Nature and Science of Sleep

Dovepress

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REVIEW

Sleep, a Governor of Morbidity in PTSD: A Systematic Review of Biological Markers in PTSD-Related Sleep Disturbances

This article was published in the following Dove Press journal:
Nature and Science of Sleep

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Background: Sleep disturbances (SD) are the most impactful and commonly reported symptoms in post-traumatic stress disorder (PTSD). Yet, they are often resistant to primary PTSD therapies. Research has identified two distinct SDs highly prevalent in PTSD; insomnia and nightmares. Those who report SDs prior to a traumatic event are at greater risk for developing PTSD; highlighting that sleep potentially plays a role in PTSD's pathology. To further understand the pathobiological mechanisms that lead to the development of PTSD, it is first imperative to understand the interplay which exists between sleep and PTSD on a biological level. The aim of this systematic review is to determine if biological or physiological markers are related to SD in PTSD.

Methods: A systematic literature search was conducted on the electronic databases; Medline, Embase, AMED and PsycINFO, using Medical Subject Headings and associated keywords.

Results: Sixteen studies were included in the final analyses. Physiological makers of autonomic function, and biochemical markers of HPA-axis activity; inflammatory processes; and trophic factor regulation were related to the severity of SDs in PTSD.

Conclusion: These findings add to the growing literature base supporting a central focus on sleep in research aiming to define the pathophysiological processes which result in PTSD, as well as emphasising the importance of specifically targeting sleep as part of a successful PTSD intervention strategy. Resolving SDs will not only reduce PTSD symptom severity and improve quality of life but will also reduce all-cause mortality, hospital admissions and lifetime healthcare costs for those with PTSD. Limitations of the current literature are discussed, and key recommendations future research must adhere to are made within.

Keywords: post-traumatic stress disorder, sleep disturbances, insomnia, nightmares, biomarkers

Introduction

Post-traumatic stress disorder (PTSD) is a debilitating condition which may develop following exposure to, witnessing, or learning about, a traumatic event such as; actual or threatened death, actual or threatened serious injury, or actual or threatened sexual violence.[1] These events are referred to as criterion A events, as per the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5).[1]

A diagnosis of PTSD is made based on the presentation of symptoms, which are arranged into four symptom clusters; alterations in arousal and reactivity, intrusions,

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submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/NSS.S260734

avoidance and negative alterations in cognitions and mood.[1] Lifetime prevalence of PTSD is approximately 2–8%, but this differs by geographical location and the level of trauma exposure experienced in a particular population.[2–5] As an example, military and emergency service personnel are exposed to more trauma than the general population, which is reflected in their respective PTSD prevalence rates of 13.4% and 22%.[3,4,6-9]

Sleep Disturbances as a Core Pathological Factor in PTSD

Difficulty sleeping is considered one of the most commonly experienced symptoms of PTSD,[5,10,11] Two distinct sleep disruptions exist, insomnia (persistent difficulty falling asleep or staying asleep) and nightmares. These fall under the DSM−5 PTSD symptom clusters of "alterations in arousal and reactivity" and 'intrusions', respectively.[1] A recent survey of 2,647 US adults exposed to potentially traumatic events by Milanak et al (2019) found that 92% of those who met the criteria for PTSD experienced at least one symptom of disturbed sleep.[10] Although experiencing insomnia and nightmares together accounted for the majority of SDs in PTSD, Milanak et al (2019) noted that where only a single sleep disturbance was endorsed, insomnia was more prevalent than nightmares (56.7% vs 24.9% vs 11.3%).[10]

A variation in the prevalence of SDs in PTSD is common in the literature.[12–14] Some of this variability may be explained by differences in population demographics such as sex and level and type of trauma exposure. However, the effect these, and other population factors have on the endorsement of SDs in PTSD, requires further research. Methodological differences in measuring sleep is a further source of variability. Modern sleep research has capitalized on advancements in wearable technology to provide objective measures of sleep in the free-living environment.[15–18] Actigraphy is the most common method, and involves participants wearing a personal accelerometer device, normally on the wrist, to record movement during sleep.[19–21] This movement data is then translated to provide information about a participants' sleep.[22–24] Incorporation of objective methods, such as actigraphy, improves upon a sole reliance on subjectively reported sleep.[17]

Sleep is a central treatment and research objective in PTSD, and may represent a modality through which PTSD treatment uptake can be improved, due to a lack of the stigmatization associated with other PTSD symptomology.[11] However, the paradigm of causality between PTSD and disrupted sleep (both nightmares and insomnia) remains ambiguous. Originally considered merely as symptoms of PTSD, recent studies have established a theory of sleep disturbances preceding traumatic exposure as a risk factor for PTSD development.[25,26] Longitudinal examination of a Dutch military cohort by Van Liempt et al (2013) revealed that experiencing nightmares before combat deployment, was somewhat predictive of the development of PTSD post-deployment.[27] Furthermore, experiencing insomnia immediately following trauma exposure has been found to be predictive of PTSD development a year later, suggesting that a potentially stunted ability of sleep to consolidate memory could contribute to the development of PTSD.[28] Moreover, primary therapies specifically targeting PTSD, such as cognitive behavioural therapy (CBT) for PTSD, are often insufficient to completely improve SDs despite a reduction in other PTSD attributable symptoms.[29] This would appear to suggest that SDs, both insomnia and nightmares, are a component of the pathology of PTSD, rather than solely a symptom; a hypothesis also postulated for depression and anxiety disorders.[30–32]

Improving sleep quality has been associated with a clinically relevant reduction in the severity and impact of PTSD symptomology, thus highlighting the importance of specifically targeting sleep as part of a multi-faceted approach for PTSD treatment.[33–35] Despite these findings, and high prevalence, a specific mechanistic role of sleep in PTSD, as well as the reciprocal nature of the relationship between SDs and PTSD, remains to be established.[25] Furthermore, subjective and objective sleep measures have yielded conflicting reports on the number of awakenings and sleep duration in PTSD, depending on the comparative population used.[12,14,36,37] Therefore, to fully establish the directionality of the relationship between PTSD and disordered sleep, and the individual contributions of insomnia and nightmares, there is a need to examine if an interplay exists between these factors on a biological level.

HPA-Axis Regulation and Inflammation in PTSD

To determine any biological interconnection between sleep and PTSD, it is important to first consider each separately. The pathobiology of PTSD remains an active area of research, which to date has focused mainly on two functional systems; 1) the hypothalamic-pituitary-adrenal (HPA) axis and 2) systemic inflammation.

PTSD and the Hypothalamic-Pituitary-Adrenal Axis (HPA-Axis)

Exposure to a threat, which may be either physical or psychological, triggers a physiological response. Termed the "stress response", this results in the activation of biological mechanisms which allow a reaction to the threat. Central regulation of this process is facilitated by the HPA-axis, functional alterations to which have been linked to psychiatric conditions such as depression, anxiety and PTSD.[38,39]

Following exposure to a stressor, neurons of the paraventricular nucleus (PVN) in the hypothalamus respond by releasing corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) into hypophysial portal blood, causing the pituitary gland to release adrenocorticotrophic hormone (ACTH) into the general circulation.[40] ATCH acts on the adrenal glands to stimulate the synthesis and release of glucocorticoids, of which cortisol is the primary in humans.[40] Regulation of HPA-axis activity is facilitated by cortisol-mediated negative feedback on the anterior pituitary, PVN and hippocampus, resulting in an inhibition of CRH, AVP and ACTH release.[40]

Two cortisol receptors exist in humans: mineralocorticoid receptors, which function as high-affinity cortisol stores, and functionally active glucocorticoid receptors (GRs).[40] FK506 binding protein (FKBP5) has recently been characterised as a functional inhibitor of GRs, preventing their activation by lowering the GRs affinity for cortisol binding.[41] Longitudinal examination of FKPB5 mRNA expression in a military cohort, revealed low predeployment expression was predictive of PTSD occurrence post deployment, a finding replicated in further studies.[41–45] This would appear to suggest that a stunted inhibition of the HPA-axis stress response could contribute to the pathobiology of PTSD. However, further research is required to explore this hypothesis as contradictory findings, such as elevated and attenuated cortisol levels, remain. Albeit, these may be somewhat explained by differences in comparative control populations, gender differences, types of traumatic events experienced and sampling time and conditions.[46] Despite controversy over the exact functional response of the HPA-axis in PTSD, inhibitors of FKPB51, the functional protein produced in response to FKBP5 expression, are being developed with the aim to use as novel therapies in the treatment of psychiatric conditions such as PTSD and depression.[39] Further understanding of the HPA-axis, GRs and associated molecular partners, in psychiatric disorders, is required before any therapeutic potential of such FKBP51 antagonists can be discussed. However, by inhibiting the activity of FBKP51 without activating GRs themselves, such antagonists may prove useful experimental tools to aid in this endeavour.[39]

PTSD and Systemic Inflammation

PTSD has been hypothesised to be accompanied by a systemic rise in pro-inflammatory activity.[47] Activation of cytotoxic T lymphocytes in response to stress (physical or psychological), results in an inflammatory response dominated by Th2 type cells, producing an unrestrained production of pro-inflammatory cytokines.[48,49] It is therefore unsurprising that in a recent meta-analysis of inflammatory markers in PTSD, increased pro-inflammatory interleukin−6 (IL−6), IL−1β, TNF-α and interferon gamma (INF-γ) were observed.[50] This is supported by increased inflammation present in the peripheral circulation, adrenal glands and neurological tissue of predator exposure mouse models of PTSD.[51]

Further fitting this inflammatory hypothesis is the established increased incidence of cardiovascular disease, type 2 diabetes, chronic fatigue syndrome and other metabolic syndromes in PTSD populations, conditions which are progressed by dysregulated inflammatory processes.[52–59] Pathological inflammation is also demonstrated to result in neuronal loss, which is interesting considering the loss of hippocampal volume noted in both humans and mouse models of PTSD.[60–62]

PTSD and Trophic Factors

Trophic factors, such as Brain-Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF) and Vascular Endothelial Growth Factor (VEGF), are central regulators of the CNS, essential for maintaining synaptic plasticity, learning and memory.[63–65] In the context of psychiatric disorders, trophic factors have demonstrated altered expression levels in both PTSD and depression, although their exact functional role remains ill-defined.[66–68] The literature surrounding trophic factors and PTSD remains particularly unclear, with findings often opposing one and other.[69–71] The intertwined relationship between trophic factors and sleep is particularly interesting in this case. BDNF and its molecular coplayers may have a central role in sleep homeostasis, particularly slow-wave sleep.[72] Trophic factors may therefore serve as a linchpin in the relationship between PTSD and its related SDs.

Interconnections Between Sleep and PTSD Pathophysiology

The physiological role of sleep remains the focus of much research but elucidated roles include cellular and tissue repair, cognitive and memory processing, maintenance of synaptic plasticity, through a process known as "pruning", and free radical detoxification.[73,74] As such, disruption of sleep through either sudden awakening from nightmares or through reduction in consolidated, sustained sleep from insomnia, may contribute to a host of pathophysiological processes.

Pressure to fall asleep, facilitated by the circadian drive, is enacted through melatonin secretion. Melatonin, under the control of the suprachiasmatic nuclei (SCN), is secreted from the pineal gland through metabolism of serotonin, upon darkness onset.[75] Light sensing is facilitated by direct communication of photoreceptive retinal ganglion cells with the SCN via the retinohypothalamic tract. Secretion increases at twilight, reaches a peak during the middle of the night and then begins to decrease to basal daytime levels.[76] Metabolization of melatonin primarily occurs in the hepatocytes of the liver where it undergoes the process of hydroxylation, producing 6-hydroxymelatonin which is then sulphated and excreted in urine.[77] However, the processes of demethylation, deacetylation and oxidation also occur, albeit to a lesser extent.[78] Hypothesised to be resultant from a circadian phase shift, alterations in melatonin production have been noted in a range of neurological and neuropsychological conditions however, this has not yet been noted in PTSD.[75,79]

Therefore, it would be of interest to investigate the rate and pathway of melatonin metabolization in PTSD, considering the neuroprotective-free radical scavenging properties of melatonin oxidation products and the hypothesised increased oxidative stress in PTSD.[78] Moreover, the role of melatonin in blood pressure regulation is interesting considering the persistently reported presence of hypertension diagnoses in PTSD populations.[80–83]

Occurrence of metabolic and cardiovascular diseases which result in increased mortality, similar to those observed in PTSD populations, has been associated with persistent insomnia in longitudinal analysis.[84] Akin to that previously mentioned in PTSD, elevation of inflammatory status has been noted in populations with persistent insomnia, in the form of increased pro-inflammatory C-reactive protein (CRP) and IL-6.[85] It would therefore be of interest to examine SDs of PTSD in relation to biological markers, differentiating and examining the individual roles played by insomnia and nightmares. SDs represent targetable symptoms of PTSD that with successful treatment not only have the potential to reduce PTSD symptomology and improve quality of life but may also reduce lifetime all-cause mortality among PTSD populations.

This review aims to systematically examine the literature to determine; 1) are biochemical or physiological markers related to SDs in PTSD, 2) are biochemical or physiological markers related to the degree of SD severity in PTSD and, 3) does improvement in SDs result in a change of biochemical or physiological markers in PTSD populations?

Methodology

Following a broad review of the literature, a search strategy was devised to identify research articles able to address the question, "Are biological and physiological markers related to sleep in PTSD?". Set out in Table 1, this strategy was used to search the electronic databases; EMBASE, Medline, AMED and PsycINFO using the

Table 1 Literature Search Strategy, Consisting of Medical Subject Headings (MeSH) and Keywords. OVID Online Platform Was to Search EMBASE, Medline, AMED, PsychINFO Databases

Component	1	2	3
MeSH Heading	Stress Disorders, Post Traumatic (All Fields)	Sleep Initiation and Maintenance disorders (All Fields)	Biomarkers (All Fields)
Function	"OR"		
Keywords	PTSD Post-traumatic Stress Disorder	Insomnia Chronically disrupted sleep Sleep initiation disorder Nightmares	Biomarker* Neuroendocrine Neurotransmitter Hormone Inflammatory Cytokine Blood pressure Hypotension Hypertension Heart Rate Bradycardia Tachycardia
Search	"1" AND "2" AND "3"		
Filter	"Published 2005 – Current Date"		

Note: *All Suffix Search.

OVID online platform. Searches were carried out periodically between March 2018 and March 2020.

Inclusion Criteria

Studies were eligible for inclusion if they contained (1) a human adult population, (2) a measurement of PTSD (either valid self-assessment methods such as the PTSD checklist (PCL), or clinical diagnosis), (3) a subjective or objective measurement of sleep and (4) either a non-invasive physiological measurement (independent of sleep quantification method) or any biochemical assessment carried out on a biological sample (blood/tissue). Randomized control trials, cohort, case-controlled, and cross-sectional studies were eligible for inclusion and were not limited based on population gender, race, age or trauma exposure. Included studies were limited to peer-reviewed articles published in English between September 2008 and March 2020.

Exclusion Criteria

Articles were excluded if they did not contain: (1) a PTSD subpopulation or PTSD assessment, (2) a subjective or objective measurement of sleep, and (3) a physiological or biochemical measurement, independent of the sleep quantification method. For example, for eligibility assessment electroencephalogram (EEG), recorded as part of polysomnography (PSG), was considered a component of sleep measurement rather than a physiological measurement. However, heart rate (HR) and peripheral oxygen saturation were deemed appropriate as a physiological measurement, if analysed independently of sleep. Pharmacological treatment trials, either for sleep or PTSD symptoms, were excluded. PTSD populations with concurrent traumatic brain injury (TBI) were excluded to minimise confounding of results. Case studies and conference abstracts were also excluded.

Screening and Data Extraction

The process of identifying, screening and assessing articles for eligibility criteria is summarized in Figure 1. Using the previously stated search strategy, 513 research entries were identified, and their references imported to a web-based reference management programme (RefWorks), for the purpose of duplicate identification and removal. Removal of duplicates resulted in 471 entries for title and abstract screening. Article titles were screened for relevance to PTSD and sleep, resulting in 129 being retained for abstract review. Abstracts were examined to confirm a PTSD population, a measure of sleep, a biological or physiological measure and that the article was original research. Where any details could not be established, articles were retained for full-text assessment. Following abstract assessment, 38 articles were retained and subject to full-text eligibility assessment. Sixteen articles were deemed to meet the eligibility criteria and were included in the final analyses.

Data extracted from the included articles (n=16) encompassed; the authors, date of publication, study inclusion and exclusion criteria, excluded participants, population size, age, sex, study design, objective sleep measurement, subjective sleep measurement, sleep intervention, PTSD symptom assessment, physiological measurement(s), biochemical measurement(s), gene expression analysis, any additional measures, key findings and key limitations. For each study, the results of this data extraction are set out in Table 2. Full references for each study are available in the bibliography.

Quality Assessment

Criteria adapted from the Critical Appraisal Skills Programme (CASP) checklist was used as a quality assessment for each included article.[86] Key findings of this review were then subject to a quality of findings assessment, using the Grading of recommendations, assessment, development and evaluations (GRADE) criteria for systematic reviews.[87] Results of GRADE analysis are shown in Table 3, produced using GRADEpro Guideline Development Tool [Software], McMaster University, 2015 (developed by Evidence Prime, Inc.), Available from gradepro.org. Summary grades available are as follows; High (Confidence in the study findings is high); Moderate (Confident that the effect observed is close to the real effect but may also be substantially different); Low (The true effect may differ significantly from that observed); and Very Low (The effect is likely to be very different from that observed).

Results

A total of 2,838 participants were included across the 16 studies, of which 68% were male and 30% female. No information on sex was available for 2% of participants. Most study populations were "male and female" (10/16), three were "female only" and two "male only". Sex was not reported in the remaining study. The overall mean age was 37.93 ± 7.35 years, with study mean ages ranging from 21.7 to 51.4 years.

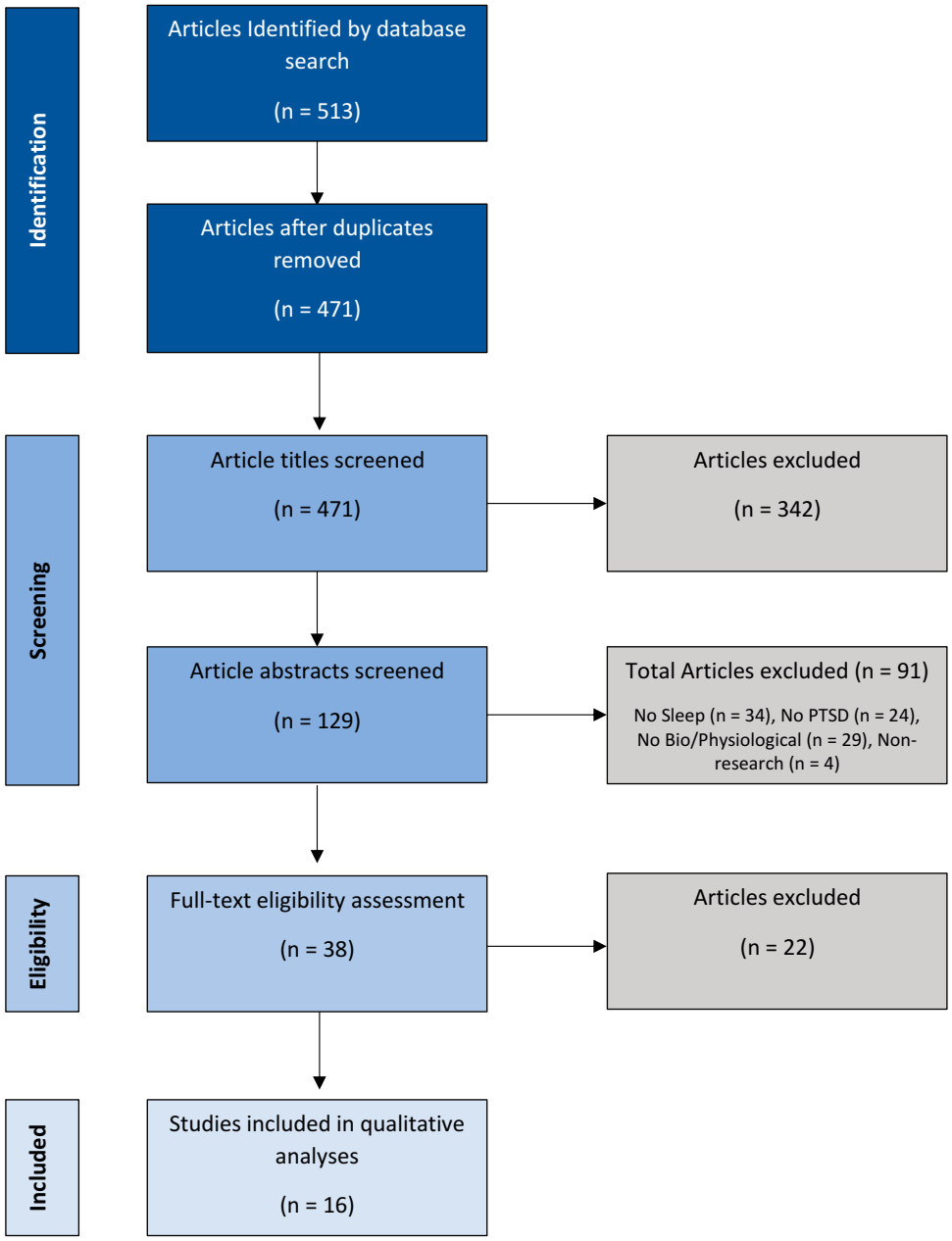

Figure 1 Summary of literature screening method employed. A total of 513 articles were identified using the search strategy developed. After removal of duplicates, 471 articles were retained for title and abstract screening, following which 38 were retained for full-text eligibility assessment. Sixteen studies were deemed to meet all the inclusion criteria and were subject to analyses.

Eight/16 studies consisted exclusive of military populations (active service and veterans), expanding to 9/16 when a further study which incorporated emergency service personnel were included. Of the remaining studies, two utilised an urban population, one a kidney transplant population, and four were population non-specific.

Relationship analysis between biological measures and sleep was routinely performed however, tri-directional analysis with PTSD, or PTSD and biological-specific analyses, was often unexplored or unreported (Tables S1 and S2). Key outcome measures included subjective and objective sleep, PTSD symptoms, depression, HR and variability, blood pressure, inflammatory and anti-inflammatory status, HPA-axis function and mRNA gene expression. Sleep assessment methods varied greatly, with 10 different tools employed across the 16 included studies, as visualised in Figure 2. Although when objective methods were employed, heterogeneity was greatly reduced with only polysomnography or actigraphy utilised.

Most studies were designed primarily to examine the role and relationship of sleep either to psychological symptomology or biological markers. Study designs varied but generally can be divided into the following three categories: epidemiological (Studies 11,13), intervention (Studies 1,3,4,6,7,8,9,10,15) or night-time specific (Studies 2,5,12,14). A further study carried out a baseline group comparison of PTSD vs non-PTSD controls (Study 16).

Physiological Measures – Assessing Autonomic Function

Physiological measurements of the cardiovascular or pulmonary systems were recorded in 11/16 studies (Studies 2,4,5,6,7,9,11,12,13,14,15). Of these, quantification of blood pressure (BP), or BP regulation was the dominant measure (6/11). Baroreceptor sensitivity (BRS), a measure of the ability to regulate BP, was found significantly lower in a PTSD sub-population (Study 7). This negative relationship was found to be exacerbated with declines, and mitigated with gains, in sleep quality, a relationship upheld with direct examination of blood pressure (Studies 2, 9.11 and 13). However, PTSD status alone was found not to predict a "non-dipping" designation of nocturnal blood pressure, an important indicator linking BP and cardiovascular disease (Study 2).[88] Although "non-dipping" was related to poorer sleep quality and was associated with a more severe PTSD phenotype, with a greater experience of traumatic events and hyperarousal symptoms.

Used as an estimate of sympathetic and parasympathetic activity, HR and/or heart rate variability (HRV) measures were examined in 6/11 studies (Studies 4,5,6,9,12,14). Standard deviation of the normal heartbeat to beat interval (SDNN), a measure indicative of vagal autonomic influence, decreased following interventions which concurrently increased sleep quality and decreased PTSD symptoms (Studies 4,9). However, a direct relationship with insomnia severity index score was not supported (Study 4). Further measures of HRV included normalised high frequency (nHF) and low frequency to high-frequency ratio (LF/HF) of respiratory sinus arrhythmia (RSA), which correlated with total sleep time in trauma controls but not PTSD (Study 5).[89] RSA, indicative of parasympathetic tone, was investigated in study 15 in relation to nightmare or distressing dream occurrence in PTSD.[90] Lower sleep period RSA was found predictive of an increased likelihood of endorsing a nightmare or distressing dream. Study 15 also noted nightmares or distressing dreams were associated with an increase in the number of sleep respiratory events (hypopneas or apneas).

Study 6 examined skin conductance level (SCL) reactivity, a measure indicative of sympathetic activity. Decreases in SCL reactivity related to decreased nightmare severity, improvements in self-assessed sleep quality and a reduction in CAPS assessed PTSD symptom severity, following exposure, relaxation and re-scripting therapy (ERRT) for nightmares.

Baseline and night-time HR was evaluated in studies 14 and 12, respectively. An increase in HR was observed immediately preceding or following nightmare occurrence (Study 12), albeit baseline comparison between PTSD and health controls yielded no significance (Study 14). Interestingly, baseline HR was significantly lower in trauma controls compared to PTSD (Study 14). HR was also recorded in study 15 however findings were not reported.

Biological Measures – Gene Expression and Biochemical Quantification

Three main biological processes, or systems, were identified as the focus of the included studies; (1) inflammation, (2) HPA-axis activity and (3) trophic factor regulation. With the aim to elucidate the effect sleep has on these systems in PTSD populations, biochemical and gene expression analyses were the main techniques employed and were performed in 7/16 studies.

Inflammation

Biomarkers pertaining to inflammatory status were investigated in 4/7 studies, in the form of peripheral blood: CRP (Studies 8,9,16), IL-6 (Studies 8, 16), IL-10 (Study 9), TNF-α (Study 16), soluble IL-6 receptor (Study 16), IL-1β (Study 16) and global mRNA gene expression analysis (Study 3). Improvements in baseline sleep resulted in differential mRNA expression in 217 coding genes of which, pro-inflammatory IL-1β, IL-6, IL-8, IL-13, CCL3, CCL4 and CCL5 genes experienced a significant fold decrease. A tandem increase in the expression of the inflammatory regulatory genes TLR1, TLR4, TLR7 and TLR8, was also observed. Taken together this suggests that improving sleep is associated with an increase in the regulation of inflammatory processes, which results in a global decrease of inflammatory status, a hypothesis reflected with decreases in plasma IL-6 and CRP mediated by improved sleep (Studies 8 and 9). However, no

Table 2 Summary of Data Extraction from Included Studies

Study	1	2	3	4	5	6	7	8
Reference	117	118	119	120	121	122	123	124
Population	Military	Military	Military	Urban	Urban	NS Civilian	NS Female	Military
Population Size	44	61	68	38	38	47	53	66
Males	NR	0	66	21	12	8	0	64
Females	NR	61	2	17	26	39	53	2
Age	33.3	38.3	22.8	NR	22.8	47.0	41.3	34.9
Study Design	Case-controlled	Cohort	Case-controlled	RCT	Cohort	RCT	Cohort	Cohort
Sleep Measures	PSG, ESS, PSQI	PSQI	PSQI	ISI	Actigraphy, Sleep diary	PSQI	Actigraphy	PSG, PSQI
Intervention	CBTI or CBTI + PAP	N/A	CBTI or CBTI + PAP	RSA Biofeedback	N/A	ERRT	N/A	SOC
PTSD assessments	PCL-M	CAPS + DTS	PCL-M	PCL-C + PTS-T	CAPS	CAPS	CAPS	PCL-M
Physiological Measures	Hypertension	BP	N/A	BPM, HRV	HR, HRV	HR, SCL	BRS	N/A
Biochemical Measures	BDNF, IGF-1	N/A	mRNA	N/A	N/A	N/A	N/A	IL-6, CRP
Sample Matrix	Plasma	N/A	Peripheral Blood	N/A	N/A	N/A	N/A	Peripheral Blood
Additional Measures	N/A	BDI-II	QIDS	BDI-II	PHQ-9	TRNS, TSI, PILL, PTCSS	N/A	QIDS, RAND HRQOL

Abbreviations: NR, not reported; N/A, not applicable; RCT, randomized control trial; PSG, polysomnography; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; AIS, Athens Insomnia Scale; CBTI, cognitive behavior therapy for insomnia; PAP, positive airway pressure; RSA, respiratory sinus arrhythmia; SOC, standard of care; CAN, closed-loop allostatic neurotechnology intervention; PCL, PTSD checklist; CAPS, Clinician Administered PTSD Scale; SCID, Structured Clinical Interview for DSM-IV; DTS, Davidson Trauma Scale; TSI, Trauma Symptom Inventory; PILL, Pennebaker Inventory of Limbic Languidness; PTCSS, Post Treatment Clinical Significance Survey; NR, nightmare recall; SCL, skin conductance level; BP, blood pressure; HRV, heart rate variability; BRS, baroreceptor sensitivity; HR, heart rate; BPM, breaths per minute; REI, Respiratory Event Index; RSA, respiratory sinus arrhythmia; IES-R, Impact of Event Scale-Revised; CTQ, Childhood Trauma Questionnaire; SAI, State-Trait Anxiety Inventory; BDI-II, Beck Depression Inventory-II; JRBANS, Japanese version of the Repeatable Battery for the Assessment of Neuropsychological Status.

relationship between Athens insomnia scale assessed sleep and IL-6, sIL-6R, CRP or TNF-α was noted in Study 16. In relation to PTSD status and inflammation, reductions to PTSD symptom severity as assessed by PCL-M followed improved sleep and were accompanied by a non-significant decrease in the expression of the inflammatory regulatory IL-10 (Study 9). However, no relationship between PTSD symptom severity and the proinflammatory, CRP, IL-6, soluble IL-6 receptor, IL-1β and TNF-α cytokines was substantiated by correlation analysis in Study 16.

HPA-Axis

HPA axis function, considered as a physiological response to physical and/or psychological stress, formed the basis of 2/7 studies, which measured cortisol, 11-deoxycortisol and adrenocorticotrophic hormone (ACTH) (Studies 10, 14). A

9	10	11	12	13	14	15	16
125 Military	126 NS	127 Military	128 Military + EMS	129 Kidney Transplant	130 Military	131 Military	132 Japanese Female
18	66	1855	35	268	45	31	105
17 1 40.9 Cohort ISI	30 36 30.0 Cohort PSG, Actigraphy, Sleep diary	1477 378 37.4 Prospective Sleep items from SC-90	34 1 43.3 Cohort PSG, sleep diary	138 129 49.9 Cohort AIS	45 0 36.5 Cohort Sleep diary, PSQI	31 0 41.2 Cohort Actigraphy, NR	0 105 37.4 Cohort AIS
CAN	Metyrapone	N/A	N/A	N/A	N/A	Canine presence	N/A
PCL-M	CAPS	SCID + DTS	CAPS + PCL-5	DTS	CAPS + SCID	CAPS	PDS DSM-IV, Japanese IES-R
HRV, BRS, BP	N/A	BP	SPO2, HR	BP	HR	HR, REI, RSA	N/A
Ag-II, Ag1/7, Epinephrine, Norepinephrine, CRP, vasopressin, IL-1, IL-6, IL-10, Cortisol, alpha-amylase, DNA methylation	ACTH, Cortisol, 11-deoxycortisol	N/A	N/A	Ht, Hb, WBC, PLT, CRP, Glucose, Urea, creatinine, proteins, albumin, Na, K, Ca, P, Fe, ferritin, TSAT, PTH, 25(OH) D3, HbcA1c	Cortisol, ACTH, Melatonin	N/A	IL-6, IL-1β, TNF-α, CRP, sIL-6R
Peripheral Blood, Saliva (Cortisol & Alpha-amylase)	Peripheral Blood	N/A	N/A	Peripheral Blood, Urine	Peripheral Blood	N/A	Serum
CES-D, GAD-7, Grip strength	N/A	BDI	Nightmare questionnaire, AUDIT, HADS	JH-RLSSS, HADA	N/A	Prior mood, kinetocardiogram	IES-R, CTQ, SAI, BDI-II, JRBANS

comparative group analysis of nocturnal or baseline cortisol and ACTH resulted in no significant difference between PTSD, trauma-exposed (TCs) or health controls (HCs) (Studies 10.14). Examination of cortisol: ACTH ratio revealed a significant ratio reduction in PTSD vs TCs, and borderline significance when compared to HCs, a finding accentuated between 07:00 and 08:00 am, i.e. the cortisol awakening response and natural circadian peak. This appears to suggest decreased responsiveness of the adrenal cortex to ACTH (Study 14). A finding further supported by increased 11-deoxycortisol at baseline, with similar ACTH, observed in PTSD when compared with controls (Study 10).

Total nocturnal ACTH was positively related to the number of awakenings, and was an independent, inverse predictor of slow-wave sleep (Study 14). Congruently, the

relationship between ACTH and delta power sleep was negative in PTSD, but not controls (Study 10). Suggesting increased ACTH in PTSD negatively affects sleep, a relationship not apparent in control populations.

Administration of a metyrapone challenge to remove negative feedback to the hypothalamus, by inhibiting cortisol synthesis, resulted in a greater reduction in delta power sleep, a greater decrease in cortisol and increase of ACTH levels in PTSD compared to controls (Study 10). This would suggest an amplified response to the negative feedback of cortisol at the level of the hypothalamus in PTSD. Interestingly, improvements to sleep resulted in a fold increase of glucocorticoid inhibitory FKB506 binding protein and FK506 binding protein 15 mRNA expression, potentially relating sleep as an additional element regulating HPA-axis function (Study 3).

Trophic Factors

Trophic factors, insulin-like growth factor-1 (IGF-1) and BDNF, implicated in the maintenance of synaptic plasticity and learning and memory consolidation, were examined following a CBT-I intervention to improve sleep (Study 1). Sleep improvements resulted in a significant increase in IGF-1 but no significant changes in BDNF were observed. At baseline, PTSD subgroup analysis revealed no difference in the concentration of either trophic factor, and CBT-I treatment reductions in PTSD symptoms were unrelated to IGF-1 or BDNF changes.

Depression

A wide range of self and clinician-administered psychological assessments were reported on, of which depression was the most common (11/16). Intervention studies which examined sleep as a function over time reported improvements in sleep were significantly associated with reductions in depression symptomology (Studies 1,3,8). Congruently, declines in sleep over time were associated with an increase in depression ratings. This finding is further supported with a noted relationship between sleep quality and depression in kidney transplant recipients (Study 13). Sleep-related improvements in depression were examined independently to PTSD status and symptoms.

In summary, five main outcomes were identified; (1) SDs regulate BP in PTSD, (2) sympathetic dominance in PTSD is mediated by sleep, (3) sleep regulates global inflammatory status, (4) protection from glucocorticoid overexposure in PTSD may be at the expense of sleep and (5) trophic factor regulation is affected by changes to sleep in PTSD.

Discussion

To understand the biological interplay between PTSD and associated SDs, this review evaluated studies which examined biochemical and/or physiological markers in PTSD populations, with a specific reference to sleep. Inclusion of intervention, night-time specific, epidemiological and baseline studies provided an all-encompassing overview. Differential sleep period assessments, such as single point quantifications and time course comparisons, while not directly comparable, together yield valuable mechanistic insights into altered biological processes potentially associated with sleep in PTSD.

The most commonly reported measure across all studies was BP or associated BRS. Baroreceptor activation responds to increased BP by increasing parasympathetic, and decreasing sympathetic stimulation of the heart and blood vessels.[91,92] Findings of reduced BRS in PTSD populations were noted to be influenced by sleep quality. Poorer sleep resulted in further reductions to BRS, which increased with improvements in sleep, suggesting sympathetic dominance in PTSD can be somewhat reduced by alterations to sleep, a finding mirrored by HRV and skin conductance measures. Furthermore, the note that attenuation of sleep RSA was predictive of nightmare/distressing dream occurrence demonstrates this phenomenon is also related to nightmares in PTSD. This is notable considering that hypertension and cardiovascular disease (CVD) rates are higher in PTSD populations, suggesting in this population both sleep quality and nightmares represent targetable and modifiable CVD drivers which with improvements, could reduce CVD development in this vulnerable population.[83]

Nocturnal BP regulation is emerging as a significant predictor of cardiovascular events in hypertension patients, with non-dipping (defined as less than 10% decrease in nocturnal BP vs daytime BP) associated with increased mortality.[93] Non-dipping nocturnal BP was associated with poorer quality sleep (Study 2). However, PTSD was not found to be a predictor of dipping status, opposing the previous observation of reduced BP regulatory ability and sympathetic dominance in PTSD. Nonetheless, non-dipping was associated with a more severe PTSD phenotype which fits with the role of cortisol in BP dipping. Reduced variation in diurnal cortisol is associated with non-dipping designation.[94] Thus, a more severe PTSD phenotype which results in a protective inhibition of glucocorticoid

response may represent a mechanism capable of accounting for this observation, as discussed further below.[93]

Findings from this review indicate that a reduced responsiveness of the adrenal cortex to ACTH stimulation may exist as a functionally protective mechanism in PTSD. This results in a reduced cortisol:ACTH ratio, particularly evident during the cortisol awakening response, and a greater responsiveness of the hypothalamus to cortisol negative feedback removal, as demonstrated via a cortisol inhibiting metyrapone challenge. The need to develop such a protective mechanism is unsurprising considering alterations to circadian oscillations of glucocorticoids (cortisol) and chronic exposure have a detrimental effect on synaptic plasticity, learning and memory.[95] However, this may be at the expense of sleep quality in PTSD, as ACTH was positively related to the number of night-time awakenings, was an inverse predictor of restorative slow-wave sleep, and had a negative relationship with delta power sleep in PTSD. Improvements to sleep resulted in alterations to glucocorticoid regulatory mRNA expression, further intertwining sleep and HPA-axis regulation in PTSD.

Specific investigations of this mechanism are warranted to establish directionality. Are detrimental effects to sleep resultant from a mechanism aiming to prevent pathologic exposure to glucocorticoids in PTSD? Or, does poor sleep quality result in an inappropriate activation of this mechanism, pre-disposing an individual to PTSD development due to a blunted glucocorticoid responsiveness to stress? Most likely, we hypothesise a combination of the two is likely to be true, representing alternative activation arms of a common mechanism. If validated, this represents a promising research avenue for the design and development of new, specific pharmaceuticals for PTSD treatment protocols. Moreover, reported poor sleep quality could be used to identify PTSD "at risk" individuals within "at risk" populations (such as military and first responders), and therapies shown to improve sleep quality, such as CBT-I for insomnia or nightmare re-scripting therapy, could be used as prophylactic treatments potentially capable of reducing PTSD susceptibility.[96]

Of further intrigue is the work in mouse models of PTSD, whereby enforced sleep deprivation following traumatic exposure has been found to reduce stress behaviours associated with recall exposure.[97] An effect that was dependant on HPA-axis activity.[97] Although such mouse models of PTSD are translationally limited, this serves as an additional point reinforcing the importance of the HPA-axis and sleep in PTSD susceptibility, progression and treatment.

An increased inflammatory status, associated with increased mortality risk, has been independently associated with SDs, PTSD and other psychiatric conditions such as depression.[49,56,84,85,98,99] Results from this review indicate improvements to sleep result in both a decrease in pro-inflammatory cytokines and mRNA expression, and an increase in inflammatory regulatory mRNA. This suggests disturbed sleep as a driver of systemic inflammation in PTSD populations, capable of contributing to comorbid conditions which are progressed by dysregulated inflammatory processes, such as type 2 diabetes and CVD, to which this population are vulnerable.[51–58] However, more research is required to fully establish the role of inflammation and provide a more complete picture of total inflammatory status in PTSD, and the role played by sleep. This review has highlighted that conflictions remain in the literature between studies examining mRNA expression and those which examine functional proteins. Perhaps future studies should aim to examine the role of post-translational modifications. Our hypothesised protective inhibition of the HPA-axis, linked to sleep, is particularly interesting when considered with inflammatory findings. HPA-axis dysfunction has been linked to dysregulated and inappropriate inflammatory responses, suggesting these processes are highly interrelated in PTSD, potentially causative of one another and possibly linked through sleep.[100]

To confirm any such relationship between sleep, inflammation and PTSD, further research should consider the following limitations of studies included in this review. Foremost, inflammatory expression changes were not directly linked to PTSD symptom assessments, therefore they cannot be assumed to directly relate to PTSD symptom changes. Secondly, it may be necessary to perform tri-directional analyses which consider depression symptom changes. Of the included studies which incorporated a measure of depression, improvements to sleep resulted in reductions to depression symptoms. As depression is an inflammatory disease, it is unclear if inflammation changes are resultant from sleep changes, reductions in depression, or reductions in PTSD symptom severity in this complex population.[101–103]

Examination of the trophic factors IGF-1 and BDNF noted increases in their expression following improvements to sleep quality, using standard of care sleep therapies. Shown to be decreased in depression, and chronic

Table 3 Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Assessment of Evidence Quality. Final GRADE Quality Assessment Possibilities; High, Moderate, Low, Very Low

Certainty Assessment						
No of Studies	**Risk of**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Certainty of Evidence**
SDs regulate BP in PTSD (assessed with: BP, BRS)						
5 studies	Not serious	Not serious	Serious	Not serious	All plausible residual confounding would reduce the demonstrated effect, dose response gradient	⊕⊕⊕◯ MODERATE
Sympathetic dominance in PTSD is mediated by sleep (assessed with: HR, nHF, nHF/LF, RSA, SC)						
7 studies	Not serious	Not serious	Not serious	Not serious	Dose response gradient	⊕⊕⊕◯ MODERATE
Sleep regulates global inflammatory status (assessed with: Peripheral blood cytokines, mRNA expression)						
4 studies	Not serious	Serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ LOW
Protection from glucocorticoid over exposure in PTSD is at the expense of sleep (assessed with: Cortisol, 11-Deoxycortisol, ACTH)						
3 studies	Not serious	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕◯ MODERATE
Trophic factor regulation improved with improved sleep (assessed with: IGF-1, BDNF)						
1 study	Serious	Not serious	Not serious	Not serious	Strong association, all plausible residual confounding would reduce the demonstrated effect, dose response gradient	⊕⊕⊕⊕ HIGH

Abbreviations: SDs, sleep disturbances; PTSD, post-traumatic stress disorder; BP, blood pressure; BRS, baroreceptor sensitivity; HR, heart rate; HRV, heart rate variability; nHF, normalized high frequency; LF, low frequency; RSA, respiratory sinus arrhythmia; SC, skin conductance; ACTH, adrenocorticotrophic hormone; IGF-1, insulin like growth factor 1; BDNF, brain derived neurotrophic factor.

stress, IGF-1 and BDNF are key regulators which modulate synaptic plasticity, learning, memory and contextual fear response.[104,105] This finding adds further weight to the modifiable, central and pathological role of sleep disturbances in PTSD.

Perhaps a surprising observation is the lack of investigation of melatonin and its associated metabolites, considering its central role in sleep promotion.[106] Only a single study incorporated a melatonin measurement, noting no significant differences in overall melatonin secretion or time of melatonin secretion onset, between PTSD and comparative populations. However, differences in urine sulphated-melatonin have been observed in PTSD populations when compared to normal controls.[107] In future studies, it would be of interest to examine melatonin metabolites in PTSD populations following changes to sleep, considering their antioxidant properties and the advantages this may present in PTSD pathobiology.[50,75,108]

Significant methodological limitations identified as part of this review are the range of sleep and PTSD assessment methods currently employed in the field, their reliability and most importantly their cross comparability. When comparing biomarkers, having a clear definition of the test condition is key, particularly if studies are to be cross-compared to derive any pathobiological mechanisms. Some of this disparity in PTSD assessment was due to the introduction of DSM-5 in 2013.[109] However, a wide range of assessment methods remain in use, which serve to limit the comparability and generalizability of biological results across studies. Therefore, this review recommends that a universal PTSD symptom assessment method should be adopted for biological investigations.

This problem of method heterogeneity extends to sleep. Although actigraphy provides a useful objective measurement of sleep in the free-living environment, a key limitation is the use of different devices in different studies, and unclear reporting of sleep parameter calculation protocols.[15,21,23] Actigraphy devices record movements which are translated into sleep parameters using scoring algorithms. To improve the comparability and

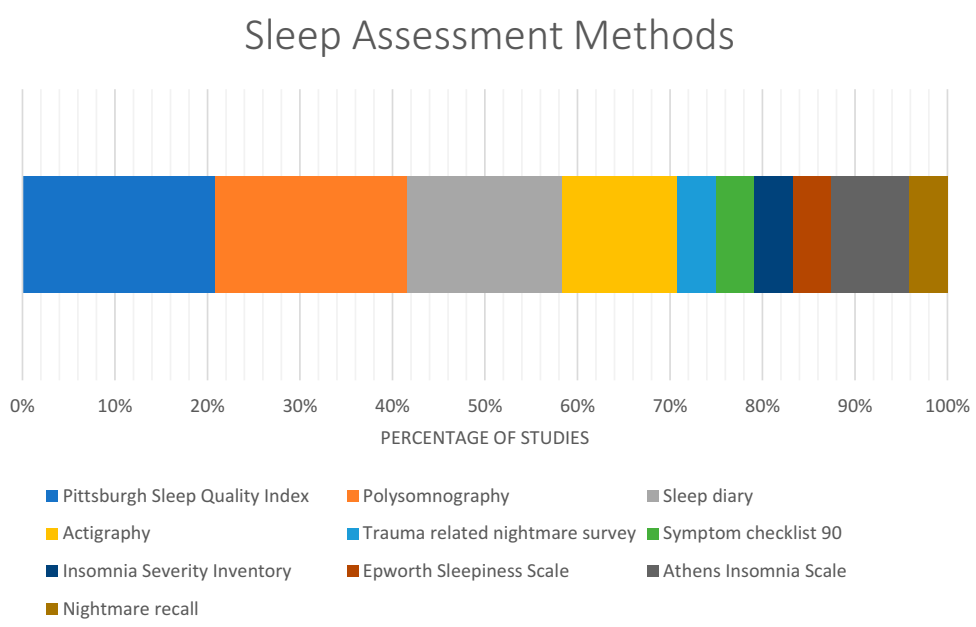

Figure 2 Graphic showing the different sleep assessment methods employed across the included studies, as a percentage of the total number methods. Pittsburgh Sleep Quality Index (21.7%), Polysomnography (21.7%), Sleep diary (17.4%), Actigraphy (13%), Trauma-related nightmare survey (4.3%), Symptom checklist 90 (4.3%), Insomnia Severity Inventory (4.3%), Epworth Sleepiness Scale (4.3%), Athens Insomnia Scale (4.3%), dichotomous nightmare recall (4.3%).

reproducibility between studies, it would be beneficial for future research to report accelerometer specifications, sleep parameter calculation algorithms and raw movement data.[19] It was surprising that none of the studies which employed actigraphy supported this with a valid subjective sleep assessment method such as the ISI. Incorporation of such a measurement would allow for greater comparability with previous studies, and may prove more robust than objective actigraphy alone.[17,18,110] Therefore, this review recommends future research should report raw accelerometer movement data, in actigraphy-based studies, where possible. This should also be accompanied by a validated self-report sleep measure.

As noted previously, recent literature has identified differences between the rates of insomnia endorsement and nightmare occurrence in PTSD.[10] Considering this, it is important to note a large proportion of the included studies were not able to separate the two, referring instead to a combined "sleep quality" measure. Therefore, in the case of PTSD, and perhaps other mental disorders, employing a combination of sleep quantification methods, so that insomnia and nightmares can be clearly differentiated, may allow any differential effects they have on biological processes to be identified. Further limitations include the lack of tri-directional analysis between PTSD symptom measures, sleep and biological markers and non-universal previous treatment continuation protocols used by intervention studies.

Less than a third of participants included in this review were female, despite a two-fold greater susceptibility of females to the development of PTSD.[111] This is most likely attributable to the dominance of military populations within the reviewed studies. Despite this disparity in sex, only five studies consisted of a single-sex population, with the remaining studies incorporating a very small number of female participants. This is not preferable when examining biochemical or physiological markers, which have normal variations due to sex, and should be addressed in future research.[112–115]

Limitations

Findings of this review are limited by the small number of studies which met all inclusion criteria and an assumed comparability between the different PTSD, subjective sleep, and objective sleep assessment methods used across studies.

Conclusions and Future Directions

The aim of this review was to establish if biochemical and/or physiological markers are related to SDs, severity of the disturbances and their resolution in PTSD. In this regard, SDs were found to directly affect physiological markers relating to autonomic function, and biochemical markers relating to HPA-axis activity, systemic inflammatory processes and trophic factor regulation thus, not only do SDs

reduce quality of life, but they also contribute to overall morbidity and mortality associated with PTSD.

Findings pertaining to changes in sleep over time established sleep as a central driver playing a role in, and potentially capable of modifying, many pathological pathways. Improving sleep was shown to decrease sympathetic dominance, increase trophic factor concentrations and reduce pro-inflammatory processes. Improving sleep quality, therefore, has the potential to reduce all-cause lifetime mortality associated with CVD, diabetes and other metabolic conditions in PTSD, and as such should be of central focus when developing treatment regimes. Resolving SDs will not only reduce the overall severity of PTSD symptoms but also has the potential to reduce hospital admission time, total lifetime healthcare costs and improve the overall quality of life for those with PTSD.

Looking into the future, mechanistic insights of this review highlight the importance of carrying out further research into the ability of prophylactic sleep therapies, such as CBT-I, to reduce PTSD risk in populations of high trauma exposure, such as the military and first responders. Such research should be conducted, and findings used in conjunction with those of this review, to inform future policy and occupational health practices in these populations. If this is carried out and appropriate practices implemented, not only could it reduce the risk of developing PTSD, but it may also bring additional economic benefits to employers through reduced sickness-related time off work, and compensation payments associated with occupational-related PTSD.[116] However, to allow cross-comparability and expand the generalizability of findings, future research must address and adhere to the methodological recommendations laid out in this review.

Abbreviations

PTSD, post-traumatic stress disorder; SD, sleep disturbances; DSM-5, Diagnostic and statistical manual of mental disorders 5th edition; CBT, cognitive behavioural therapy; CBT-I, cognitive behavioural therapy for insomnia; PCL, PTSD checklist; PVN, paraventricular nucleus; CRH, corticotrophin-releasing hormone; AVP arginine vasopressin; ACTH, adrenocorticotrophic hormone; FKBP5, FK506 binding protein; IL-6, interleukin-6, IL-1β; TNF-α, tumour necrosis factor-α; INF-γ, interferon gamma; SCN, suprachiasmatic nuclei; CRP, C-reactive protein; MeSH, Medical Subject Headings; EEG, electroencephalogram; PSG, polysomnography; HR, heart rate; HRV, heart rate variability; nHF, normalised high frequency; LF, low frequency; BRS, baroreceptor sensitivity; BP, blood pressure; SCL, skin conductance level; ERRT, exposure, relaxation and rescripting therapy; TLR, toll-like receptor; CVD, cardiovascular disease.

Funding

This research was funded as part of the Ulster University and Randox Laboratories Ltd Industrial PhD Academy.

Disclosure

MWR is a paid employee of Randox Laboratories but holds no shares in the company. No other authors have any conflicts of interests to declare.

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