

Review Article

Traumatic brain injury and sleep disturbances in combat-exposed service members and veterans: Where to go next?

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Abstract.

OBJECTIVE: To synthesize the current evidence on sleep disturbances in military service members (SMs) and veterans with traumatic brain injury (TBI).

METHODS: An electronic literature search first identified abstracts published from 2008–2018 inclusively referencing sleep, TBI, and military personnel from Operation Enduring Freedom, Operation Iraqi Freedom, Operation New Dawn, and Persian Gulf veterans. Selection criteria eliminated studies on non-combat TBI, open or penetrating injuries, and articles where the relationship between sleep and TBI was not directly examined. Articles on all military branches and components, those currently serving and veterans—ranging from medical chart reviews to clinical trials, were included. Forty-one articles were selected for full text-review.

RESULTS: Twenty-four papers estimated the prevalence of sleep disturbances in TBI. Eight studies demonstrated the contribution of common co-occurring conditions, most notably posttraumatic stress disorder, to the relationship between disrupted sleep and TBI. Ten studies differentiated sleep profiles between military SMs and veterans with and without acute TBI and detected significant differences in sleep disturbances across the course of injury. Longitudinal studies were scarce but helped to establish the temporal relationship between sleep disturbances and TBI and isolate sleep-related mechanisms influencing TBI prognosis. Only three studies reported on interventions for improving sleep quality and TBI symptoms. Systematic research testing assessments and interventions that target sleep disturbances for improving sleep, TBI symptoms, and long-term functional outcomes were identified as critical knowledge gaps.

CONCLUSION: Findings unequivocally establish that sleep disturbances are highly prevalent in SMs and veterans with TBI. However, studies testing the effectiveness of treatments for improving sleep in military groups with TBI have been limited and their results inconsistent. This review highlights a critical opportunity for advancing military medicine through future research aimed at identifying and testing sleep-focused treatments in SMs and veterans with combat-related TBI.

Keywords: Sleep disturbance, traumatic brain injury, military, service members, veterans, Operation Iraqi Freedom, Operation Enduring Freedom, Operation New Dawn, Persian Gulf veterans

1. Background

Traumatic brain injury (TBI) has been broadly defined by both the World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) as the occurrence of a head injury from an external physical force after

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which at least one of the following symptoms manifests as a direct result: alteration in level of consciousness; retrograde or posttraumatic amnesia (PTA); other alterations in neurologic or neuropsychological function; cranial fracture; intracranial lesions; or death (Thurman, Alverson, Dunn, Guerrero, & Sniezek, 1999). The majority of the literature on TBI has been conducted in either the community-dwelling adults or inpatient populations. However, military Service Members (SMs) and veterans represent a group at higher risk for TBI than observed in the general population (James, Strom, & Leskela, 2014).

Between 2000–2015 alone, the incident rate of TBI sustained by members of the US Armed Forces reached 375,230 cases (Defense and Veterans Brain Injury Center, 2017). These numbers are believed to be underestimated due to prevalence estimates being based solely on individuals who report a TBI and receive treatment. Although approximately 82 percent of all TBIs experienced by SMs are considered ‘mild’ and have an average 10-day period before full return to duty, residual symptoms often manifest and become chronic (e.g., sleep disturbances; Si et al 2018). A report by the Veterans Health Administration (VHA) estimated that the health care costs for SMs with TBI are approximately four to six times as much during the first year of treatment as SMs without a TBI—over 60 percent of the total funds received (Congressional Budget Office, 2012). From 2004 to 2009 alone, combined costs related to TBI and PTSD health care for veterans in the first year of treatment was estimated to be 2.2 billion dollars (Congressional Budget Office, 2012). Thus, TBI is considered a hallmark operational stress injury associated with the Global War on Terror (Armed Forces Health Surveillance Center, 2013). Although the etiology of TBIs experienced by SMs extends beyond injuries resulting directly from combat (e.g., during training or in garrison), this paper focuses solely on TBIs resulting from combat exposure (e.g., blast and blunt force head trauma) due to blast and blunt-force injuries being the leading cause of TBI in warzones and the impact of sustaining a TBI during deployment operations on long-term individual outcomes and force readiness.

1.1. Sleep disturbances in military populations

Deployed active duty SMs are expected to perform optimally in high-risk operational environments where maintaining a normative sleep schedule is

often not possible, such as night missions or forced extended wakefulness during multi-day missions. Further, chronic insufficient sleep has been shown to compromise safety, which suggests sleep restricted combat-exposed soldiers may be at an increased risk for sustaining mission-related injuries that compromise individual and unit-level readiness (e.g., TBI).

Although sleep loss is inherent to operational missions, chronic sleep loss is also prevalent among non-deployed SMs. Military personnel report sleep disturbances (e.g., insufficient or non-restorative sleep, insomnia, nightmares) before, during, and after deployment at alarming rates (Breen, Blankley, & Fine, 2017; Caldwell, Knapik, & Lieberman, 2017; de Dassel, Wittmann, Protic, Hollmer, & Gorzka, 2017; Mysliwiec et al, 2013; Troxel et al, 2015). Numbers have continuously grown over the years and have well surpassed prevalence and incidence rates of the general population. Further, upwards of 75% of deployed SMs rate the quality of their sleep as significantly worse while in theater when compared to before deployment (Peterson, Goodie, Satterfield, & Brim, 2008), many of whom meet for clinically significant insomnia. It is estimated that over 87% of SMs report at least one sleep disturbance, with the most commonly reported being insomnia, sleep fragmentation, obstructive sleep apnea, and hypersomnia (Bramoweth & Germain, 2013; Mysliwiec, Gill, et al., 2013; Schiehser et al., 2017). Approximately 40% of soldiers report more than one sleep disturbance (Gill et al., 2014; Mysliwiec, Gill, et al., 2013), making the selection of targeted treatments exponentially more complex. Sleep disturbances are a critical issue facing the US military due to their impact on maintaining force readiness, health, well-being (Caldwell et al., 2017). Further, the economic burden of providing both acute and long-term behavioral health services related sleep disturbances has become a major concern. It is important to note that studies examining prevalence of sleep disturbances in military samples often ignore, or at the very least downplay, the contribution of pre-military service or pre-deployment sleep factors. Therefore, greater representation of baseline sleep parameters is needed in future research in order to fully examine the trajectory of sleep disturbances in military groups.

1.2. Sleep disturbances in combat-related TBI

Sleep disturbances are one of the most prevalent sequelae of TBI (AFHSC, 2013). In a sample of 114 post deployment military SMs and veterans

who had sustained blast-related mTBI, 77% endorsed experiencing sleep disturbances (Farrell-Carnahan, Franke, Graham, & McNamee, 2013). Collen and colleagues reported that 97% of soldiers with TBI reported at least one sleep disturbance (Collen, Orr, Lettieri, Carter, & Holley, 2012). These self-reported sleep disturbances were corroborated by polysomnographic sleep/wake studies and included hypersomnia (85%), insomnia (55%), sleep fragmentation (54%), and obstructive sleep apnea syndrome (OSAS; 35%). Sleep disturbances were more severe among SMs with comorbid TBI and posttraumatic stress symptoms (PTSS) or anxiety. There is preliminary evidence that blast- vs. blunt force-related TBI may be accompanied by distinct sleep disturbance profiles. Specifically, Kempf and colleagues reported that blast injuries were associated with insomnia and elevated anxiety symptoms, whereas blunt force injuries were more commonly associated with OSAS. These sleep disturbances are chronic: Over 60% of those with TBI continued to endorse clinically significant sleep disturbances three years post-injury (Kempf, Werth, Kaiser, Bassetti, & Baumann, 2010).

Sleep disturbances can also impede the TBI rehabilitation process (Bell et al., 2018; Sandsmark, Elliott, & Lim, 2017) and are risk factors for the development of anxiety and mood disorders following stress exposure (Babson & Feldner, 2010; Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2010; Gehrman et al., 2013). Realizing the impact TBI has on functional outcomes and quality of life, as well as the role of disturbed sleep as a risk factor for the development and maintenance of death, disease, and disability, the comorbidity between TBI and chronic sleep disturbance may increase the risk for poor health outcomes among SMs and veterans relative to the general population (Barr et al., 2015).

The purpose of this review is to synthesize the literature focusing on sleep disturbances and TBI as it pertains specifically to military SMs and veterans. This review uniquely contributes to the existing science due to the overall scarcity of prior summaries of sleep disturbances and TBI, as well as existing reviews focusing primarily on the general population (see Barshikar & Bell, 2017; Bogdanov, Naismith, & Lah, 2017; Orff, Ayalon, & Drummond, 2009; Ponsford et al., 2012 for reviews), on sleep disturbances occurring post-TBI (Bogdanov et al., 2017; Ponsford et al., 2012), or that isolate only one sleep disturbance (i.e. insomnia; Sandsmark, Elliott, & Lim, 2017). First, we discuss the nature and prevalence of sleep disturbances based on varying TBI assessment meth-

ods. Specific sleep profiles that may guide diagnostic and treatment efforts targeting disruptive sleep in TBI relative to other diagnostic groups are then suggested. Second, a summary of findings regarding the role of sleep in the trajectory of TBI is presented. Finally, critical knowledge gaps that, if filled, have a high potential for enhancing sleep health and functional outcomes in SMs and veterans with TBI are discussed.

2. Methods

An electronic scoping review of the literature on sleep and TBI in military SMs and veterans was conducted using the PubMed, PsychInfo, and Google Scholar databases. Sleep, TBI, and military were identified as three search term categories and the following terms were used in combination: “sleep”, “sleep disturbance”, “TBI”, “traumatic brain injury”, “closed head injury”, “military”, “servicemembers”, “veterans”, “Operation Enduring Freedom” (OEF), “Operation Iraqi Freedom” (OIF), “Operation New Dawn” (OND) and “Persian Gulf War” to generate the initial search. The search was limited to peer-reviewed, full-text publications printed in English from January 2008 through January 2018 inclusively. The beginning year for the selection range was determined based on the exponential growth of studies focused on post-9/11 military groups extending from that time and previous reports summarizing the literature prior to 2008. A total of 63 published manuscript were found. Abstracts were reviewed by the first and second authors, and only those containing at least one search term from all three categories (i.e. sleep, TBI, military) were considered. Selection criteria then eliminated studies on non-combat TBI, open or penetrating injuries, or articles where the relationship between sleep and TBI was not directly examined. Articles on all military branches and components, those currently serving and veterans—ranging from reviews to clinical trials, were included. A total of 41 articles went through full-text review. These studies are summarized in detail in Table 1.

3. Summary of the literature

3.1. Time course of sleep disturbances & TBI

Two of the 41 papers selected explicitly sought to evaluate the time course between sleep disturbance

Table 1
Literature on sleep in military service members and veterans with traumatic brain injury (TBI) from 2008 to 2018 inclusively

Reference	Objective(s)	Sample	TBI parameters	Measures	Major findings
(Armed Forces Health Surveillance Center, 2013)	To examine TBI symptoms at 3- and 12-months post injury in military SMs	N = 821,611 OEF/OIF/OND military SMs divided into five TBI-injury groups	Mild: n = 150,125 Severe: n = 32,761 Non-current: n = 28,765 Other injury: n = 186,659 Non-injury: n = 423,301	Electronic medical health records from a 13-year surveillance period	Of all symptoms measured, sleep disorders had the second largest proportion increase from 3 to 12 months post-injury. Those with severe TBI showed the greatest increase in sleep disorders relative to all other injury groups.
(Barr et al., 2015)	To examine the effects of sleep treatment (cognitive behavioral therapy [CBT], medication, and continuous positive airway pressure [CPAP]) on sleep disturbance, inflammation, and health related quality of life (HRQoL) in military SMs with TBI	N = 70 recently deployed military SMs with TBI	Not specified	Pittsburgh Sleep Quality Index (PSQI); C-reactive protein (CRP) concentration	Participants who reported restorative sleep at 12 months had significant reductions in PTSD and depressive symptoms, and increased HRQoL. Those who reported no change or worse sleep at 12 months had a slight increase in PTSD and depressive symptoms. Improved sleep may be related to reduced inflammation.
(Bramoweth & Germain, 2013)	To review the recent literature on insomnia related to military deployment	N/A	Mild Chronic mild Blast Blunt	PTSD Checklist (PCL); PSQI; Insomnia Severity Index (ISI); Dysfunctional Beliefs About Sleep (DBAS-10)	Insomnia increases risk for emotional and physiological combat-related injuries. Insomnia and other sleep/wake disturbances are prevalent and persist in SMs with TBI, often impeding rehabilitation and recovery.
(Bryan, 2013)	To examine the effect of multiple TBIs on insomnia	N = 150 male, active-duty, military SMs	TBI frequency	ISI; Depression subscale of the Behavioral Health Measure (BHM); PCL; Military Acute Concussion Evaluation (MACE)	Number of TBIs significantly predicted insomnia severity, and remained robust when controlling for PTSD, depressive, and concussive symptoms. Compared to those with zero TBIs, four times as many participants with one TBI and ten times as many with multiple TBIs met for clinical insomnia.
(Capaldi, Guerrero, & Killgore, 2011)	To examine the specificity of sleep disturbances related to PTSD and TBI in combat veterans	N = 69 active duty OEF/OIF combat veterans (60 male; 9 female)	No TBI Mild Moderate Severe	Electronic health record review; Polysomnography (PSG) sleep data; Apnea Hypopnea Index (AHI); PTSD diagnosis, TBI, Major depression, Other anxiety/mood disorders; Epworth Sleepiness Scale (ESS)	Rate of sleep problems, obstructive sleep apnea (OSA), hypoxia, nighttime awakenings, and daytime sleepiness were elevated in across all injury severities. PSG did not significant differentiate groups, but revealed higher frequency of nighttime arousals in PTSD and more slow wave sleep in TBI.

(Collen, Orr, Lettieri, Carter, & Holley, 2012)	To examine the prevalence of sleep disturbances in military veterans with TBI sustained during combat	N = 116 OEF/OIF combat veterans (96.6% male)	Mild Moderate Severe Blast Blunt	Electronic health record review: Brief TBI screen; ESS; Visual analog fatigue scale, Directed questioning on sleep disturbances; PSG; AHI	97.4% of participants endorsed at least one sleep complaint Those with blast-related TBI reported significantly greater insomnia and anxiety symptoms when compared to blunt-related TBI Individuals with blunt-related TBI reported significantly greater levels of OSA when compared to blast-related TBI
(DeGutis et al., 2018)	To explore the associations between sleep dysfunction and a wide range of common physical and psychological consequences of trauma exposure	N = 283 combat-exposed veterans deployed in support of OEF/OIF/OND	Mild Moderate Severe	PSQI; PSQI-A; CAPS; Traumatic Life Events Questionnaire (TLEQ); DRR1; Depression; Anxiety; and Stress Scale (DASS); BAT-L; Lifetime Drinking History Questionnaire; SFMPQ; Blood screen and brief physiological exam; Fagerstrom Test for Nicotine Dependence	PTSD was associated with the sleep efficiency, perceived sleep quality, and sleep disturbance subscales of the PSQI
(Elliott et al., 2017)	To examine the ability for resiliency to predict adjustment in veterans with and without TBI, while covarying for level of combat exposure	N = 127 veterans (n = 107 men; n = 20 women)		Multidimensional Personality Questionnaire	Veterans with the resiliency personality phenotype experienced less sleep troubles and more health-promoting behaviors, psychological flexibility, and emotional distress tolerance when compared to other phenotypes.
(Eitlenhofer, Meltrose, Delawalla, Castellon, & Okonek, 2012)	To examine the associations between level of functioning, demographic, psychiatric, neuropsychological, and TBI factors in military veterans with TBI	N = 57 OEF/OIF veterans (96.5% male)	Mild w/o loss of consciousness (LOC) or posttraumatic amnesia (PTA) Mild with LOC and/or PTA Moderate Severe Single Multiple	Electronic health record review: Demographic information; Current work/school involvement; NSI; Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV) diagnoses; Neuropsychological evaluation battery	Reduced overall functioning of veterans with TBI was associated with decreased cognitive functioning, ongoing post concussive symptoms; lower education; and psychotropic treatment for psychiatric and sleep difficulties
(Farrell-Camahan, Franke, Graham, & McNamee, 2013)	To examine subjective sleep disturbances in military veterans with history of blast-related mTBI receiving services for PCS	N = 114 military veterans (96% male)	Blast	Electronic health record review: Clinical Tracking Form (CTF); NSI; PLC for civilians (PCL-C); Sleep disturbance (item 13 on PCL-C)	LOC at time of injury was significantly associated with more sleep disturbances compared to those without LOC Those with sleep disturbance endorsed more nightmares, depression, headaches, and fatigue

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Reference	Objective(s)	Sample	TBI parameters	Measures	Major findings
(Gilbert, Kark, Gehrman, & Bogdanova, 2015)	To review the current work related to sleep in OEF/OIF veterans with PTSD and TBI, emphasizing: sleep pathophysiology and neurobiology; treatment options; and methodological concerns	N/A	Mild	N/A	Sleep remains a primary symptom and mediating factor of treatment outcomes in both TBI and PTSD There are limited numbers of treatment protocols for TBI and PTSD that target sleep as a primary symptom Sleep research has been inconsistent due to the variability of sleep patterns and drive in individuals with comorbid diagnoses Sleep research is limited due to the nature of measuring sleep and individual sleep differences
(Gill et al., 2014)	To examine the role of PTSD and comorbid depressive symptoms on HRQoL in military SMs subsequent to deployment, and determine the contribution of inflammation	N = 110 military SMs w/ and w/o diagnosed sleep disorders and TBI (n = 70 in low comorbidity group; n = 40 in high comorbidity group; 97.3% male)	Mild	PSG; Quick Inventory of Depressive Symptomatology (QIDS); PCL-M; Structured Clinical Interview for DSM III (SCID-III); Warrior Administered Casualty Assessment Tool (WARCAT); Short Form Survey (SF-36); Blood collection with plasma IL-6 and C-reactive protein measurement	One-third of the sample met for two or more service-related disorders Lower HRQoL and elevated IL-6 concentrations were found in both individuals with depression or PTSD. The greatest group differences were observed in those with more service-connected disorders, independent of sleep difficulties
(Holster, Bryan, Heron, & Seegmiller, 2017)	To examine the longitudinal relationships between TBI, sleep, and mental health in OIF U.S. Air Force SMs pre- and post-deployment	N = 168 (87.1% male)	Not Specified	Concussion Questionnaire (CQ); ISI; PCL-M; Patient Health Questionnaire (PHQ)	SMs with baseline history of prior TBI endorsed more PTSD and insomnia symptoms than those without prior TBI Chronic insomnia was associated with pre-deployment history of TBI and TBI during deployment
(Jaramillo et al., 2015)	To identify clinical subgroups of OEF/OIF veterans based upon distinct PTSD, TBI, depression, and medical condition symptoms	N = 303,716 OEF/OIF veterans	TBI alone TBI with comorbid diagnoses	Electronic health record review: TBI, PTSD, depression, and other medical condition diagnoses	Model fit statistics revealed the presence of 7 subgroups, 2 of which involved sleep 1) Pain (other pain complaints and sleep disturbance; 19.8%) and 2) High Distress (high probabilities of all symptoms aside from fatigue)

(Kaplan, Vasterling, & Vedak, 2010)	To review the neuropathological & neuroanatomical features of TBI and PTSD, the roles of neurotrophic factors (specifically Brain-Derived Neurotrophic Factor [BDNF]) in brain plasticity, and potential treatment approaches for TBI and PTSD	N/A	Mild Moderate Severe Blast	N/A	Treatment approaches stimulating BDNF production including, exercise, certain antidepressants, intracerebral infusion of BDNF, and histone deacetylase inhibitors may help to improve sleep, TBI, and PTSD symptoms
(Lang, Vezzey-Morris, & Andrasik, 2014)	To explore the role of insomnia in PTSD and pain outcomes in combat-exposed military veterans with TBI	N = 137 military veterans with combat-related TBI (95.6% male)	Combat-related, severity not specified	PCL-C; ISI; Brief Pain Inventory-Short Form (BPI)	Insomnia, pain, and PTSD co-occurred together in 51.8% of the sample Increased PTSD symptoms correlated with increased pain severity, pain interference, and insomnia Insomnia was shown to be a partial mediator for the relationships between PTSD and pain severity and pain interference
(Lew et al., 2010)	To examine the effect of the "polytrauma clinical triad" (pain, PTSD, and TBI) on sleep disturbances in OEF/OIF veterans	N = 200 OEF/OIF veterans from a VA polytrauma clinic	Mild Moderate Severe	Standardized TBI evaluation; NSI	Sleep disturbances were more severe when either pain or TBI co-occurred with PTSD TBI alone did not predict sleep disturbances
(Lippa et al., 2015)	To examine the effect of deployment-related psychiatric and behavioral conditions on disability in veterans and SMs	N = 255 OEF/OIF SMs and veterans	Mild	Deployment Risk and Resilience Inventory (DRRI); CES; Boston Assessment of TBI-Lifetime (BAT-L); Clinical Administered PTSD Scale (CAPS); SCID-IV; PSQI; Short Form McGill Pain Questionnaire (SFMPQ); World Health Organization Disability Assessment Schedule II (WHODAS); Validity 10 Scale of the NSI	90% of sample were diagnosed with a psychiatric and/or behavioral condition Approximately 50% presented with 3 or more conditions An exploratory factor analysis showed 4 factors accounted for 76.9% of the variance: [1] Depression, PTSD, and mTBI (deployment-related factor) [2] Pain and sleep (somatic factor) [3] Anxiety disorder other than PTSD (anxiety factor) [4] Substance use/abuse (substance use factor) Those with all 3 deployment-related factors were most likely to present with substantial disability
(Maccera, Aralís, Rauh, & MacGregor, 2013)	To explore sleep as a potential mediating factor in the development of PTSD and/or depression in military SMs with TBI	N = 29,640 male military SMs deployed to OEF/OIF in 2008–2009	Blast Non-blast Severity not specified	Post-Deployment Health Assessment (PDHA); Post-Deployment Health Reassessment (PDHRA)	The relationships between TBI, PTSD, and depression, were largely mediated by sleep problems Those who screened positive for TBI were approximately 3 times more likely to report sleep disturbances Sleep problems typically manifested immediately post-deployment; however, PTSD or mood symptoms did not manifest for months

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Reference	Objective(s)	Sample	TBI parameters	Measures	Major findings
(Magnen, Lau, Madden, & Seal, 2012)	To differentiate overlapping and distinct screen-based symptoms of TBI, PTSD, and depression in OEF/OIF veterans using factor analytic techniques	N = 1,549 OEF/OIF military SMs (89.6% male)	Mild	VA TBI screen; Primary Care PTSD screen; PHQ-2	Four separate constructs emerged during factor analysis and included: TBI, PTSD, depression, and sleep problems with hypervigilance Sleep problems, along with irritability, increased the rate of false positives of TBI that could be accounted for by PTSD and/or depression Sleep problems may be health difficulties distinct from PTSD, TBI, and/or depression in military SMs post-deployment
(Matthews, Signoracci, Stearns-Yoder, & Brenner, 2016)	To examine perspectives of veterans with chronic moderate-severe TBI on sleep-wake disturbance characteristics, factors, consequences, and management strategies	N = 19 male veterans with post-acute TBI and comorbid sleep-wake disorder enrolled at the VA at least 1-year post-injury	Moderate Severe	Semi-structured interview; ISI, Ohio State University TBI-Identification Method (OSU-TBI-ID)	Perspectives fell into two main dimensions: "messed up sleep" and surviving/management of sleep-wake disturbance Participants described pervasive impact of sleep troubles on their lives and cited difficulty falling asleep, nighttime awakenings and poor sleep quality as having the greatest impact Medication, OSA treatment, and isolation were management strategies reported by veterans Veterans reported an overall willingness to try new sleep management approaches
(Mysliwiec et al., 2015)	To evaluate adherence to positive airway pressure (PAP) in active duty SMs, and the effects of PAP adherence on sleep quality, sleepiness, and HRQOL	N = 58 male OEF/OIF veterans w/ and w/O mTBI	Mild	Auto-titrating PAP (APAP); PCL-M; QIDS; SF-36; WARCAT; PSG; ESS; PSQI	SMs' APAP adherence demonstrated significantly improved sleepiness, quality of sleep, depressive symptoms, levels of energy/fatigue, and overall emotional well-being Results appeared to be independent of the presence of mTBI, as there were no significant differences in those with or without mTBI between the adherence and non-adherence groups
(Mysliwiec, Gill, et al., 2013)	To evaluate the presence of sleep disorders in SMs referred for post-deployment sleep disorder evaluations, and the relationships between sleep disorders and depression, mTBI, pain, and PTSD related to military service	N = 110 combat veterans (97.3% male) deployed in support of Overseas Contingency Operations	Mild	PSG; AHI; CES; WARCAT; PCL-M; QIDS; SF-36; ESS; Self-reported sleep duration and quality	47.3% of participants met for two or more service-related diagnoses Sleep disorders were diagnosed in 88.2% of veterans. 62.7% met for OSA and 63.6% met for insomnia 25.5% met exclusively for insomnia and 24.5% met exclusively for OSA. 38.2% met for comorbid insomnia and OSA Those who were more likely to meet for depression and PTSD had comorbid OSA and insomnia

<p>(Myslwiiec, McGraw, et al., 2013)</p>	<p>To describe the prevalence of sleep disorders in active duty military SMs and identify relationships between sleep disorders, comorbid diagnoses, and demographics</p>	<p>N = 725 active duty military SMs</p>	<p>Mild</p>	<p>Electronic health record review; Diagnostic PSG data; Self-reported sleep duration; ESS; PTSD diagnosis; Mtbi; Other mood or anxiety disorders</p>	<p>51.2% of SMs diagnosed with OSA, 24.7% diagnosed with insomnia, 8.9% diagnosed with behaviorally-induced insufficient sleep syndrome, and 5.1% diagnosed with paradoxical insomnia Significant relationships between insomnia, mTBI, PTSD, and pain</p>
<p>(Norris, Sams, Lundblad, Franz, & Harris, 2014)</p>	<p>To compare symptom presentation in military SMs with blast mTBI with and without LOC at 72 hours post-injury, and again 48–72 hours later</p>	<p>N = 210 active duty SMs who reported mTBI to a US military-operated concussion clinic in Afghanistan</p>	<p>Blast-related mTBI LOC No LOC Single Multiple</p>	<p>Concussion symptoms were assessed using a 16-item checklist from the MACE with and an additional 9 items assessing concussion symptoms; Self-reported lifetime history mTBI; screening for Acute Stress Reactions (ASRs); PHQ-2; ANAM TBI version</p>	<p>At initial evaluation, those with LOC reported more difficulty with sleep, hearing loss, and memory challenges; however, the magnitude of these relationships weakened after adjusting for ASRs During follow-up, those with LOC reported difficulty sleeping, and this relationship remained robust after adjusting for ASRs</p>
<p>(Pettie et al., 2014)</p>	<p>To characterize the relationships between mTBI (blast and impact-related) and structural and functional brain abnormalities, behavioral characteristics (i.e., PTSD, depression, alcohol use, sleep), and postconcussive symptoms (PCS) in OEF/OIF veterans</p>	<p>N = 52 (n = 34 blast, 100% male and n = 18 non-blast, 94.4% male) OEF/OIF veterans</p>	<p>Mild Blast Non-blast Blast + Impact</p>	<p>Quantification of Cumulative Blast Exposure (QCuBE); SCID; CAPS; CES; PCL-M; PHQ-9; PSQI; Alcohol Use Disorders Identification Test-Consumption Questions (AUDIT-C); NSI; Unified Parkinson's Disease Rating Scale (UPDRS) motor section; Brief Smell Identification Test (BSIT); Brain FDG-PET scan; Fractional Anisotropy (FA) mapping; Macromolecular Proton Fraction (MPF) mapping</p>	<p>Blast-exposed veterans endorsed more frequent and severe PCS, greater levels of combat exposure, higher PTSD symptoms, higher depressive symptoms, higher levels of alcohol abuse/dependence, and higher levels of sleep disturbances compared to those mTBI history without blast</p>

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Table 1
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Reference	Objective(s)	Sample	TBI parameters	Measures	Major findings
(Pugh et al., 2014)	To examine and identify comorbidity clusters based upon diagnoses of conditions specific to deployment (TBI, PTSD, pain) and chronic medical conditions (i.e., hypertension, diabetes)	N = 191,797 OEF/OIF veterans who received health care through the VA during 2008–2010	Not specified	Diagnoses identified through face-to-face clinic or hospital care utilizing ICD-9-CM codes; Demographics characteristics; Healthcare utilization indicators; Adverse outcomes according to ICD-9-CM codes	6 comorbidity clusters were revealed, including: [1] Polytrauma clinical triad (JPCT); i.e. TBI, PTSD, and pain) with chronic disease (5%) [2] PCT (9%) [3] Mental health and substance abuse (24%) [4] Sleep, amputation, and chronic disease (4%) [5] Pain and moderate PTSD (6%) [6] Relatively healthy (56%) Cluster 1 had the highest rates of depression, anxiety, and sleep disturbances All individuals in Cluster 4 had a diagnosed sleep disorder
(Robinson et al., 2015)	To examine the impact of blast exposure sustained at close range on neuronal integrity of the default mode network (DMN), while considering the influence of concussive symptoms, PTSD, pain, sleep	N = 134 (85.1% male) OEF/OIF SMs	Mild Moderate Severe Blast Blunt	Demographics; DRRI; CES; Intelligence quotient from the Wechsler Test of Adult Reading (WTAR); SFMPQ; PSQI; BAT-L; CAPS; SCID; fMRI neuroimaging data	Veterans with blast occurring within 10 meters showed significant reductions in functional connectivity in the primary somatosensory cortex and pre-supplementary motor cortex than veterans with blast exposure at greater distances or no TBI TBI severity, length of deployment, PTSD symptoms, concussive symptoms, pain, sleep quality, and LOC did not influence relationships
(Ruff, Riechers, Wang, Piero, & Ruff, 2012)	To evaluate if reduced PCS are associated with decreased PTSD symptoms, neurologic deficits (ND), or both, subsequent to sleep interventions	N = 63 OEF/OIF veterans (90.5% male) with combat mTBI with LOC, ND, and PTSD	Mild Blast	BSIT; MOCA; Headache evaluation; PCL-M; ESS	Veterans showed marked improvements in daytime sleepiness, headache severity, and cognitive functioning following a 9-week intervention of sleep counseling and prazosin More than 50% of the participants reported > 50% reduction in pain, and over 75% reported > 50% reductions in headache frequency and daytime sleepiness Veterans maintained and showed continued improvement in headache pain, frequency, and daytime sleepiness at follow up
(Ruff, Ruff, & Wang, 2008)	To examine if veterans with blast mTBI who experience residual cognitive difficulties endorse greater frequency and intensity of headaches and sleep disturbances	N = 126 OEF/OIF veterans with blast mTBI; 80 of whom demonstrated impairment on neurological or neuropsychological examinations for TBI	Mild Blast	Veterans Health Administration TBI screening tool; Neuropsychological evaluation; Montreal Cognitive Assessment (MOCA); BSIT; Queries regarding headaches; 4-item PTSD screen; PCL	Veterans with PTSD and both greater sleep difficulties had neurocognitive impairment.

(Ruff, Ruff, & Wang, 2009)	To examine if sleep behavioral and prazosin interventions increase self-reported sleep quality, headache frequency and severity, and cognitive performance	N = 126 OEF/OIF veterans w/ blast mTBI (74 with severe headaches and neurological or neuropsychological deficits; 71 with PTSD; 5 with restful sleep)	Mild Blast	Neurologic evaluation; Neuropsychological evaluation; 4-item PTSD screen; PCL, MOCA; Queries regarding headaches and sleep impairment; ESS	The combination of prazosin and behavioral sleep treatment demonstrated improvement in sleep quality, reduced daytime sleepiness, and frequency and severity of headaches Behavioral sleep treatment in the absence of prazosin showed reduced ESS scores, but no improvement in perceived sleep quality Prazosin alone demonstrated both improvement in sleep quality and decreased ESS
(Schiehser et al., 2015)	To examine QoL among OEF/OIF/Persian Gulf veterans with and without TBI, and examine the relationships between postconcussive symptoms (PCS), sleep, TBI, and quality of life (QoL)	N = 82 OEF/OIF/Persian Gulf veterans (61 w/ history of TBI; 21 controls)	Mild Moderate Blast Blunt Blast + Blunt	Neurological/psychological screen; World Health Organization Quality of Life (WHOQOL-BREF); Neurobehavioral Symptom Inventory (NSI); Combat Exposure Scale (CES)	Moderate to strong negative association was observed between depression and sleep quality Sleep quality was found to be the strongest predictor of physical QoL
(Schiehser et al., 2017)	To examine the impact of physical and cognitive fatigue on post-acute mild-moderate TBI, and the associations between psychiatric, sleep, cognitive, and psychosocial sequelae	N = 100 veterans (n = 60 with history of mild-moderate TBI; n = 40 military controls)	Mild Moderate	MFIS; PSQI; BAI; BDI-II; PCL-M; AUDIT; Drug Abuse Screening Test	In the TBI group, psychiatric symptoms, sleep disturbance, and PTA all helped to explain cognitive and physical fatigue
(Stocker et al., 2014)	To evaluate the neurobiological underpinnings of the relationship between sleep and blast mTBI by examining relative cerebral metabolic rate of glucose in wakefulness, rapid eye movement (REM) sleep, and non-REM (NREM) sleep in veterans with and without history of blast exposure or mTBI	N = 25 OEF/OIF veterans (14 with a history of blast mTBI; 11 without history of blast mTBI)	Mild Blast	SCID; CAPS; SLID; CES; BDI; Life Events Checklist (LEC); MACE; PSQI; Magnetic resonance imaging (MRI) brain scan; PET scan	PET imaging revealed hypometabolism during wakefulness and REM sleep in neurobiological networks in veterans reporting blast mTBI compared to those without blast mTBI, independent of effects of PTSD

(Continued)

Table 1
(Continued)

Reference	Objective(s)	Sample	TBI parameters	Measures	Major findings
(Stocker et al., 2016)	To examine if self-reported blast exposure during deployment effects subjective and objective sleep measures in OEF/OIF SMs and veterans with and without PTSD	N = 71 OEF/OIF SMs and veterans (n = 37 with blast exposure, n = 2121 with PTSD, n = 34 without blast exposure, and n = 26 with PTSD)	Mild Blast	SCID; CAPS; SLD; CES; BDI; Beck Anxiety Inventory (BAI); ISI; LEC; MACE; PSQI; PSQI Addendum for PTSD (PSQI-A); PSG	While persistent concussive symptoms following blast exposure were associated with sleep disturbances, self-reported blast exposure without concurrent symptoms did not appear to contribute to poor sleep quality, insomnia, and disruptive nocturnal disturbances beyond the effects of PTSD Reduced REM sleep fragmentation may be a sensitive index of the synergistic effects of both psychological and physical insults
(Tanev, Pentel, Kredlow, & Charney, 2014)	To summarize the existing literature on PTSD and TBI, their comorbidity, diagnosis, symptoms, and treatment considerations	N/A	Mild Moderate Severe Blast Blunt	N/A	30-50% of TBI outpatients endorsed insomnia Individuals with TBI have higher prevalence rates of sleep apnea, hypersomnia, delayed sleep phase, REM sleep behavioral disorder, narcolepsy, periodic limb movements, decreased melatonin production, and sleep bruxism Individuals with both moderate/severe TBI and PTSD endorse greater sleep difficulties than those with PTSD and mTBI or PTSD alone TBI is associated with greater slow wave sleep Those with TBI and PTSD subjectively endorse more daytime sleepiness despite objective measures indicating they have more sleep at night compared to those with PTSD alone
(Verfaellie, Lee, Lafleche, & Spiro, 2016)	To examine the contribution of sleep disturbances to cognitive performance in veterans with history of blast exposure	N = 160 OEF/OIF veterans exposed to blast (n = 55 no mTBI; n = 63 mTBI w/o LOC; n = 42 mTBI w/LOC)	Mild	CAPS; clinical TBI interview; PSQI; neuropsychological measures: Wechsler Adult Intelligence Test – III (WAIS-III) Digit Symbol Coding; D-KEFS (Trail Making Test, Color-Word Interference, Verbal Fluency); California Verbal Learning Test, Brief Visual Memory Test-Revised; Finger Tapping Test, Grooved Pegboard test	A negative association was observed between PTSD symptoms and cognitive performance across multiple cognitive domains and was mediated by self-reported sleep disturbances mTBI w/LOC was uniquely associated with lower manual dexterity, but this relationship was not mediated by sleep disturbances

(Vuletic et al., 2016)	A randomized clinical trial of the effect of telephone-based problem-solving treatment (PST) on sleep quality and its correlates in active duty, post-deployment SMS with mTBI	N = 352 active duty SMS with combat-related mTBI (n = 175 receiving PST; n = 177 education-only [EO] control group)	Mild	PSQI; Rivermead Post-Concussion Symptom Questionnaire (RFSQ); Behavioral Symptoms Inventory-18 (BSI-18); PCL-M, European Quality of Life questionnaire (EuroQoL)- question 4; PHQ-9; Sheehan Disability Scale, SF-12, AUDIT-C	The PST and EO groups both displayed poor sleep quality at baseline. The PST group saw significant improvement in sleep quality at 6-months, but not at 12-months. Low sleep quality was associated with concussion symptoms, pain, depression and PTSD at all time points
(Waldron-Perrine, Henrick, Spencer, Pangilinan, & Bieliauskas, 2014)	To investigate demographic, injury-related, psychiatric symptoms, and sleep disturbances as predictors of postconcussive syndrome in veterans	N = 164 veterans (97% male) from a Midwest VA polytrauma/TBI clinic	Mild	Electronic health record review: NSI; PCL-M; The Hospital Anxiety and Depression Scale; ISI; Shipley Institute of Living Scale-Vocabulary Test; Trail Making Test	Emotional distress and sleep disturbances distinctively predicted the four post-concussive symptom constructs typically thought to be associated with injury-related characteristics
(Wallace et al., 2011)	To compare sleep characteristics of OEF/OIF veterans separated into three groups: healthy sleepers; insomnia related to PTSD and mTBI; and insomnia related to PTSD alone	N = 30 OEF/OIF veterans (n = 15 with PTSD/mTBI, n = 9 with PTSD, n = 6 healthy sleepers)	Mild Blast Mixed (blast followed by blunt force from motor vehicle collision, shrapnel, or fall)	ISI; ESS; Fatigue Severity Scale (FSS); BDI-II; PCL-M; Pain visual analog scale (VAS); Short form survey (SF-36); HRQOL; PSG; Actigraphy; Neurological examination	Insomnia severity and subtypes were similar in veterans with PTSD/mTBI and PTSD alone. Veterans with PTSD/mTBI subjectively endorsed greater daytime sleepiness. Waking after sleep onset (WASO) was significantly lower in PTSD/mTBI
(Wiseman-Hakes et al., 2013)	To longitudinally track rehabilitation outcomes in community-dwelling adults with TBI receiving individualized sleep interventions	N = 12 adults with chronic TBI and co-occurring sleep/wake disturbance	Mild Moderate Severe	ISI, BDI, BAI, Latrobe Communication Questionnaire, Speed and Capacity of Language Processing, Test of Everyday Attention, Repeatable Battery for the Assessment of Neuropsychological Status, Daily Cognitive-Communication and Sleep Profile	All rehabilitation outcome measures showed a positive trend toward performance or symptom improvement. Statistically significant changes were observed for insomnia severity, depression severity, language, and language processing speed

and TBI is SMS or veterans. Only one study to date at the time of this publication assessed sleep in the acute phase following TBI. Norris showed that TBI with loss of consciousness (LOC) was associated with greater self-reported difficulty sleeping compared to TBI without LOC in 210 active duty SMs who reported sustaining an mTBI to a US military-operated concussion clinic in Afghanistan. The greatest self-reported sleep difficulty associated with LOC was endorsed at 72 hours post-injury and again 48–72 hours after the initial TBI assessment (Norris, Sams, Lundblad, Frantz, & Harris, 2014). These findings suggest that the onset of sleep disturbance can occur immediately following the point of injury and are strongly associated with LOC.

The Armed Forces Health Surveillance Center ([AFHSC]; 2013) reviewed the electronic medical records of 821,611 SMs with TBI at 3- and 12-months post injury from a 13-year surveillance period examining 14 common TBI-related symptoms or conditions. Severity of sleep disturbance had the second greatest increase from three to 12 months across all levels of TBI severity when compared to a non-TBI control group. Other highly prevalent symptoms included headache, alcohol and substance abuse, and PTSD—all sequelae or comorbidities of TBI with known links to disrupted sleep. (AFHSC, 2013).

3.2. *Prevalence & characterization of sleep disturbances in TBI*

Three studies focused primarily on estimating the prevalence of sleep disturbances in SMs and veterans with combat-related TBI using a wide variety of assessment tools including, self-report subjective and objective questionnaires, medical records review, objective sleep measurement (e.g., actigraphy, polysomnography (PSG)) and clinical interviews conducted in different settings (e.g., sleep clinics, laboratories). In a study by Collen et al (2012), one-hundred sixteen OEF/OIF combat-exposed active duty SMs with documented mild to moderate TBI underwent a comprehensive sleep evaluation, including PSG and subjective assessments of sleep quality and daytime somnolence in a hospital sleep medicine clinic. Almost all (97.4%) SMs experienced sleep disturbances, with the most common being hypersomnia, sleep fragmentation, insomnia, and OSAS (Collen et al., 2012). Using a large self-report battery of health assessments, Gill and colleagues estimated that one-third of 110 combat-exposed SMs with diagnosed sleep disorders

and sleep disturbances also met criteria for two or more service-related disorders (Gill et al., 2014). The most commonly reported sleep disturbances were insomnia and OSA. SMs with sleep disturbances were divided into two groups: low-comorbidity (0–1 comorbid conditions) and high-comorbidity (2–3 comorbid conditions). SMs in the high comorbidity group were significantly more likely to be diagnosed with PTSD, depression, and/or TBI symptoms compared to SMs in the low comorbidity group. In combat-exposed active duty SMs, the percentage of soldiers endorsing two or more service-related sleep disturbances has been reported to be as high as 47.3% (Mysliwiec, Gill, et al., 2013; Mysliwiec, McGraw, et al., 2013).

Capaldi and colleagues isolated sleep features present in 69 active duty combat-exposed veterans with TBI and sleep disturbances through an electronic medical record review (including PSG, OSAS, and daytime sleepiness data) and found that frequency of trouble sleeping, number of nighttime awakenings, and daytime sleepiness were elevated across all TBI injury severity groups (Capaldi, Guerrero, & Killgore, 2011). Compared to SMs without TBI, SMs with TBI are three times more likely to report sleep disturbances immediately following deployment (Macera, Aralis, Rauh, & MacGregor, 2013). Focusing on more chronic, post-deployment sleep disturbances, Tanev and colleagues reported that veterans with TBI history had higher rates of OSAS, hypsomnias, REM sleep behavior disorder, narcolepsy, periodic limbic movements, sleep bruxism and increased slow wave sleep relative to veterans without TBI (Tanev, Pentel, Kredlow, & Charney, 2014).

The variable prevalence estimates reported across studies of SMs and Veterans with TBI are likely a reflection of different assessment methods (e.g., PSG vs. self-report questionnaires) and a bias that may be introduced by studying patients in different settings (e.g., sleep clinics vs. general survey).

3.3. *Influence of TBI-related factors on sleep disturbances*

Eight studies suggested that injury-related factors may influence the nature and trajectory of sleep disturbances in SMs and veterans, as well as health factors and functional impairment.

The mechanism of injury leading to TBI is a primary factor that may influence sleep disturbances in military samples. In the sample previously referenced by Collen and colleagues, participants with blast TBI

reported significantly worse insomnia, whereas those with blunt TBI had greater levels of OSAS (Collen et al., 2012). Petrie et al. showed that when compared to veterans with TBI history without blast exposure, veterans with TBI history and blast exposure endorsed higher levels of sleep disturbances overall (Petrie et al., 2014). Furthermore, blast exposure followed by concussive symptoms has been associated with sleep disturbances, but this relationship was not found in those exposed to blast without current symptoms. These findings suggest that both blast- and blunt-TBI may increase risk for specific sleep disturbances, and that blast exposure may be especially important to the development of sleep disturbances in military samples, especially when concussive symptoms follow the initial injury.

TBI severity may also impact the severity of sleep disturbances and injury prognosis. In one of the few studies measuring sleep disturbances longitudinally after TBI, the AFHSC used electronic medical records to track changes in sleep disturbances change from three to 12 months post injury in SMs and veterans. Results showed that severe TBI was associated with the greatest increase in occurrence of new sleep disorders at 12 months relative to mild and moderate TBI, those with prior TBI, and SMs and veterans with no current symptoms (AFHSC, 2013).

LOC has also shown to be significantly associated with more sleep disturbances, in particular nightmares, in those with TBI compared to those with TBI without LOC (Farrell-Carnahan et al., 2013). As detailed above, Norris et al. also found that LOC at time of injury was associated with more severe sleep disturbances (Norris et al., 2014).

The number of TBIs may also be of particular importance when estimating the prevalence of sleep disturbances in military samples with TBI. Bryan assessed the prevalence of clinical insomnia across TBI frequency and found compared to those with zero TBIs, four times as many participants with one TBI and 10 times as many participants with multiple TBIs met for clinical insomnia (Bryan, 2013). These results remained robust when controlling for PTSD, depressive symptoms, and post-concussive symptoms.

Finally, the presence or absence of prior TBI may also impact sleep disturbances in TBI. In a longitudinal study of the relationship between TBI status and sleep disturbances, Holster et al. found that Air Force veterans with a pre-deployment history of TBI endorsed more insomnia symptoms at baseline when compared to those without prior TBI history (Holster, Bryan, Heron, & Seegmiller, 2017). In turn, baseline

insomnia symptoms were associated with increased risk for sustaining a TBI during deployment. Chronic insomnia at baseline was also associated with both pre-deployment TBI history and TBI during deployment. It is important to note that differences have been observed in neurological changes between military SMs with blast exposure occurring both within and greater than 10 meters that were not influenced by sleep quality (Robinson et al., 2015).

Of note, none of the articles reviewed accounted for the timing of injury occurrences in those with more than one TBI. This is likely a critically important factor to consider when assessing the impact of TBI frequency and prior TBI on sleep disturbances. More specifically, it is important to consider the timing between the injuries themselves. When full recovery from one injury does not precede the onset of a second injury, symptoms are likely to exacerbate and become pervasive. Thus, summative TBIs may result in unique profiles of sleep disturbances that influence treatment effectiveness and outcomes.

Together, the findings to date unequivocally establish a strong relationship between TBI and sleep disturbances in SMs and veterans. Furthermore, a number of factors related to injury etiology may modulate or mediate this relationship but remain underexplored. Larger samples and more comprehensive study designs are needed to further characterize this relationship and determine whether assessment and treatments strategies should be informed by these factors. Recognizing the challenges of conducting longitudinal studies, access to medical records would provide a more efficient and cost-effective study design for better determining estimates of time between injury and symptom onset.

3.4. Interactions between sleep disturbances, TBI, and comorbid conditions

Sleep disorders and TBI are complex and heterogeneous conditions with shared symptomology that are both independently and jointly associated with psychiatric and medical comorbidities. Twenty-four of the studies included in this review reported on comorbid psychiatric and medical conditions of TBI. For instance, Gill et al. showed severity of PTSD, sleep disturbances, and depressive symptoms increase as the number of comorbid conditions increase in SMs with TBI (Gill et al., 2014). The combination of these conditions complicates assessment and management strategies and uniquely impacts functional outcomes. TBI resulting

from combat exposure has been shown to most commonly co-present with psychological trauma-related disorders (i.e. PTSD), chronic pain, and insomnia in over 51% of veterans (Lang, Veazey-Morris, & Andrasik, 2014). The tight relationship between TBI, sleep disturbance and psychiatric conditions has risen the possibility that sleep may serve as a common factor linking TBI with its comorbidities, which in turn may suggest a summative effect of co-occurring conditions and TBI on sleep disturbances relative to TBI alone. Lew and colleagues observed that sleep problems were more severe when PTSD was comorbid with TBI compared to those with TBI alone (Lew et al., 2010).

Furthermore, Macera et al. observed that veterans who screened positive for TBI and PTSD were 3-times more likely to report sleep problems compared to TBI alone. This suggests that the relationship between TBI and its associated comorbidities may even be moderated or mediated by sleep disturbances (Macera et al., 2013). This finding was supported in two studies by Verfaellie et al. and Waldron-Perrine that each reported sleep disturbances mediated the relationships between emotional distress, cognitive functioning, and self-reported post concussive symptoms more so than TBI alone (Verfaellie, Lee, Lafleche, & Spiro, 2016; Waldron-Perrine, Hennrick, Spencer, Pangilinan, & Bieliauskas, 2014). In one of the few studies on pre-TBI sleep factors, Elliott et al. showed that the resiliency personality phenotype predicted less sleep troubles in military samples who go on to develop TBI when compared to other phenotypes (Elliott et al., 2017). This finding suggests that pre-injury factors may play a role in the course of TBI and provides support for future research examining pre-injury sleep factors in military SMs and veterans prior to deployment. A greater understanding of the role of sleep in the trajectory of TBI may yield novel, modifiable sleep-related targets for preventive efforts or engagement through sleep-focused, individualized interventions aimed at mitigating symptoms and restoring function through improved sleep.

Stocker and colleagues examined positron emission tomography (PET) scans of OEF/OIF veterans with and without comorbid blast TBI and PTSD and found that there was a detectable decrease of regional cerebral metabolic rate of glucose during REM sleep and wakefulness among veterans with prior blast TBI than those without blast TBI history when adjusting for any effects of PTSD (Stocker et al., 2014). It was suggested that the areas of glucose hypometabolism, including the right basal ganglia,

amygdala, hippocampus and parahippocampal gyrus, culmen, associative visual cortices and medial frontal cortices may be susceptible to long-term effects of blast TBI, including chronic concussive symptoms and/or maladaptive responses to stress (Stocker et al., 2014). A separate study examining objective sleep features in a comorbid TBI/PTSD sample from Stocker and colleagues revealed that REM sleep fragmentation may be a potentially sensitive index to the synergistic effects of TBI and PTSD, as the only significant interaction effect between TBI and PTSD was observed in the amount of REM sleep fragmentation (Stocker et al., 2016). A summative effect of comorbid TBI on sleep problems has also been observed in clinical settings, where individuals at a polytrauma clinic had the highest rates of sleep disturbance, anxiety, and depression (Pugh et al., 2014).

Wallace and colleagues showed that insomnia severity was not significantly different between those with PTSD/TBI and PTSD alone (Robinson et al., 2015; Wallace et al., 2011). These results do contrast the literature; however, it is likely that the difference in findings is due to the heterogeneity of the sample when using sleep quality as an outcome or other factors unique to neurological changes.

Finally, those with comorbid TBI and PTSD report more daytime sleepiness despite objective measures indicating they have greater total sleep time relative to those with TBI alone (Tanev et al., 2014). This finding was replicated in a study by Wallace et al (Wallace et al., 2011) and highlights the importance of using multimodal data collection methods to best understand the complex relationships between TBI and its common comorbidities and sleep disturbances. Self-reported sleep disturbances provide rich subjective data, that when taken in combination with objective sleep measures is likely to better support optimal intervention selection compared to intervention selection based solely from objective data sources.

An enhanced understanding of how sleep disturbances present in TBI when comorbidities are present and how the sleep profiles of comorbid groups compare to those with TBI alone is needed to improve assessment and guide optimal courses for intervention (Lang et al., 2014). This line of research is especially important considering around 50% of SMs and veterans experience three or more deployment-related conditions, and that those with three or more deployment-related conditions are more likely to present with substantial disability relative to those with TBI alone (Lippa et al., 2015). Nevertheless, the

literature to date highlights that more severe sleep disturbances occur when TBI presents with co-morbid conditions.

3.5. *Sleep disturbances: Distinct domain or secondary condition?*

Findings from two studies using factor analysis suggest a TBI diagnosis presents with both overlapping and distinct symptom clusters with its most common comorbid conditions (e.g., PTSD), and even highlights sleep disturbances as a distinct cluster that transcends diagnostic categories (Jaramillo et al., 2015; Maguen, Lau, Madden, & Seal, 2012).

These studies identified distinct symptom clusters (i.e. low/high distress) across larger diagnostic groups that may improve the ability to differentiate SMs experiencing comorbid conditions with shared symptomology. While these studies chose to cluster on symptoms and not diagnoses, results did show some clusters were more likely than others to contain a particular diagnosis. For example, a 'moderate/high distress' cluster represented by headache and memory impairment capturing a high rate of those with TBI (Jaramillo et al., 2015) or a high rate of those with PTSD being represented in a 'high distress' or 'pain and behavioral health' cluster represented by anxiety and substance abuse (Jaramillo et al., 2015). Maguen and colleagues used factor analysis to differentiate distinct from overlapping screening-based symptoms in 1549 veterans with TBI, PTSD, and depression from postdeployment screening data (Maguen et al., 2012). Four constructs merged, three of which were represented by the diagnoses themselves (i.e. PTSD, TBI, depression) and an intriguing 4th construct: "hypervigilance and sleep problems" (Maguen et al., 2012). The findings from Maguen's study show symptoms unique to TBI that may help improve assessment and targeted treatments when attempting to separate TBI from its comorbid conditions. Arguably, the most notable finding is the evidence for a distinct 'hypervigilance/sleep disturbance' cluster that highlights the needs to further examine hypervigilance and disrupted sleep symptoms as a unique, combined factor influencing post-deployment health in military groups with TBI. Overall, the findings from studies using factor analysis suggest that while the co-occurring diagnoses themselves may be difficult to differentiate, distinctive phenotypes may exist that can aid more optimal assessment and selection of treatment targets.

Pugh et al., and Lippa et al., both showed that although disrupted sleep was distinct from both TBI and PTSD, TBI and PTSD failed to be different from one another across sleep variables (Lippa et al., 2015; Pugh et al., 2014). Capaldi and colleagues also examined the specificity of sleep disturbances related to TBI and PTSD in 69 active duty combat veterans and found that PSG failed for the most part to significantly differentiate TBI from PTSD (Capaldi et al., 2011). However, those with PTSD did have a higher frequency of nighttime arousals and those with TBI had more slow wave sleep. This finding may be reflective of arousal brain states linked to sleep in those with PTSD (Germain, Buysse, & Nofzinger, 2008) theories supporting slow wave sleep as a critical component for recovery after TBI (Shekleton et al., 2010).

3.6. *Sleep-focused interventions may improve TBI symptoms*

TBI interventions rarely include sleep-specific assessments and strategies, and few studies have used sleep-focused interventions to assess TBI symptom change and improvements in functional outcomes in military SMs and veterans (Gilbert et al., 2015).

As previously highlighted, OSA is a prevalent sleep disorder in SMs and veterans with TBI. Barr et al reported over 50% of recently deployed military SMs with TBI endorsed more restorative sleep and improved health-related quality of life (HRQoL) of life at 12 months following provision of standard care, which included continuous positive airway pressure (C-PAP) therapy and/or cognitive behavioral therapy (Barr et al., 2015). Additionally, those with TBI who experienced improved sleep post-treatment also saw a reduction of PTSD and depression symptoms at 3-months. Mysliwiec et al also showed reduced daytime sleepiness and improved sleep quality in 58 male military personnel with and without TBI following autotitrating positive airway pressure (APAP) (Mysliwiec et al., 2013). Participants who improved used APAP for four hours or more a night for at least 70 percent of all nights during a consecutive one-month period. Participants in the improved sleep group also experienced functional improvement related to depressive symptoms, energy/fatigue, and emotional well-being. Although these two studies used a treatment specific to OSAS, findings support the modifiable nature of sleep in TBI and show the potential for using sleep-focused interventions for improving not only sleep, but also health and functioning.

Ruff et al. used a 9-week combination treatment consisting of a behavioral intervention (i.e. sleep hygiene counseling) and prazosin in 126 veterans with blast mTBI to assess change in disrupted sleep and daytime sleepiness (Ruff, Ruff, & Wang, 2009). Disrupted sleep was assessed through two questions on whether or not participants experienced impaired sleep and what they believed to be the nature of their sleep impairment and daytime sleepiness was measured by the Epworth Sleepiness Scale (ESS). At post-treatment, those in the combination treatment group reported, on average, improved self-report sleep quality and decreased or complete remission of nightmares. Furthermore, 100 percent of participants saw a significant reduction in daytime sleepiness. A second study by Ruff and colleagues using a 9-week combination behavioral-pharmacological treatment of sleep counseling and prazosin in 63 veterans with combat mTBI with LOC saw a greater than 50 percent post-treatment reduction in daytime sleepiness in over 78% of participants, as measured by the ESS (Ruff, Riechers, Wang, Piero, & Ruff, 2012). This greater than 50% reduction in daytime sleepiness was maintained and improved upon (78 % to 89%) at a 6 month follow up. It is important to note that this study also found improved outcomes with behavioral and pharmacological interventions alone, which is evidence of the potential relative utility of these approaches.

Finally, in the only randomized clinical trial on sleep disturbances and TBI known at date, Vuletic et al tested the effectiveness of a 6-month telephone-based problem-solving treatment (PST) intervention for improving sleep quality in 356 active duty SMs with TBI and poor baseline sleep quality (Vuletic et al., 2016). The PST intervention involved 12 bi-weekly phone calls addressing participated-selected issues related to their sleep. Results showed that when compared to an education only (i.e., educational brochures on sleep) control group, the PST group saw improved sleep quality at 6 months, but not at 12 months, as measured by the Pittsburgh Sleep Quality Index (PSQI). This finding suggests PST may be an effective treatment to improve sleep acutely in military cohorts, but more work needs to be done to determine the long-term effectiveness of this approach.

In a community-based, single-blind longitudinal study, Wiseman-Hakes and colleagues examined objective and self-report cognitive and emotional rehabilitation outcomes in adults with TBI and comorbid sleep/wake disturbances (2013). This study

used individualized sleep/wake disorder treatment, which included sleep hygiene, pharmacological intervention, and sleep apnea interventions. Statistically significant post-intervention changes in mood, performance, and cognitive symptoms were observed—suggesting sleep-focused treatments may help to improve rehabilitation outcomes in those with TBI across all levels of severity.

When examining the perspectives of 19 male veterans with post-acute TBI and comorbid sleep-wake disorder enrolled at the VA at least 1-year post-injury using semi-structured sleep-related interviews, Matthews and colleagues qualitatively extrapolated two perspective dimensions based on qualitative analysis of responses: “messed up sleep” and surviving/management of sleep disturbances (Matthews, Signoracci, Stearns-Yoder, & Brenner, 2016). This sample of veterans also reported that their sleep troubles had a significant negative impact on daily living. Specifically, difficulty falling asleep, nighttime awakenings, and poor sleep quality were cited as having the greatest adverse impact on overall daytime functioning. This study suggests veterans recognize the challenging nature of managing sleep disturbances and that sleep problems can be difficult to manage.

Findings from these studies provide preliminary support for the effectiveness of sleep interventions to improve not only sleep symptoms, but also health and functioning in military samples with TBI. These studies suggest that both sleep-focused pharmacological and behavioral interventions may be efficacious for improving outcomes for SMs and veterans with TBI either individually or in combination. Albeit promising, these studies warrant confirmatory controlled effectiveness trials. It is important to note that only a scarce body of literature to date has looked at how sleep interventions may improve TBI symptoms in military SMs and veterans (Ruff et al., 2012)—another underexplored area to guide future research efforts.

4. Discussion

The purpose of this article was to conduct a scoping review to synthesize the current science on disrupted sleep and TBI as it pertains to combat-exposed military SMs and veterans. The 41 articles included in this review were published between 2008–2018 inclusively and were on military samples predominantly from the OEF/OIF/OND conflicts, with some studies including Persian Gulf War veterans.

Most of the literature to date has focused on the establishing the prevalence of sleep disturbances in combat- TBI and the identification of unique sleep profiles between military SMs and veterans with and without TBI, using a variety of sampling methods and sleep measurement methods. Eight of the studies reviewed examined the influence of TBI-related factors on sleep and co-occurring psychiatric and medical conditions, such as PTSD. Further, two studies reviewed suggested that sleep symptoms may help to distinguish TBI from its co-occurring conditions, but results remain inconclusive as to which symptoms provide the best utility demarcating TBI from co-occurring conditions with shared symptomology. The majority of studies reviewed were descriptive and cross-sectional in nature, with few testing the effectiveness of interventions and measuring change in symptomology over time. This review demonstrated there is a rich and diverse existing foundational literature on sleep profiles and influencing health and injury factors in military samples with TBI for researchers can build upon in future research. This review also sheds light on the work yet to be done measuring pre-TBI or pre-deployment sleep symptoms that may infer TBI risk, determining prodromes for the development of sleep disturbances after TBI, sleep-related mechanistic processes that influence symptoms and functional outcomes after TBI, and the long-term effects of chronic sleep disruption in TBI on functioning, health, and quality of life. There is a clear need for evidence-based, systematic research developing and testing sleep-related interventions aimed and improving both sleep and TBI symptoms and long-term functional and health outcomes.

4.1. Clinical and research implications

Historically, disturbed sleep has been viewed as a symptom of TBI. This implies a temporal relationship where TBI onset precedes the development of sleep symptoms. Much of the literature in this review examined the co-occurring nature of sleep disturbances and TBI or disturbed sleep as a mediator or moderator in the relationship between TBI and poor outcomes in combat-exposed military samples. Furthermore, it is known that sleep disturbances are associated with reduced overall functioning in military samples with TBI (Ettenhofer, Melrose, Delawalla, Castellon, & Okonek, 2012) and that improving sleep can lead to TBI symptom reduction and increased HRQoL (Barr et al., 2015). Thus, disrupted sleep likely plays a much

greater role in the course of TBI—one where sleep disturbances and TBI share bidirectional and even cyclical relationship (Gilbert et al., 2015). Future research efforts are needed to examine the full trajectory of sleep disturbances and TBI in military groups.

Although the current state of the field is keenly attuned to sleep disturbances profiles following TBI, research examining TBIs sustained among individuals with preexisting sleep disturbances remains scarce. There is even less research related to the examination of whether sleep/wake difficulties can be conceptualized as presenting independently of TBI rather than as a symptom of TBI. Although disturbance in normative sleep may be a manifestation of the neurobiological changes of TBI in civilians and veterans alike, it is possible for that for military SMs, the nature of military service, specifically while deployed, may give rise to disrupted sleep patterns prior to sustaining a TBI—an area yet to be studied. This is an intriguing line of research to explore not only due to the ability to demonstrate sleep disturbances as a risk factor for injury to the head, but given the existing literature linking inadequate sleep to increased risk for physical injuries it also warrants examining the effect of disrupted sleep on other physical injuries while in the field. Further, it could be argued that just as sleep disturbances can develop during deployment in those who do not sustain TBI, sleep disturbances could develop subsequent to a TBI and be better accounted for by the same factors as those without TBI than the TBI itself.

As our previous studies (Germain et al., 2014; Germain, Shear, Hall, & Buysse, 2007) have demonstrated the effectiveness of brief behavioral sleep treatments in SMs and veterans with deployment-related comorbidities, behavioral sleep treatments offer a promising treatment approach. There is also a need to improve treatment approaches for OSA (to improve adherence), better extend trials on hypersomnia to military populations, and identify and test novel pharmacological agents for improving sleep in SMs that do not violate military drug policies. Research has shown that both military SMs and veterans are willing to try novel approaches to improving their sleep, which establishes this cohort as an engaged population (Matthews et al., 2016).

4.2. Limitations

Although this broad overview of the literature on TBI and sleep disturbances in military samples may

lack the rigor that comes with a more exhaustive systematic review or even meta-analysis, this review was intended to gather a diverse representation of the research that has been conducted to date. This method allowed for visual inspection of any skewness in the current literature, which this review did demonstrate. This approach also allowed for the identification of knowledge gaps that will be critical to fill moving forward to advance the state of the science on combat-related TBI and sleep disturbances. Scoping reviews are commonly implemented when the goal is to lay the foundation for a guide for when working with specific cohorts and when the extant literature would not be appropriate to summarize through systematic review (Peters et al., 2015). With that in mind, the nature of this review leads to the possibility that articles examining the topics of interest were missed. As such, the current review may not fully characterize the literature to date.

A challenge often presents when consolidating evidence from current bodies of literature is heterogeneity among the articles examined. This review of the literature resulted in diverse patterns across studies on operational definitions and inclusion/exclusion criteria (e.g., how TBI was defined or assessed), variables used to represent constructs of interest (e.g., the use of varying subjective or objective sleep parameters to measure the construct of 'poor sleep'), and the diversity of assessment tools used for measurement (e.g., semi-structured interviews, PSG, self-report scales). This heterogeneity becomes especially difficult to interpret when research lacks universally accepted terminology, operational definitions, and measurement tools for the constructs being examined. For example, differences in criteria used to identify the presence or absence of a TBI may create unintentional baseline differences between groups across studies that have a direct influence on outcomes independent of the variables measured. For example, two independent studies that established neuropsychological differences between military veterans with and without mTBI, but used different assessment batteries, makes it challenging for researchers to feel confident about the true effect. It is important to note that the issue of research methodological heterogeneity is not a challenge specific to military research, but in fact a widespread challenge the greater field of research is currently facing; and therefore, something researchers should be cognizant of when conducting their own studies. We advise that future research move towards implementing a more standardized methodology, which

should include multi-modal assessment of sleep disturbances. Improved and comprehensive assessment methods will lay a strong and much needed foundation for more optimal selection of interventions and their potential for success. Finally, this review represents a bias towards articles that were published only in English speaking, peer-reviewed journals.

5. Conclusion

This scoping review synthesized the existing literature on sleep disturbances and TBI in military SMs and veterans and sheds light onto critical knowledge gaps that can guide future research aimed at answering the many remaining questions regarding the relationship between sleep disturbances and combat-related TBI. Our goal for this review was to add to the preexisting knowledge in the realm of TBI and sleep in SMs and military veterans. Moreover, it is our hope that this information can ultimately be utilized by researchers and clinicians to further expand the fields' awareness to and knowledge of the extant literature, while also encourage the advancement of novel and innovative research focused on prevention efforts, the treatment of, and long-term care for the unique population of military SMs and veterans with TBI and sleep disturbances.

Conflict of interest

None to report.

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