OSA, hypersomnia, and circadian rhythm disorders [43].

Discussion

Sleep disturbances and sleep disorders were consistently associated with worse pain outcomes such as greater chronic pain frequency, severity, interference, and poorer functional outcomes among veterans with chronic nonmalignant pain. Sleep improvements with treatment ameliorated chronic pain outcomes; however, the evidence was limited and of

moderate to low quality. These findings parallel the study results in the civilian population [18,19,21,66,67]. In a recent systematic review of longitudinal studies, adults with reduced sleep quality and duration experienced a two to three times greater risk of developing a pain condition, and a decline on self-reported pain-related physical health status [33]. Sleep improvements resulted in better physical functioning in the same analysis [33].

Similar to results of this scoping review, studies have identified that nonpharmacological treatments for sleep disorders have yielded improved pain outcomes [69,71,72] in non-veteran samples. A meta-analysis of randomized trials testing non-pharmacological interventions for insomnia in people with chronic pain found small reductions in pain post-treatment (standardized mean difference = 0.18; 95% CI = 0, 0.36, $P < 0.05$) [71]. Likewise, CPAP-treated OSA was associated with improvements in pain among samples with pre-existing and experimentally induced pain [69]. These results support the hypothesis that treatment of sleep disorders contributes to improved pain outcomes. Consistent with our results, existing evidence in non-veteran samples should also be considered with caution due to the observational nature of the evidence [69,73,74], modest sample sizes [69,73], and/or absence of control conditions [73].

The observed negative independent effects of OSA and insomnia on chronic pain outcomes are concerning, as these sleep disorders rank as the first and second most prevalent sleep disorders among veterans, respectively [27]. Insomnia is commonly co-morbid with OSA, with an estimated occurrence between 29 and 50% [75]. When compared to those with insomnia only, adults with comorbid OSA/insomnia experience increased rates of heart disease, more depressed mood, decreased quality of life [75], and higher chronic pain severity [76]. Considering the multi-morbidity associated with comorbid OSA/insomnia coupled with the extremely high prevalence of chronic non-malignant pain in veterans, prioritization of the management of these sleep disorders may be a real opportunity to improve veteran health outcomes.

None of the studies assessed the effect of circadian misalignment on chronic pain outcomes in veterans. Given the suggested modulatory effects of circadian processes on pain [90], future research will investigate the impact of circadian factors on chronic pain outcomes in this population. While natural light exposure history (intensity, frequency, and duration) in the context of military life may be a relevant factor to consider among veterans who recently departed from active duty and present circadian misalignments, no studies included in the review sampled recently separated from military duty samples. The samples included in this review were of middle-aged veterans, who were separated from active duty for several years and were established in civilian life and routine. As evidenced by the results of included studies (N = 2), the therapeutic use of light through MBLT holds great potential as a non-pharmacologic treatment for chronic pain and sleep disturbances even among veterans with no circadian misalignment.

Sleep disorder diagnoses are increasingly common among veterans, with the highest rates observed among those with PTSD and other mental health comorbidities [27]. A recent study by Dunietz et al. observed that anxiety symptoms, but not depressive symptoms, partially mediated the effect of insomnia symptoms on incident pain among a sample of

older adults [77]. Given the high prevalence of mental illnesses and psychological symptoms in military veterans [28], there is a necessity to better understand how psychological factors may qualify the sleep and pain association. This knowledge may potentiate new intervention targets for chronic pain in veterans. Furthermore, future research will continue exploring the effects of hypothesized biopsychosocial mediators of the sleep and pain relationship, identifying moderators (e.g., the potential role of varied social determinants of health) and confounders of this association, as well as potential mechanistic pathways relating specific sleep and pain disorders.

Given the homogeneity of veteran samples included in this review (mostly white, middle-aged men), it is unclear whether sleep disturbances and/or disorders differentially influence pain outcomes based on sociodemographic factors such as age, sex, and race/ethnicity. Age and sex-based differences in the expression of sleep disorders [78,79] and chronic pain [80,81] are well-documented. Similarly, some racial/ethnic groups have higher prevalence of sleep disorders and/or disturbances [82,83], chronic pain [84], and comorbidities [85,86] that heighten likelihood for sleep disorders and/or chronic pain. Thus, as the veteran population is becoming increasingly more diverse [87,88] – with a greater proportion of female and less non-Hispanic white members– studies are needed to examine if demographic-based differences exist for the experience of chronic pain relative to sleep disturbances and/or disorders. This line of inquiry is consistent with VA Women's Health Research statements that highlight the need for inclusion of women veterans in research [89]. Other opportunities for future studies include the influence of sleep disturbances and/or disorders on chronic pain outcomes by veteran cohorts (e.g., Vietnam, OIF, OEF, OND), and the time since separation from active duty. These veteran-centric factors were underreported in the included studies.

This systematic scoping review suggests that attention must be given to the operationalization and measurement of sleep disturbances and chronic pain. Most studies (93.4%) with a sleep disturbance(s) variable failed to provide a definition of this construct, resulting in a lack of conceptual clarity and thereby concerns for the validity of the results. This threat is exemplified in a study that classified the sample as having sleep disturbance, where in fact participants met the threshold for clinically significant insomnia [43]. It is essential that future work in the field prioritize conceptualizing a well-defined construct of sleep disturbance and then align an operational definition with appropriate measurement tools. This should be explicated in published study reports to permit more precise knowledge of the effect of sleep disturbance on pain will result.

Furthermore, sleep disturbances were most commonly assessed by using global scores (Table 2S). While self-reported instruments are important tools for assessing the sleep-wake experience, overreliance on global scores from such instruments as a summary measure of the complex sleep disturbance experience fails to accurately capture the distinct dimensions of the phenomena. Sleep disturbances are better characterized (and defined) by interference with multiple aspects of the complex sleep experience; if characterized in this manner, sleep disturbances variables such as total sleep time, sleep continuity, and perceived sleep quality are recommended. Respective measurement opportunities include actigraphy, sleep diary, and perceived sleep quality that are measured proximate to the sleep experience to minimize

recall bias. If retrospective self-report measures are employed, standardized instructions that ask participants to reflect over a short recall period, ideally also proximate to the sleep experience, should be employed and reported to support reproducibility. Objective measurement of sleep disturbance dimensions should be prioritized for improved rigor but not to the exclusion of patient-reported outcomes.

Innovative measurement strategies such as ecological momentary assessment (EMA) have great potential for the assessment of night-to-night variability in sleep quality. In veterans, EMA and EMA-based techniques have been successfully employed to investigate the relationship between sleep and daily PTSD symptoms [91], daily alcohol use and PTSD symptoms [92], and the effect of sleep treatments on the volatility of pain, mood, and sleep [68]. Together, these studies demonstrate feasibility of employing EMA methods among veteran samples. Future studies will use EMA and electronic diaries to further investigate the influence of daily fluctuations of sleep parameters on chronic pain.

The systematic scoping review also revealed that chronic pain was inconsistently defined and operationalized; further, the duration of pain was often not reported. Only a few studies classified chronic nonmalignant pain beyond its duration. In instances where pain type was reported, chronic pain affecting the musculoskeletal system was predominant. Musculoskeletal pain is the most common type of chronic pain in veterans [23]. Future research will specify the type of chronic pain based on factors such as region affected, etiology, and causal mechanisms. This approach will support reproducibility but also pooled statistical estimation across the evidence to more robustly evaluate outcomes and effects. Historically, chronic pain diagnoses have not been systematically represented in widely used nosologic systems such as the ICD [36]. Chronic pain was not considered a primary diagnosis until the 11th ICD edition was published in 2018 [36]. The lack of an appropriate classification system may have contributed to the paucity of samples with clearly defined chronic pain diagnoses. With ICD-11, the landscape of future research will likely change as the new edition allows for better classification of a variety of chronic pain conditions. Of note, most studies featured unidimensional measures recording pain severity. Chronic pain is a complex phenomenon; thus, comprehensive biopsychosocial assessments – using a single comprehensive tool, or multiple unidimensional ones – must be prioritized [93,94].

Although preliminary results suggest that sleep management may improve pain, more rigorous and adequately powered studies are needed to establish the effect of non-pharmacologic sleep treatments such as PAP for OSA and MBLT on pain and sleep outcomes. Ideally, this will be accomplished with randomized controlled trials that include an adequate comparator. Only in this way will the field be able to determine causality and mechanisms. Data mining of clinical records stored within the VA's Corporate Data Warehouse (CDW) should also be considered in future studies assessing the sleep-pain association among veterans. The VA has collected electronic health records (EHR) of more than 23.5 million veterans over 30 y of continual EHR use [95], and yet, this resource is underutilized by researchers [96]. Large observational studies on the phenomenon can be conducted using existing EHR data, and further optimized by using advanced data science methodologies such as propensity score matching for sample selection.

Our findings highlight sleep management as a potential opportunity for improving chronic pain outcomes among the veteran population. Pain assessment as the “fifth vital sign” has been a decades-long clinical practice in VA. Recognizing that sleep is a potential opportunity to improve chronic pain management, routine screening for sleep disorders and sleep disturbances in the care of veterans is recommended. This approach will necessitate that pain management and sleep experts develop collaborative practice approaches that align with the state of the science. At this point, the strongest recommendations for clinical care implications is provider awareness of the relationship between chronic pain and sleep disorders/disturbances and consistent employment of screening for sleep disorders and disturbances in the clinical setting. With the roll-out of the Mission Act, which, in part, supports veteran care by non-VA providers in community-based settings, chronic pain and sleep disorder “best practices” of the VA will necessarily need to be shared and communicated with civilian providers. By doing so, a consistent standard of care can be ensured for veterans, regardless of their care access point.

Limitations

This review could not pursue direct comparison across studies due to the heterogeneity of included studies and mixed level and quality of evidence. Most studies were classified as low quality/major flaws; readers should be mindful of the methodological limitations of the current evidence when interpreting the results of this systematic scoping review as more rigorous studies may not demonstrate similar findings. The findings should be interpreted in the context of the veteran samples included in this review – i.e., predominantly middle-aged, white, American male veterans. Furthermore, due to the high proportion of low quality, level 3 studies, uncontrolled variables could have introduced bias to study results. Although the presence of presumed or diagnosed chronic pain was carefully assessed, it is possible that some of the included studies had samples inclusive of veterans without chronic pain as defined by standardized diagnostic manuals. However, the existence of contextual cues such as the inclusion of a pain interference measure [39,42,49,51,55], discussion of results in the context of chronic pain [49,50], and personal communication with corresponding authors [39,51] supports the chronic nature of the pain symptoms assessed among participants included in those studies. Chronic pain definitions were absent or minimally developed or reported across studies. Thus, it is possible that the influence of sleep disturbances and/or sleep disorders on chronic pain outcomes may be different if chronic pain types were better specified.

Conclusion

This systematic scoping review has highlighted that sleep disturbances and sleep disorders are associated with worse pain outcomes among U.S. veterans with chronic nonmalignant pain. Insomnia and OSA were the most common diagnoses among studies assessing the effect of sleep disorders on pain outcomes. Having an OSA diagnosis significantly increased the odds of a reported chronic pain diagnosis and greater pain intensity and sensitivity, while having insomnia was associated with greater pain interference on sleep, increased odds of headache diagnosis, and greater pain-related disability. Preliminary evidence suggests that treatment-induced sleep improvements ameliorate pain. Thus, the relationship of sleep and

pain should be considered for the management of chronic pain outcomes in veterans. Further research is needed to expand the current understanding of how sleep disturbances and sleep disorders influence pain, and subsequently inform the development of targeted interventions, particularly those that are non-pharmacological, for the management of chronic pain in veterans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AHI	apnea hypopnea index
CPAP	continuous positive airway pressure
CBT-I	cognitive behavioral therapy for insomnia
EHR	electronic health record(s)
ICD	International Classification of Diseases
MBLT	morning bright light therapy
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
OSA	obstructive sleep apnea
PAP	positive airway pressure
PTSD	post-traumatic stress disorder
SDB	sleep disordered breathing
TBI	traumatic brain injury
US	United States
VA	veteran administration

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* The most important references are denoted by an asterisk.

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Practice points

When sleep disturbances and/or sleep disorders co-occur with chronic pain in veterans:

1. Worse chronic pain outcomes are observed
2. When chronic pain is evaluated, screening for sleep disorders and sleep disturbances should be prioritized
3. Treatment-induced sleep improvements ameliorate pain
4. Sleep disturbance and/or disorder management are potential nonpharmacological opportunities for managing chronic pain

Research agenda

1. Recruit & enroll large diverse veteran samples with respect to age, sex, race/ethnicity, and veteran cohort to support a priori planned sub-group comparisons
2. Carefully conceptualize and operationalize the accurate and precise measurement of distinct sleep disturbances and chronic pain dimensions
3. Prioritize higher level and quality study designs, including rigorous trials that are adequately powered to determine the magnitude of effect of non-pharmacologic interventions on pain outcomes
4. Use data mining approaches to analyze existing EHR within the VA's Corporate Data Warehouse (CDW)

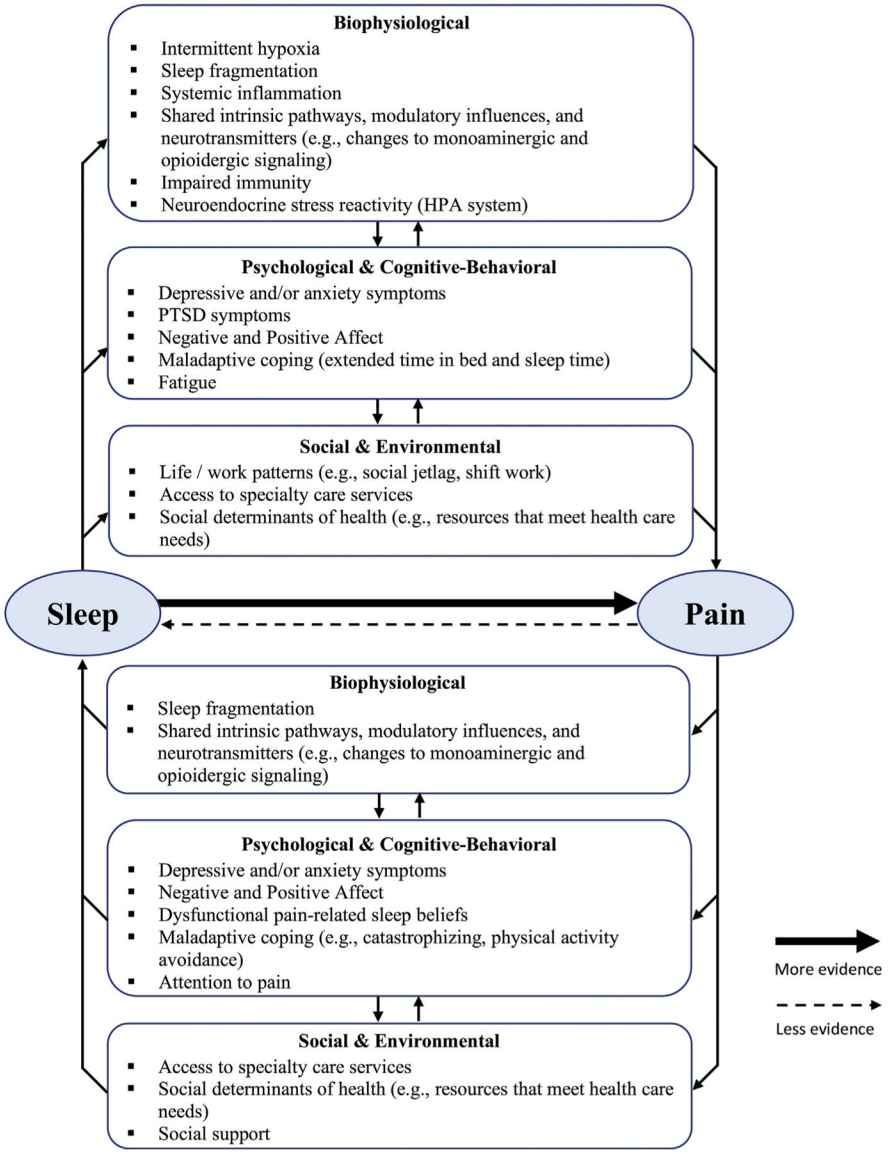

Fig. 1.

Hypothesized mediational mechanisms model underlying the association between sleep and pain. Multiple mediators may help explain the observed relationship between sleep and pain. Social determinants of health inclusive of many variables may be either/both mediator and/or moderator. *HPA* = hypothalamic pituitary adrenal. *PTSD* = post-traumatic stress disorder.

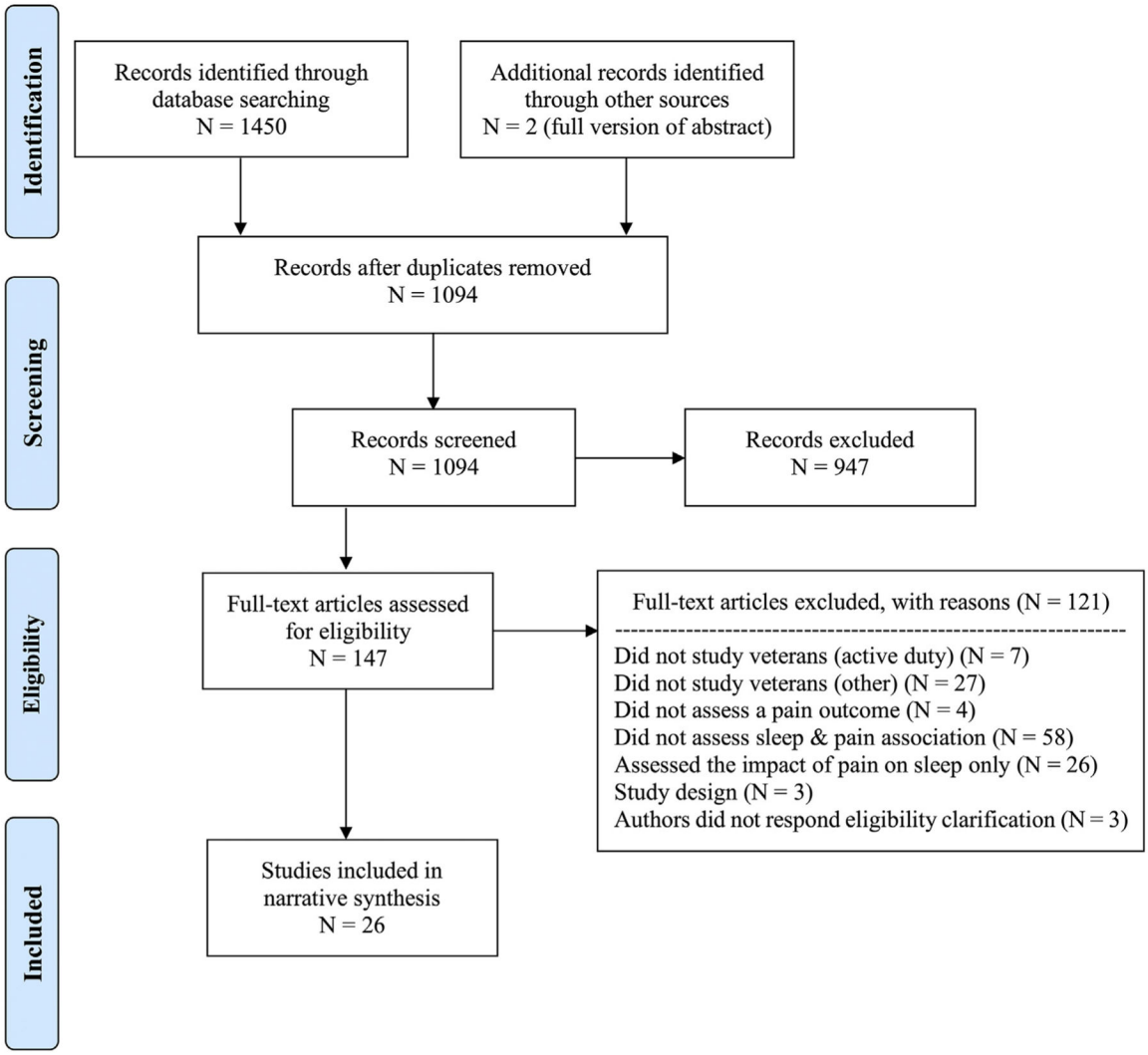

Fig. 2.
PRISMA flow diagram showing the study search and selection process.

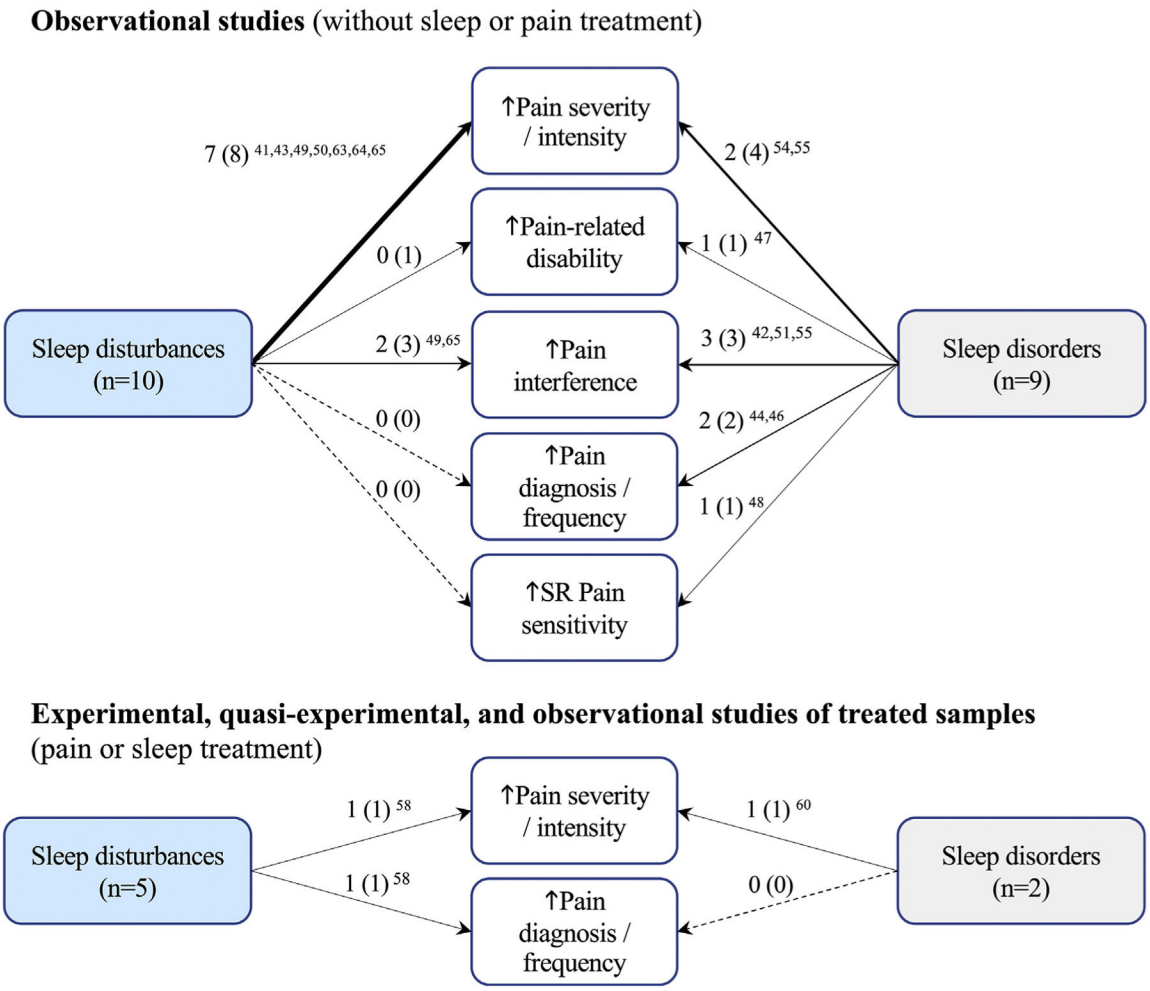

Fig. 3.

Summary of the total number of studies that supported the influence of sleep disturbances and sleep disorders on pain outcomes in the context of poor or worsened sleep. *Notes*: #A (#B) [#A ref.]: A = # of studies with findings that support the relationship (B = #total number of studies assessing the relationship) [# references for A]. Thicker arrows indicate higher frequency of evidence on the studied relationship. Dashed line indicates absence of evidence. Self-reported (SR).

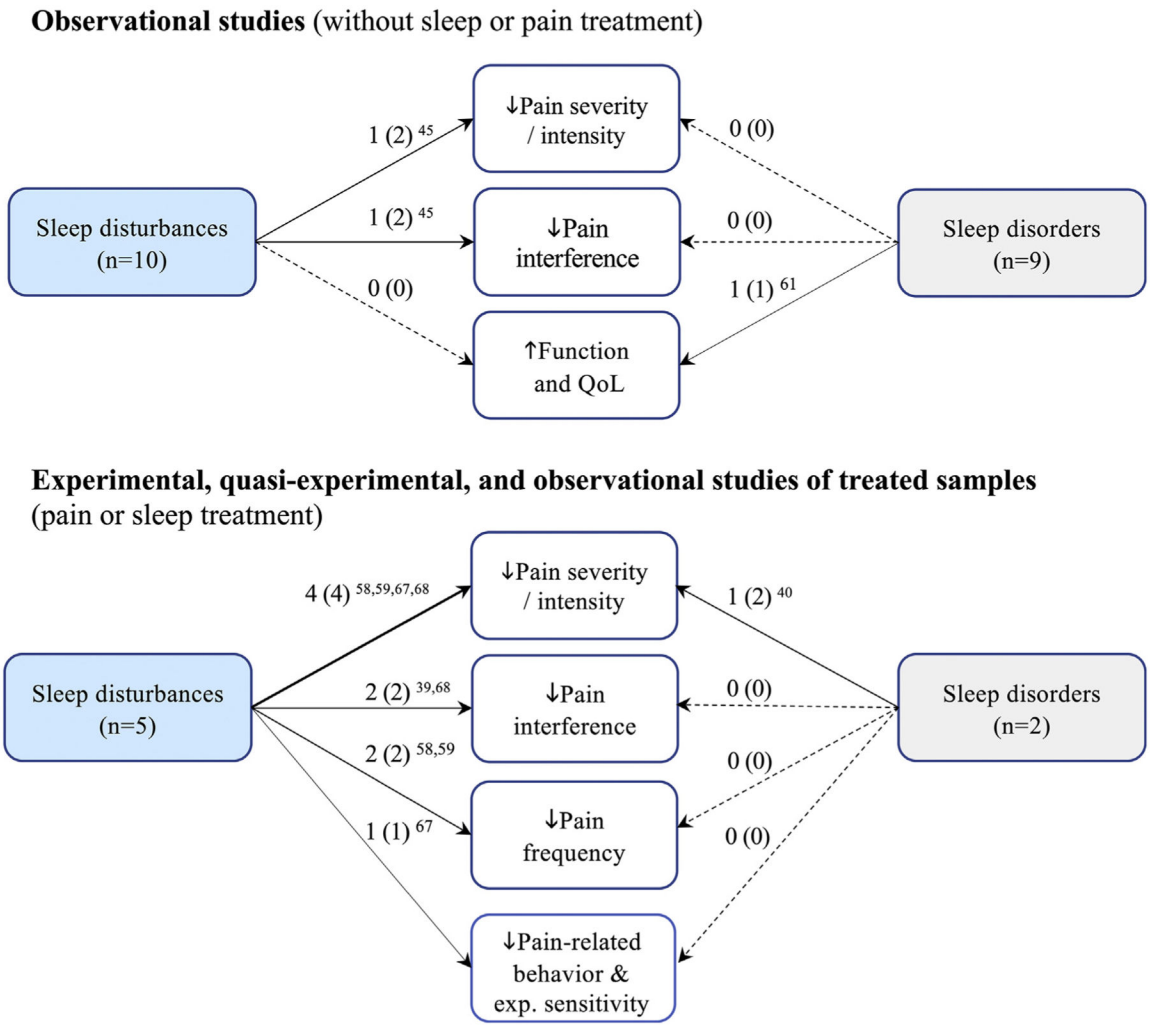

Fig. 4.

Summary of the total number of studies that supported the influence of sleep disturbances and sleep disorders on pain outcomes in the context of good or improved sleep. *Notes*: Quality of Life (QoL). #A (#B) [#A ref.]: A = # of studies with findings that support the relationship (B = #total number of studies assessing the relationship) [# references for A]. Thicker arrows indicate higher frequency of evidence on the studied relationship. Dashed line indicates absence of evidence. Experimental (Exp.).

Table 1

Study characteristics.

Citation (year) *Publication Type*	Study Design (Intervention, if applicable)	Veteran Cohort	Final sample (N) Gender Mean age ± SD	Ethnicity	Timing of Assessments
Amin et al., 2011 [40] *Journal Article*	P, L, E Nasal CPAP vs. sham-CPAP	Deployed to the Persian Gulf between 8/90 & 8/91	N = 18 100% male 42 ± 4 y	89% white 11% black	Baseline 3 wk posttreatment
Balba et al., 2018 [43] *Journal Article*	P, C, O	NR	N = 639 91.7% male 55 ± 15 y[§]	85% white[§]	Baseline
Burgess et al., 2019 [67] *Journal Article*	P, L, Q Morning Bright Light	NR	N = 37 73% male 48.4 ± 14.1	59% black 22% white 14% Hispanic 5% multiracial	Baseline Mid-treatment (6 days on therapy) Final treatment assessment (13 days on therapy)
Burns et al., 2020 [68] *Journal Article*	P, L, Q Morning Bright Light	NR	N = 22 77% male 48.4 ± 13.9 y	50% black 45.5% white 4.5% other	Baseline Final treatment assessment (13 days on therapy) 30 days follow-up.
Card et al., 2018 [54] *Abstract*	R, C, O	OEF, OIF, OND	N = 858,226 NR 30 ± NR years	NR	Baseline
Chapman et al., 2006 [53] *Journal Article*	P, L, O	NR	N = 201 88% male 56 ± 13 y	87% white 5.5% black 5.5% Hispanic	Baseline 2 mo
Cunningham & Oehlert, 2018 [48] *Abstract*	R, C, O	NR	N = 9403 84% male[†] 59.4 ± NR years[†]	72% white[†] 21% black[†]	Baseline
Eakman et al., 2017 [39] *Journal Article*	P, L, Q Multicomponent CBT-I	Post 9/11 veterans	N = 7 100% male 35.6 ± 7.4 y	100% white	Baseline (twice; 1 wk apart) Posttreatment (within 48h of the end of an 8-wk intervention)
Hoot et al., 2018 [49] *Journal Article*	P, C, O	OEF, OIF, OND	N = 454 86.78% male TBI group: 36 y (median) No TBI group: 38 y (median)	67.6% white 22.7% black 9.7% other	Baseline
Hughes et al., 2013 [50] *Abstract*	P, C, O	NR	N = 39 95% male 78 ± NR years	NR	Baseline
Jaoude et al., 2016 [60] *Journal Article*	R, L, O Nasal CPAP on opiates vs. NASAL CPAP no opiates	NR	N = 226 95.6% male 60 ± 10.8 y	90.7% white 8.9% black	Baseline 12 mo

Citation (year) *Publication Type*	Study Design (Intervention, if applicable)	Veteran Cohort	Final sample (N) Gender Mean age ± SD	Ethnicity	Timing of Assessments
Jaramillo et al., 2016 [44] *Journal Article*	R, L, O	OEF, OIF	N = 38.426 82.8% male[§] 17–30 y (45.3%)[§] 31–40y(27%)[§]	65.3% white[§] 16.4% black[§] 11.3% Hispanic[§]	Baseline (FY2008) Yearly until FY2011
Koffel et al., 2016[45] *Journal Article*	P, L, O Automated symptom monitoring to optimize analgesics	NR	N = 250 82.8% male 55 ± 8.45 y	76.8% white	Baseline 3 mo 12 mo
Koffel et al., 2019[65] *Journal Article*	P, L, O	NR	N = 238 87% male 57.05 ± 13.45 y[§]	86% white 7.5% black 6.5% other or multiple	Baseline 3 mo 6 mo 9 mo 12 mo
Koffel, Amundson, & Wisdom, 2019 [61] *Journal Article*	Qualitative semistructured interviews	NR	N = 17 82.35% male 35–45 y (18%) 45–54 y (18%) 55–65 y (29%) >65 y (35%)	88% white	Baseline
Lang et al., 2014 [55] *Journal Article*	R, C, O	OED, OIF	N = 137 95.6% male 30.9 ± 7.8 y	52.4% white 21.1% black	Baseline
Martin et al., 2017 [42] *Journal Article*	P, C, O	NR	N = 660 0% male 50.9 ± 17.7 y	49.4% white 30.1% black 17% Hispanic	Baseline
Munds, 2017 [52] *Doctoral Dissertation*	P, C, O	NR	N = 10 80% male 34.6 ± 8.25 y	90% white 10% black	Baseline
Powell et al., 2015 [63] *Journal Article*	R, C, O	OEF, OIF, OND	N = 171 86.5% male 33.26 ± 8.56	68.4% white 17% Hispanic 10.5% black	Baseline
Ruff et al., 2009 [59] Journal Article	P, L, O Oral prazosin at bedtime	OEF, OIF	N = 74 93% male 29.4 ± 2.9 y	NR	Baseline 9 wk 6 mo follow-up
Ruff et al., 2012 [58] Journal Article	P, L, O Oral prazosin at bedtime	OEF, OIF	N = 63 90.48% male 29.5 ± 0.92 y	NR	Baseline 9 wk 6 mo follow-up
Sangani & Baker, 2016 [41] Abstract	P, C, O	NR	N = 51 86% male 63 y (range 27–77)	NR	Baseline
Tighe et al., 2020 [64] Journal Article	P, C, O	NR	N = 517 72.9% male 63.72 ± 8.47	52% non-Hispanic black 48% non-Hispanic white	Baseline

Citation (year) *Publication Type*	Study Design (Intervention, if applicable)	Veteran Cohort	Final sample (N) Gender Mean age ± SD	Ethnicity	Timing of Assessments
Taylor et al., 2019 [46] Abstract	R, C, O	NR	N = 13,444 NR NR	NR	Baseline
Travaglini et al., 2019 [51] Journal Article	P, C, O	Vietnam (31.6%); between Vietnam & Gulf(45.6%); Gulf (14%), Gulf & OEF, OIF, OND (5.3%); OEF, OIF, OND (5.3%)y	N = 57 80.7% male 53.82 ± 7.83 y	29.8% white 61.4% black 7% multiracial	Baseline
Weiner et al., 2019 [47] Journal Article	P, C, O	NR	N = 47 87.2% male 68 ± 6.5 y	66% white 29.8% black	Baseline

Notes.

† = Data comes directly from the author or subsequent publication.

§ = pooled estimate.

Cognitive behavioral therapy for insomnia (CBT-I), continuous positive airway pressure (CPAP), chronic low back pain (CLBP), cross-sectional (C), experimental (E), fiscal year (FY), Golf war illness (GWI), longitudinal (L), Millon behavioral medicine diagnostic (MBMD), not reported (NR), observational (O), obstructive sleep apnea (OSA), Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), Operation New Dawn (OND), prospective (P), qualitative (Qual), quasi-experimental (Q), post-traumatic stress disorder (PTSD), retrospective (R), sleep disordered breathing (SDB), standard deviation (SD), and traumatic brain injury (TBI).

Table 2

Main findings on the influence of sleep disturbance and sleep disorders on pain outcomes among veterans.

Citation (year)	Baseline adjusted variables	Independent (sleep) variable(s)	Dependent (self-reported pain) outcome(s)	Results: Poor or worsened sleep	Results: Good or improved sleep
Group 1: Observational Studies (without treating pain or sleep)					
Balba et al., 2018 [43]	n/a	Self-reported insomnia symptoms	Pain severity	↑ pain severity across all studied groups	NR
Card et al., 2018 [54]	Sociodemographic characteristics and mental health diagnoses	OSA diagnosis	Pain intensity	↑ likelihood of reporting moderate/ severe pain intensity	NR
Chapman et al., 2006 [53]	Analysis #1: Opioid prescription, baseline pain, 2-month sleep med. prescription, and depressive symptoms	Self-reported sleep quality and sleep disturbance	Pain severity, Pain interference, and General activity level	No association	NR
	Analysis #2: Opioid prescription, baseline pain, sleep quality and disturbance, and depressive symptoms	Sleep medication prescription	Pain severity, Pain interference, and General activity level	NR	No association
Cunningham & Oehlert, 2018 [48]	n/a	Sleep disorder diagnoses (see list of codes on Table 2S)	Pain sensitivity	↑ pain sensitivity ***	NR
Hoot et al., 2018 [49]	Age, site, time since index injury, depression, PTSD, anxiety, combat exposure and duration, number of controlled and uncontrolled blast exposures	Self-reported sleep quality and sleep disturbance	Pain intensity & Pain interference	↑ pain interference * ↑ pain intensity *	NR
Hughes et al., 2013 [50]	Analysis #1: n/a	Self-reported sleep quality and sleep disturbance	Pain intensity	↑ pain intensity **	NR
	Analysis #2: n/a	Self-reported insomnia symptoms	Pain intensity	↑ pain intensity ***	NR
Jaramillo et al., 2016 [44]	Demographic and military characteristics, TBI, PTSD, and/or postconcussive symptoms.	Insomnia disorder diagnosis	Posttraumatic headaches (PTHA) prevalence & PTHA persistence	Insomnia at baseline was associated with: ↑ PTHA prevalence *** ↑ headache persistence ***	NR
Koffel et al., 2016 [45]	Baseline covariates and depression & anxiety symptoms.	Changes in self-reported sleep disturbance (insomnia symptoms [difficulties falling and staying asleep] and lassitude [fatigue])	Pain (intensity & interference, loaded as a single factor after EFA)	NR	Sleep disturbance improvement from baseline to 3 mo predicted ↓ pain (intensity & interference) at 12 mo ***
Koffel et al., 2019 [65]	Baseline BPI values and treatment group assignment	Self-reported sleep disturbance	Pain severity & Pain interference	↑ pain interference *** & ↑ pain severity ***	NR

Citation (year)	Baseline adjusted variables	Independent (sleep) variable(s)	Dependent (self-reported pain) outcome(s)	Results: Poor or worsened sleep	Results: Good or improved sleep
				↓ improvement in pain interference *** & pain severity *	
Koffel, Amundson, & Wisdom, 2019 [61]	n/a	n/a	Pain perception	NR	Sleep improvement "enhanced functionality [*and quality of life*] in the context of chronic pain"
Lang et al., 2014 [55]	Service connection (mediation models only)	Self-reported insomnia symptoms	Pain severity & Pain interference	↑ pain severity ** ↑ pain interference ** Partially mediated relationship between PTSD symptoms and pain severity ** & PTSD symptoms and pain interference **	NR
Martin et al., 2017 [42]	n/a	Insomnia disorder diagnosis	Pain interference with sleep	↑ frequency of pain interference on sleep ***	NR
Munds, 2017 [52]	None	Self-reported sleep disturbance	Pain-related disability	No change	NR
Powel et al., 2015 [63]	PTSD severity, current mood disorder diagnosis, current anxiety disorder diagnosis, and alcohol use.	Self-reported sleep quality and sleep disturbance	Pain severity	↑ pain severity ** among the total sample (presumed chronic pain), but not among the subset (n = 65) with confirmed chronic pain	NR
Sangani & Baker, 2016 [41]	n/a	Self-reported sleep disturbance	Pain intensity	↑ pain intensity *	NR
Taylor et al., 2019 [46]	Age, race, sex, combat exposure, Charlson comorbidity index, marital status, and combat exposure †	OSA diagnosis	Low back pain diagnosis	↑ odds of LBP diagnosis OSA diagnosis mediated the effect of PTSD on risk of LBP diagnosis	NR
Tighe et al., 2020 [64]	Sociodemographic and clinical characteristics	Self-reported sleep disturbance	Pain severity & Pain catastrophizing.	Frequency of sleep disturbance was associated with: ↑ pain severity *** ↑ pain catastrophizing ***	NR
Travaglini et al., 2019 [51]	n/a	Self-reported sleep quality and sleep disturbance	Pain intensity & Pain interference	↑ pain interference *	NR
Weiner et al., 2019 [47]	n/a	Insomnia disorder diagnosis	Pain disability & Pain severity	↑ Back pain disability *	NR
Group 2: Experimental, quasi-Experimental Studies, or observational studies with treatment of pain or sleep					
Amin et al., 2011 [40]	n/a	Nasal CPAP (treatment) vs. sham CPAP (control)	Pain severity	NR	↓ pain intensity ***
Burgess et al., 2019 [67]	n/a	Morning bright light therapy	Pain intensity, pain behavior, pain interference, pain sensitivity	NR	↓ pain intensity * ↓ pain behavior * ↓ pain sensitivity *

Citation (year)	Baseline adjusted variables	Independent (sleep) variable(s)	Dependent (self-reported pain) outcome(s)	Results: Poor or worsened sleep	Results: Good or improved sleep
			(objectively measured), and physical function		
Burns et al., 2019 [68]	The three study epochs: baseline, bright light treatment, and follow-up	Morning bright light therapy	Pain intensity, Pain intensity volatility, and Pain interference	NR	↓ mean pain intensity *** ↓ pain intensity volatility ***
Eakmen et al., 2017 [39]	n/a	Multicomponent CBT-I	Pain interference	NR	↓ pain interference
Jaoude et al., 2016 [60]	n/a	Nasal CPAP	Pain intensity	Non-adherent participants reported ↑ pain intensity at baseline * and 12 mo (p = 0.05)	No change in pain intensity among adherers (≥4 h/night on 70% of nights)
Ruff et al., 2009 [59]	n/a	Taking Prazosin (yes/no)	Headache severity & Headache frequency	None reported	↓ pain severity and frequency (baseline to 9-wk posttreatment) *** ↓ pain severity and frequency among those who completed dosing of prazosin (9-wk posttreatment) *** ↓ pain severity and frequency among those taking prazosin (6-month follow-up) ***
Ruff et al., 2012 [58]	n/a	Daytime Sleepiness	Headache severity & Headache frequency	↑ HA pain intensity at 9-wk *** and 6-mo *** ↑ HA pain frequency at 9-wk* and 6-mo ***	Differences on daytime sleepiness from endpoint to baseline (Δ) were associated with: ↓ HA pain intensity at 9-wk ***, and 6-mo *** ↓ HA pain frequency at 9-wk *, and 6-mo *

*Note*s.

* = significant (p < 0.05);

** = significant (p < 0.01);

*** = significant (p < 0.001);

† = Data from some of those columns come directly from the author or subsequent publication.

Adjusted odds ratio (AOR), brief pain inventory (BPI), continuous positive airway pressure (CPAP), exploratory factor analysis (EFA), fiscal year (FY), headache (HA), low back pain (LBP), non-applicable (n/a), none reported (NR), obstructive sleep apnea (OSA), osteoarthritis (OA), post-traumatic stress disorder (PTSD), sleep disordered breathing (SBD), standardized mean difference (SMD), traumatic brain injury (TBI).