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CLINICAL REVIEW

Treating sleep disorders following traumatic brain injury in adults: Time for renewed effort?

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SUMMARY

Traumatic brain injury (TBI) disrupts normal brain function and can lead to chronic symptoms of sleep disturbance, pain, irritability, and depression. Sleep disorders occur in 30–70% of individuals who have experienced TBI. Disturbed sleep impairs the recovery process and may exacerbate other issues that arise because of brain injury (e.g., headaches, depression). Noticeable benefits have been reported when sleep problems due to TBI are addressed and treated; for instance, treating post-TBI insomnia reduces the expression of inflammatory genes, potentially reducing ongoing neurological damage. In this review, we discuss twenty-four randomised clinical trials (RCT) published to date (August 2021), exploring interventions for sleep disturbances resulting from TBI. Treatment effects were observed for insomnia, circadian rhythm disorders, hypersomnia, and general sleep disturbance. However, the evidence remains limited and significant methodological issues are discussed with a recommendation for further research.

Introduction

Traumatic brain injury (TBI) is reported to be more frequent in the adult population than any other medical disorder, including HIV-AIDS, Parkinson's disease, multiple sclerosis, and breast cancer [1]. Humphreys et al. (2013) [2], estimated that roughly 10 million people annually will experience and suffer from TBI, the term used for an injury to the brain caused by an external force (e.g., car collision, falls). The most common causes of head injury in the civilian population are: falls (28%), motor vehicle collisions (20%), being hit by/against an object (19%), and physical attack (11%) [3]. TBI has been shown to carry a 3.2 times higher risk of premature mortality compared to a control group without TBI, matched for age and gender [4].

Diagnosis and treatment of TBI

The severity of TBI is clinically assessed acutely using the Glasgow Coma Scale (GCS), by gauging the duration of loss of consciousness (LOC), by the presence or absence of post-traumatic amnesia (PTA), and by using structural brain imaging. TBI can be classified based on a combination of these measures as mild (GCS = 13–15; LOC ≤30 min; PTA ≤24 h; normal structural brain imaging), moderate (GCS = 9–12; LOC ≥30min; PTA ≥24 h; ≤7 days; normal or abnormal structural brain imaging) or severe (GCS = 0–8; LOC >24 h; PTA >7 days; normal or abnormal structural brain imaging) [5]. Following stabilisation of the patient and attending to any associated injuries, further treatment recommendations are dependent upon the presence of new or persistent symptoms.

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In the first two years post-TBI, individuals are likely to suffer from a variety of persistent physical, cognitive, emotional, or behavioural impairments [6]. Post-TBI symptoms often lead to further morbidity if left untreated. Common symptoms include headaches, sleep disturbance, depression, anxiety, and irritability.

Sleep disturbance following TBI

A meta-analysis by Mathias and Alvaro (2012) [7] revealed that 50% of people with TBI have sleep disturbances, with 25–29% being diagnosed with a sleep disorder. Frequently reported sleep disorders resulting from TBI are insomnia (29%), obstructive sleep apnoea (OSA) (25%), post-traumatic hypersomnia (28%), narcolepsy (4%) and nightmares (27%). More generally, post-TBI patients are two to four times more likely to suffer from inefficient sleep, excessive daytime sleepiness (EDS), nightmares, somnambulism, early morning wakening, and problems with sleep maintenance [7].

Chaput et al. reported that patients with post-TBI sleep complaints were 2.9 times more likely to suffer from headaches in the six weeks following a mild-TBI, compared to those with TBI without sleep issues [8]. Pain (e.g., headaches), depression, or anxiety resulting from TBI can lead to impaired sleep quantity and quality [3]. In a sample of military personnel of whom 40% disclosed having had a TBI in the past, Livingstone et al. demonstrated that an improvement in sleep following sleep disorder-specific treatment (i.e., continuous positive airway pressure (CPAP) for obstructive sleep apnoea (OSA) and Cognitive Behavioural Therapy for insomnia (CBTi)) resulted in less severe symptoms of depression, a decreased risk for post-traumatic stress disorder (PTSD), and a lower expression of inflammatory genes after TBI [9].

Treating sleep disorders post-TBI

Treating sleep disorders following TBI is informed primarily by the treatment effects found in non-TBI populations. Previous literature reviews in the area have focussed on specific sleep disorders such as insomnia [10], specific treatment interventions such as modafinil [11,12] and otherpharmacological approaches [13,14] or non-pharmacological approaches [15,16]. Oullet and colleagues [17] conducted a literature review of treament effects on sleep in TBI, noting that TBI-related morbidities such as cogntions and memory should also be taken into account. They noted that despite limited evidence for supporting the effectiveness of sedating medications such as benzodiazepine drugs, these continue to be heavily prescribed in the TBI populaton. Another review conducted by Orff et al. [18], found that despite the effectiveness of CBT in individuals post-TBI, pharmacological treatments remain the most common, accessible forms of treatment and remain largely understudied. So far, no coherent review has been conducted which identifies and discusses treatment options across all sleep disorders post-TBI. This review aimed to identify all randomized, controlled trials to date in adults investigating any aspect of sleep disturbance post-TBI.

Methods

Literature search

From February 2020 to March 2020 we conducted an extensive literature search of electronic databases: EMBASE, MEDLINE, PsycINFO and SCOPUS using defined search terms: (“traumatic brain injury” or “traumatic brain inuries” or “TBI” or “brain concussion”) and (“sleep” or “sleep intiation and maintenance disorders” or “sleep wake disorders” or “insomnia” or “circadian rhythm” or “disorders of excessive somnolence” or “hypersomnia or parasomnia” or “rest-activity” or “somnolence” or “sundowning”) and (“randomized/randomised” or “placebo” or “drug therapy” or “randomly” or “groups” or “intervention” or “treatment” or “therapy” or “controlled clinical trial” or “RCT” or “trial”). Reference lists from relevant studies were hand-searched for additional literature.

Inclusion criteria

A study was included if it met the following criteria: 1) the study was randomised, controlled, double or single-blind and either a parallel or cross-over trial; 2) the study consisted of treatment and control groups that had sustained non-penetrating TBIs; 3) participants were 16 years or older; 4) a measure of sleep was assessed pre- and post-treatment; 5) the study sample consisted of more than one participant in each group; 6) data enabled the review of treatment effects on sleep (i.e., raw data, mean and SD, t-tests, one-way analysis of variance, exact p-values).

Study selection

The literature search yielded 2494 articles after duplicates were removed. Studies were then eliminated according to the six criteria listed above. At criterion three, 532 articles were considered by four researchers independently. Abstracts were reviewed on the fourth, fifth and sixth criteria and 71 articles met criteria for inclusion. Of these 71 articles, 24 articles met all six criteria and consensus was reached by all four researchers that a treatment effect on sleep was evaluated in the article (see Fig. 1).

Study measures

All post-TBI sleep disorders and disturbances were considered. To allow for inclusion of treatment programs specific to TBI-related symptoms we included all studies that investigated the treatment effect on sleep, with or without a specified sleep condition.

Study quality was assessed using GRADE criteria (see Table 1 – appendix).

Results

Study characteristics

The 24 studies (18 papers and six conference abstracts) examined 14 treatments. Sample sizes ranged from seven to 356 patients and patients were predominately male (68.9%). There were 16 randomized, double-blind, controlled studies, three randomized, single-blind, controlled studies, and five randomized, controlled studies that did not report blinding. Table 1 summarises the quality of the studies using most recent GRADE criteria (Table 1; see also Table 2 for specific study details). Fourteen studies matched individuals on age; five on injury severity; 16, on sex; and nine, on education. Nine studies recruited individuals with mild TBI only, three studies recruited individuals with mild to moderate TBI and the remaining 12 studies either did not have any criteria regarding TBI severity or did not report this information. Fewer than half of the studies reported specific injury severity data (i.e., Glasgow coma scale, n = 5; post-traumatic amnesia, n = 4; loss of consciousness, n = 1). Only 13 of the studies reported the average injury-to-treatment interval. Ten studies conducted a follow-up assessment ranging from 23 days to one-year post treatment. Nineteen of the recorded RCTs evaluated sleep as a primary outcome. Subjective measures used included the Epworth Sleepiness Scale (ESS) [19] (n = 12); the Pittsburgh Sleep Quality Index (PSQI) [20], (n = 10); sleep diary/log, (n = 4); and Insomnia Severity

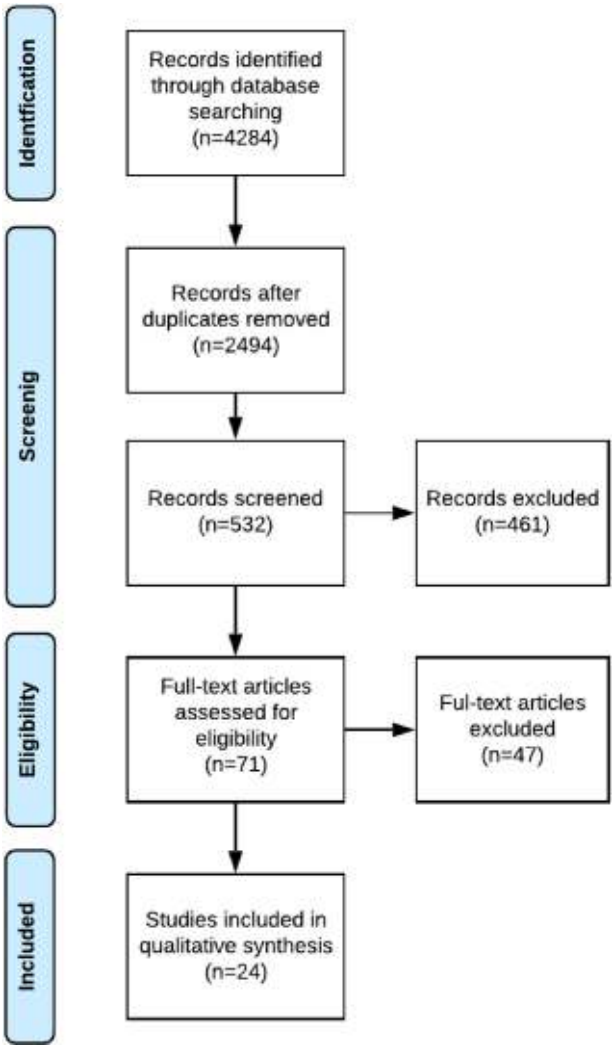

Fig. 1. PRISMA flow diagram of studies included in the meta-analysis of treatment of sleep disorders in adults post-TBI.

Index (ISI), (n = 3) [21]. Objective measures included actigraphy, (n = 9) and polysomnography (PSG), (n = 1). The results of all the studies are summarised in Tables 2 and 3 and briefly discussed below according to sleep disorder classification.

Treatment of insomnia disorder post-TBI

Pharmacological treatment

Melatonin. Two studies explored the effects of melatonin on post-TBI insomnia. Kemp et al. [22] showed that neither melatonin nor amitriptyline had a significant effect on sleep initiation or maintenance changes using a self-reported questionnaire and sleep diary (this study revealed high risk of bias; Table 1). By contrast, Grima et al. [23], published a well conducted study demonstrating that a 4-week-long prolonged release 2 mg melatonin course resulted in a significant reduction in PSQI scores compared to placebo ($p < 0.0001$) and an improvement in sleep efficiency as measured using actigraphy ($p < 0.05$).

Non-Pharmacological treatment

Cognitive behavioural therapy for insomnia (CBTi). Two studies deployed CBT-I as a treatment for insomnia post-TBI. Interestingly, both studies enrolled just 24 patients each. Following an 8-week course [24] and a 6-week course [25] programme, participants had significant reductions on the PSQI compared to the control group. In the Theadom study [25], no significant differences between groups were found on actigraphy data in terms of sleep duration (see Table 1 for risk of bias assessment in the studies).

Acupuncture

Zollman et al. [26] tested the effectiveness of acupuncture in a population of 20 post-TBI patients diagnosed with clinical insomnia. The intervention consisted of five weeks of bi-weekly acupuncture treatment which exhibited a favourable effect on the subjective perception of insomnia severity using the ISI score ($p < 0.01$). However, actigraphy data revealed total sleep time (TST) did not differ between the treatment and control groups after the intervention ($p = 0.54$). Both studies had a moderate risk of bias using GRADE criteria (Table 1).

Warm footbath

In 2017, Chiu et al. [27] tested the effectiveness of a warm footbath compared to usual care in a population of 23 post-TBI patients reporting insomnia. The cross-over, double-blind design consisted of 3 days of 30-min exposure to 41 °C footbath, 1–2 h before bedtime. In this study, actigraphy data revealed reduced sleep onset latency (SOL; $p < 0.001$) and significantly suppressed wake after sleep onset (WASO; $p = 0.006$) for the intervention. Sleep efficiency (SE) and total sleep time (TST) showed no significant differences between groups ($p > 0.05$). Both studies were of reasonable quality as assessed by GRADE criteria (Table 1).

Table 1
Risk of bias assessment of studies included in the review using GRADE criteria (BMJ 2019; 366).

Study	R	D	Mi	Me	S	O
Kemp et al. (2004) [22]	+	+	?	?	–	High
Grima (2018) [23]	+	+	+	+	+	Low
Nguyen et al. (2017) [24]	+	+	+	+	+	Low
Theadom et al. (2018) [25]	–	–	–	–	?	High
Zollman et al. (2012) [26]	+	–	+	+	+	Moderate
Chiu et al. (2017) [27]	+	–	+	+	+	Moderate
Jha et al. (2008) [28]	+	+	+	+	+	Low
Kaiser et al. (2010) [29]	+	+	+	+	+	Low
Menn et al. (2014) [30]	+	+	–	+	?	Moderate
Weber et al. (2016) [31]	?	?	–	–	?	High
Raikes (2019) [32]	–	?	?	+	+	High
Lequerica et al. (2015) [33]	+	+	+	?	?	High
Lee et al. (2005) [34]	+	?	?	+	+	High
Killgore et al. (2020) [36]	+	+	+	+	+	Low
Kataria et al. (2017) [37]	–	–	–	–	–	High
Hoffer et al. (2013) [38]	+	+	+	+	+	Low
Wolf et al. (2012) [39]	+	+	+	+	+	Low
Walker et al. (2018) [40]	+	+	+	+	+	Low
Sinclair et al. (2014) [41]	–	–	+	–	+	High
Shane et al. (2015) [42]	–	?	?	?	?	High
Bogdanova et al. (2017) [43]	–	?	?	?	?	High
Geib (2019) [44]	+	?	?	+	+	Moderate
Jonas et al. (2016) [45]	+	+	?	+	+	Moderate
Vuletic et al. (2016) [46]	–	–	?	+	+	High

Abbreviations.
R = bias arising from the randomisation process.
D = bias due to deviations from intended interventions.
Mi = bias due to missing outcome data.
Me = bias in measurement of the outcome.
S = bias in selection of the reported result.
O = overall risk of bias.
+ = accounted for in the study.
- = not accounted for in the study.
? = no information available in the study to make an informed assessment.

Table 2
Summary Results of Studies included in the Review.

	N (% male)	Mean Age, yrs (SD)	GCS Range, n (%)			Time post-TBI (SD)	Blinding	Follow up conducted	No of sleep measures used	
			Mild TBI	Moderate	Severe				Subjective	Objective
Kemp et al. (2004) [22]	7 (100%)	39.6 (nr)	2 (28.57%)	3 (42.86%)	2 (28.57%)	36.3 mths (8.9–73.2)	Double	No	1	0
Grima (2018) [23]	33 (67%)	37 (11)	2 (6.06%)	3 (9.09%)	28 (84.84%)	46 mths (nr)	Double	No	3	1
Nguyen et al. (2017) [24]	24 (66.67%)	43.87 (12.95)	5 (20.83%)	2 (8.33%)	17 (70.83%)	1390.17 days (1671.23)	Double	Yes (2 mths)	3	0
Theadom et al. (2018) [25]	24 (37.5%)	35.9 (11.8)	22 (91.67%)	2 (8.33%)	0	12.75 mths (8.995)	nr	No	1	1
Zollman et al. (2012) [26]	20 (45%)	T: 44.5 (15.15) C: 43.5 (16.1)	Not reported (nr)			T: 2.17 yrs (1.27) C: 3 yrs (1.85)	Single	Yes (1 mth)	1	1
Chiu et al. (2017) [27]	23 (34.78%)	35.9 (12.5)	18 (78.3%)	3 (13%)	1 (4.3%)	27.6 mths (34.8)	Double	No	3	1
Jha et al. (2008) [28]	51 (68.6%)	38.25 (12.20)	13 (25.5%)	12 (23.5%)	26 (51%)	5.77 yrs (4.97)	Double	Yes (4 wk open-label)	1	0
Kaiser et al. (2010) [29]	20 (85%)	T: 37 (9) C: 43 (19)	Not reported (nr)			T: 1.8 yrs (0.9) C: 2.0 yrs (1.2)	Double	No	1	3
Menn et al. (2014) [30]	117 (55%)	31.3 (10.54)	116 (99.15%)	1 (0.85%)	0	1–10 Years (nr)	Double	Yes (12 mths open-label)	1	1
Weber et al. (2016) [31]	30 (50%)	Not reported (nr)	30 (100%)	0	0	Less than 18 mths (nr)	nr	No	1	0
Raikes (2019) [32]	27 (33.3%)	26.85 (8.39)	27 (100%)	0	0	275.42 days (167.04)	nr	No	1	0
Lequerica et al. (2015) [33]	13 (nr)	42.5 (17.7)	7 (53.85%)	6 (46.15%)		62.1 mths (91.5)	Double	No	2	1
Lee et al. (2005) [34]	30 (80%)	34.8 (9.167)	24 (80%)	6 (20%)		32.2 mths (5.4)	Double	No	2	0
Killgore et al. (2020) [36]	32 (46.88%)	23.25 (7.25)	32 (100%)	0	0	6.75 mths (4)	Double	No	2	2
Kataria et al. (2017) [37]	19 (nr)	Not reported (nr)	Not reported (nr)			Not reported (nr)	Double	Yes (23 days)	1	1
Hoffer et al. (2013) [38]	81 (98.77%)	<24 h T: 24.92 (6.52) C: 23.58 (4.16) 26–72 h T: 27.68 (6.96) C: 25.42 (6.19)	81 (100%)	0	0	60 participants less than 24 h post-TBI (nr) 21 participants 26–72 h post-TBI (nr)	Double	No	1	0
Wolf et al. (2012) [39]	50 (96%)	28.3 (7.7)	47 (94%)	3 (6%)		3-71 mths (nr)	Double	No	1	0
Walker et al. (2018) [40]	71 (98.59%)	32.8 (7.3)	71 (100%)	0	0	26 mths (nr)	Double	Yes (6 mths)	2	1
Sinclair et al. (2014) [41]	30 (80%)	42 (13.6)	7 (23%)	8 (27%)	15 (50%)	1106 days (993.27)	Single	Yes (4 wks)	2	0
Shane et al. (2015) [42]	26 (46.15%)	21.6 (3.9)	26 (100%)	0	0	Less than 18 mths (nr)	nr	No	1	0
Bogdanova et al. (2017) [43]	8 (nr)	Not reported (nr)	8 (100%)	0	0	Not reported (nr)	Double	No	1	0
Geib (2019) [44]	60 (76.67%)	40 (nr)	60 (100%)	0	0	Greater than 3 mths (nr)	Single	Yes (4 wks)	1	1
Jonas et al. (2016) [45]	31 (88.37%)	34 (8.8)	43 (100%)		0	Not reported (nr)	Double	Yes (6 wks)	1	0
Vuletic et al. (2016) [46]	356 (93.26%)	29.35 (7.23)	356 (100%)	0	0	Less than 2 yrs (nr)	nr	Yes (6 mths)	1	0

Abbreviations: **GCS** = Glasgow Coma Scale; **TBI**Traumatic Brain Injury; **nr** = not reported; **sd** = standard deviation; **n** = sample size; **wks** = weeks; **mths** = months; **yrs** = years; **T**Treatment condition; **C**= Control condition.

Table 3
Summary of articles included in the review.

Study	Post-TBI Sleep condition	Intervention	Sleep measures	Results
Kemp et al., 2004 [22]	Insomnia	1 mth, crossover **melatonin** 5 mg/d vs **amitriptyline** 25 mg/d 2-wk washout	Sleep diary	Effect sizes showed melatonin enhanced daytime alertness compared to baseline ($d = 0.42$). Amitriptyline, improved sleep duration as measured by sleep diary compared to baseline ($d = 0.56$). No main treatment effect ($F(2,48) = 0.98$, $p > 0.05$), nor interaction ($F(2,48) = 2.2$, $p > 0.05$) was found.
Grima 2018 [23]	Chronic Insomnia	4 wk, crossover Prolonged release **melatonin** 2 mg/d vs placebo 48-hr washout	Sleep diary ESS PSQI Actigraphy	Melatonin significantly reduced global PSQI scores indicating improved sleep quality compared to placebo ($d = 0.46$; $p < 0.0001$). Melatonin had a significant effect on actigraphy measured sleep efficiency ($d = 0.28$, $p = 0.04$) but no effect on sleep onset latency ($d = 0.18$; $p = 0.23$). No treatment effect was found for daytime sleepiness on ESS ($d = 0.17$, $p = 0.15$).
Nguyen et al., 2017 [24]	Insomnia	8 wk, parallel **Cognitive Behavioural Therapy (CBT)** vs Treatment as Usual (TAU) Follow up 2 mths post-treatment	PSQI ISI ESS	Significant difference of 3.10 points on PSQI between groups post-treatment (95% confidence interval [CI], 1.50−4.70; $p < 0.01$) and 4.85 points at follow-up (95% CI, 2.56−7.14; $p < 0.01$). For the CBT condition, mean improvement at follow-up equated to a very large treatment effect (Hedges $g = 1.71$). Relative to TAU participants, CBT participants reported significantly reduced insomnia post-treatment by 3.12 points (95% CI, 1.29−4.95; $p < 0.01$). Improvements were maintained at follow-up with a mean difference of 5.96 points between groups (95% CI, 3.00−8.93; $p < 0.01$). Magnitude of change at the end point indicated a very large treatment effect (Hedges $g = 2.50$). There were no significant interactions on secondary measures of ESS ($p > 0.05$).
Theadom et al., 2018 [25]	Clinical Insomnia	8 wk, parallel **Cognitive Behavioural Therapy (CBT)** vs Education Only (EO) Intervention	PSQI Actigraphy	The CBT group experienced a significant reduction in self-reported sleep disturbance (mean individual change = −4.00; $F = 5.47$, $p = 0.04$) compared to controls (mean individual change = −1.50) with a moderate effect size of 1.17. There were no significant group differences on objective sleep onset, sleep efficiency, time awake or the number of awakenings ($p > 0.05$).
Zollman et al., 2012 [26]	Clinical Insomnia	5 wk, parallel **Acupuncture** 20min twice/weekly vs no treatment Follow up 1 mth post-treatment	ISI Actigraphy	ISI scores significantly decreased in the treatment group from baseline to post treatment ($Z = -3.07$; $p < 0.01$) and at 1-month follow up ($Z = -3.07$; $p < 0.01$) but did not reach significance in the control group ($p > 0.05$). However, ISI scores did not significantly differ between groups at-post treatment ($Z = -1.51$, $p = 0.14$) or at 1-month follow up ($Z = -1.78$; $p = 0.8$). Sleep time did not significantly differ between groups at post-treatment ($Z = -0.68$; $p = 0.54$).
Chiu et al., 2017 [27]	Insomnia	3 d, crossover **Warm footbath** vs usual care 3 d washout	ISI Actigraphy	The individuals in the warm footbath group had a reduced sleep onset latency (difference = −5.11 min) and a suppressed wake after sleep onset (difference = −2.57 min) in comparison with those in the usual care group ($p < 0.001$ and $p = 0.006$, respectively). No difference in sleep efficiency and total sleep time was found between the groups ($p > 0.05$).
Jha et al., 2008 [28]	Hypersomnia	8 wk, crossover **Modafinil** 400 mg/d vs placebo 4 wk washout Optional 4 wk open-label extension	ESS	Significant improvement in ESS score with modafinil post-treatment ($p = 0.02$), but not at follow up ($p = 0.56$). Insomnia was reported significantly more often with modafinil compared to placebo ($p = 0.03$).
Kaiser et al., 2010 [29]	Hypersomnia	6 weeks, parallel **Modafinil** 100 −200 mg/d vs placebo	ESS MWT PSG Actigraphy	Significant improvement with modafinil as measured by ESS score changes from baseline (treatment = −2.3 ± 2.3, placebo = 0.7 ± 1.8, $p = 0.005$), MWT mean sleep latency (treatment = 8.4 ± 9.6, placebo = 0.4 ± 6.2 p=0.04) and decreased sleep pressure as measured by PSG ($p = 0.03$) when compared to placebo group. No significant difference was found in the time awake per 24 h across treatment groups as measured by actigraphy ($p = 0.33$).

(*continued on next page*)

Table 3 (*continued*)

Study	Post-TBI Sleep condition	Intervention	Sleep measures	Results
Menn et al., 2014 [30]	Hypersomnia	12 wk, parallel **Armodafinil** 50 mg/d vs **Armodafinil** 150 mg/d vs **Armodafinil** 250 mg/d vs placebo Optional 12 mth open-label extension	ESS MSLT	The change from baseline in the ESS total score post-treatment and at follow-up did not show statistically significant differences between the armodafinil and placebo treatment groups at either time point ($p > 0.05$). Significant dose-dependent improvement on MSLT scores were found post-treatment for 150 mg ($p = 0.0371$) and 250 mg ($p = 0.0005$) compared to placebo.
Weber et al., 2016 [31]	Hypersomnia	6 wk, parallel **Blue light therapy** 30 min/d vs Amber light therapy 30 min/d	ESS	Significant reduction in ESS scores for the blue compared to the amber light group ($p = 0.04$). 88% of those exposed to blue light showed a decline in sleepiness scores whereas only 40% of those exposed to amber light showed a decline ($p = 0.008$).
Raikes 2019 [32]	Hypersomnia	6 wk, parallel **Blue light therapy** 30 min/d vs Amber light therapy 30 min/d	ESS	Individuals in the blue light condition had significantly improved daytime sleepiness ($t = 2.46$, $p = 0.025$) compared to those in the amber light condition. Bivariate correlations indicated that improvements in ESS scores were significantly associated with improvements in somatic symptoms ($r = 0.49$, $p = 0.014$).
Lequerica et al., 2015 [33]	Circadian rhythm disorder	3 wk, crossover **Ramelteon** 8 mg/d vs placebo 2 wk washout	PSQI Sleep log Actigraphy	For total sleep time, a significance difference was noted between ramelteon and placebo ($F_{1,12} = 10.67$, $p = 0.007$, $n_p^2 = 0.47$). For objectively measured sleep onset latency, significant main effects were noted for treatment ($F_{1,12} = 9.95$, $p = 0.008$, $\eta_p^2 = 0.45$) however for subjective SOL, no significant main effect was found ($p > 0.05$, $n_p^2 = 0.17$).
Lee et al., 2005 [34]	Circadian rhythm disorder	4 wk, parallel **Methylphenidate (MPD)** 5−20 mg/d vs **Sertraline** (**SER**) 25−100 mg/d vs placebo	CESS LSEQ	All three groups showed significant improvements from baseline in quality of sleep and integrity of behaviour following wakefulness as measured by LSEQ (MPD and SER $p < 0.01$; Placebo $p < 0.05$). Getting to sleep was significantly improved only in the SER group ($p < 0.05$). Ease of waking in the morning from sleep was significantly improved in MPD and placebo groups ($p < 0.01$ and $p < 0.001$ respectively) and MPD group showed a significant superior effect to the SER group in the post hoc analyses ($p = 0.009$). Daytime sleepiness was significantly improved in MPD and the placebo groups as well ($p < 0.01$ and $p < 0.05$, respectively). No significant group effects were found across measures ($p > 0.05$).
Killgore et al., 2020 [36]	Circadian rhythm disorder	6 wk, parallel **Blue light therapy** 30 min/d vs Amber light therapy 30 min/d	ESS SSS MSLT Actigraphy	Participants in the blue light condition were phase advanced in sleep onset and offset times, on average falling asleep 57.5 min earlier ($p = 0.004$) and awakening 55.9 min earlier by the final week of treatment compared to baseline ($p = 0.037$). Those in the amber condition showed no significant difference from baseline in sleep onset and offset times post-treatment ($p = 0.508$ and $p = 0.576$, respectively). There were no significant changes in mean total sleep time (TST) per night between pre- and post-treatment assessments, regardless of light-condition ($p > 0.05$). Relative to placebo, the blue light intervention led to reduced typical daytime sleepiness; $F(1,26) = 5.49$, $p = 0.027$. Only the second MSLT, occurring in the early afternoon (1:50 p.m) showed a significant light-condition x time interaction, $F(1, 26) = 5.26$, $p = 0.030$.
Kataria et al., 2017 [37]	Obstructive sleep apnea	7 d, crossover **Reminder text message** vs standard of care (SOC) Follow up 30 days post-baseline	ESS Mean overall percent compliance Percent compliance >4 h per night	Mean overall percent compliance during the first 7 days was significantly greater in the reminder group than the SOC group (83.9% vs. 55.4%, $p = 0.04$).Mean overall percent compliance at 30 days was also greater in the reminder group, but not statistically significant (58.9% vs. 36.9%, $p = 0.22$). The reminder group demonstrated greater 4-h threshold compliance at 7 days (48.2% vs. 30.4%, $p = 0.29$) and 30 days (36.9% vs. 15.4%, $p = 0.13$), although neither reached significance. Compared to baseline, reminder group ESS scores improved to the normal range with a medium effect size ($d = -0.39$).

Table 3 (*continued*)

Study	Post-TBI Sleep condition	Intervention	Sleep measures	Results
Hoffer et al., 2013 [38]	Fatigue/Sleep disturbance	7 d, parallel **N-acetyl cysteine (NAC)** vs placebo	Self-reported sleep complaints	Despite the low prevalence of abnormal sleep in this series, it was significantly less likely in the NAC treated subject population on day seven (1/41) than in the placebo treated subjects (7/40; exact test, $p = 0.029$)
Wolf et al., 2012 [39]	Sleep disturbance	8 wk, parallel **Hyperbaric Oxygen (HBO^2)** vs sham exposure 40 sessions	ImPACT scale items: Trouble falling asleep Sleeping more than usual Sleeping less than usual Drowsiness	Using ImPACT scale means, significant post-treatment improvements were found for sleeping less than usual and trouble falling asleep in both conditions (Control: $p = 0.038$, $p < 0.001$; HBO2: $p = 0.03$, $p = 0.01$, respectively). Sleeping more than usual showed an improvement for the control condition only ($p = 0.038$). No significant improvements post-treatment were found in either condition for drowsiness ($p > 0.05$). No significant differences post-treatment were found between HBO^2 and Sham on measures of drowsiness ($p = 0.08$), trouble falling asleep ($p = 0.43$), sleeping less than usual ($p = 0.77$) or sleeping more than usual ($p = 0.33$).
Walker et al., 2018 [40]	Sleep disturbance	13 wk, parallel **Hyperbaric Oxygen (HBO^2)** vs sham chamber intervention Follow up 6 mths post-treatment	PSQI Sleep diary Actigraphy	Significant between-intervention differences in changes in PSQI scores post-treatment were found on sleep quality ($p = 0.003$), sleep disturbances ($p = 0.002$), and daytime dysfunction ($p = 0.002$) as well as for the global score ($p = 0.02$). Significant differences were sustained at follow-up for sleep quality ($p = 0.04$) and sleep disturbances ($p = 0.001$). Improvement favoring HBO^2 over sham at follow-up was additionally revealed for the sleep latency score ($p = 0.02$). Actigraphy, sleep diary and PSQI measures of sleep duration, wake time after sleep onset and sleep maintenance efficiency revealed no significant difference in change scores between groups post-treatment ($p > 0.05$) nor at follow-up ($p > 0.05$)
Sinclair et al., 2014 [41]	Fatigue/Sleep disturbance	4 wk, parallel **Blue light therapy** 45 min/d vs yellow light therapy 45 min/d vs no treatment Follow up 4 wks post-treatment	ESS PSQI	The blue light group compared to no treatment controls, revealed a significantly greater linear drop in daytime sleepiness by 1.46 units per week, $p < 0.01$. PSQI scores found no evidence of significant changes in symptom severity across time that were unique to any treatment condition ($p > 0.05$).
Shane et al., 2015 [42]	Sleep disturbance	6 wk, parallel **Blue light therapy** 30 min/d vs sham placebo light therapy 30 min/d	ESS	There was a significant treatment × time interaction on ESS scores ($F(1,24) = 4.485$, $p = 0.04$). Individuals in the blue light group showed a 15.08% decrease in daytime sleepiness ratings on the ESS compared to a 4.26% increase for individuals in the sham placebo light group ($p = 0.015$).
Bogdanova et al., 2017 [43]	Sleep disturbance	8 wk, parallel **transcranial plus intranasal red/near-infrared light-emitting diode (NIR-LED)** vs sham LED	PSQI	The Active LED treatment group showed significant improvement on sleep (PSQI total) ($p < 0.05$) post-treatment as compared to pre-treatment. No significant changes on these measures were observed in the Sham LED control group ($p > 0.05$).
Geib 2019 [44]	Sleep disturbance	5 wk, parallel **Verum acupuncture** twice/wk vs sham needling procedure Follow up 4 wks post-treatment	PSQI Actigraphy	PSQI score changes on sleep quality showed a significant group effect (verum group = +4.4 points, sham group = +2.4 points; $p = 0.04$). The presence of PTSD had no influence on the result ($p = 0.79$). Actigraphy measures showed a significant group effect on sleep efficiency with an improvement of 2.7% under verum acupuncture and a deterioration of 5.3% in the Sham group ($p = 0.016$). Actigraphy measures of sleep latency, time in bed and sleep duration showed no differences between the groups ($p > 0.05$). At follow-up ($n = 52$), no significant difference between verum and sham acupuncture could be found in terms of sleep quality and sleep efficiency ($p > 0.05$).
Jonas et al., 2016 [45]	Sleep disturbance	10 treatments 6 wk, parallel **Auricular Acupuncture (AA)** vs **Traditional Chinese Acupuncture (TCA)** vs Usual Care (UC) Follow up 6 wks post-treatment	PSQI	There was no statistically significant difference in PSQI score changes between groups ($p > 0.05$). Small to medium effect sizes were found between conditions; TCA vs UC ($d = 0.36$), AA vs UC ($d = 0.26$) and Acupuncture vs UC ($d = 0.33$).

(*continued on next page*)

Table 3 (*continued*)

Study	Post-TBI Sleep condition	Intervention	Sleep measures	Results
Vuletic et al., 2016 [46]	Sleep disturbance	6 mth, parallel **Problem Solving Treatment (PST)** vs Education Only (EO) Follow up 6 mth post-treatment	PSQI	There was significant difference between PST and the EO group post-treatment (p=0.003), but not at follow-up ($p > 0.05$). There was significant improvement in sleep quality (PSQI) in the treatment group post-treatment ($p = 0.001$), but not over the follow-up ($p = 0.65$). Low sleep quality (PSQI) was related to concussion symptoms (pain, depression, and posttraumatic stress disorder) for all time points ($p < 0.0001$).

Abbreviations: **EES** = Epworth Sleepiness Scale; **ISI**= Insomnia Severity Index**; MSLT** = Multiple Sleep Latency Test; **MWT** = Maintenance of Wakefulness Test; **PSG**= Polysomnography; **PSQI**= Pittsburgh Sleep Quality Index; **LSEQ**Leeds Sleep Evaluation Questionnaire; **CESS** Chinese version of the Epworth Sleepiness Scale; **ImPACT**Immediate Post-Concussion Assessment and Cognitive Testing; **TBI**Traumatic Brain Injury; **wks** = weeks; **mths** = months; **yrs** = years.

Treatment of hypersomnia/excessive daytime sleepiness (EDS) post-TBI

Pharmacological treatments

Modafinil/armodafinil. Three well-conducted studies (Table 1) over a decade ago each, demonstrated that treatment with modafinil/armodafinil resulted in a moderate but significant reduction in sleepiness post-TBI as measured using the ESS. However, follow-up in the two modafinil studies did not demonstrate persistence of the effect. Numbers in both studies were small: n = 51 [28] and n = 20 [29]. Objective sleep measures demonstrated a significant reduction in sleep pressure in both studies, but no increase in wakefulness as measured using actigraphy. In the study by Menn et al. [30], using armodafinil, a reduction in sleepiness was demonstrable on the MSLT at 12 weeks for the 150 mg dose ($p = 0.0371$) and even more so for the 250 mg dose ($p = 0.0005$).

Kaiser et al. [29] administered modafinil or placebo daily to 20 participants who reported EDS or fatigue following TBI for a 6-week period. Measures included ESS, maintenance of wakefulness test (MWT), PSG, and actigraphy. Modafinil was found to significantly improve EDS as measured by the ESS (p=0.005), and MWT ($p = 0.04$) and reduced sleep pressure as measured by PSG ($p = 0.03$) compared to the placebo group. No significant difference was found in the time awake over 24 h across treatment groups as measured by actigraphy ($p = 0.33$).

Non-pharmacological treatment

Blue light therapy (BLT). Two studies reported trialling blue light therapy for 6 weeks to reduce sleepiness, comparing it to amber light therapy [31,32]. Despite this unusual comparator, both studies revealed a significant improvement in sleepiness as measured by the ESS in 30 and 27 participants, respectively. Both studies revealed high risk of bias (Table 1).

Circadian rhythm disorder (CRD) treatment

Pharmacological treatment

Ramelteon. Lequerica et al. [33], investigated the effectiveness of ramelteon (a sedative medication and a synthetic agent that functions at the melatonin receptor) on sleep and daytime functioning in 13 mild to severe post-TBI patients with reported sleep problems (PSQI scores greater than 5). Three weeks of ramelteon treatment significantly improved objective measures of total sleep time, compared to the placebo group. However, significant differences between treatment groups on subjective sleep latency measures were not found ($p > 0.05$). Unfortunately, in this study it was impossible to determine whether there was any bias due to missing outcome data or in the selection of the reported results (Table 1).

Methylphenidate and sertraline

In 2005, Lee et al. [34] recruited 30 patients who showed an 'intermediate' circadian rhythm [35] following TBI. Participants were randomly allocated to methylphenidate, sertraline, and placebo treatment groups. Interestingly, neither medication has any evidence base for its use in the management of CRDs. Outcome measures were scores on the Leeds Sleep Evaluation Questionnaire and the Chinese version of the ESS. Four-week parallel treatment periods resulted in significant improvements in 'getting to sleep' on sertraline ($p < 0.05$), 'awakening in the morning from sleep' on methylphenidate and placebo ($p < 0.01$ and $p < 0.001$, respectively) and a reduction in daytime sleepiness on methylphenidate and placebo ($p < 0.01$ and $p < 0.05$, respectively). Study quality may have suffered due to bias in deviation from intended interventions and missing data, both aspects of which were not fully discussed (Table 1).

Non-pharmacological treatment

Blue light therapy. In a sample of 32 participants, Killgore et al. [36] conducted a 6-week blue vs amber light treatment period to re-entrain circadian rhythm and reduce sleep problems in this high quality study(Table 1). Significantly earlier awakening and a reduction in daytime sleepiness were found by the final week of treatment for the blue light condition ($p = 0.037$). No significant changes in total sleep time were found using actigraphy pre- and post -assessment in either condition ($p > 0.05$).

Obstructive sleep apnoea (OSA) following TBI

Non-pharmacological treatment

Continuous positive airway pressure (CPAP). No RCTs have been published to date assessing the beneficial effects of CPAP in a post-TBI, sleep disordered breathing population. Kataria et al. [37] conducted a text message reminder service vs no reminder to assess CPAP adherence in 19 newly-diagnosed OSA veterans with chronic TBI. During the 7-day period of nightly reminders, the mean overall percent compliance was significantly greater in the reminder group; 83.9% vs 55.4%; $p = 0.04$. Significant improvements in overall percent compliance between groups were not maintained at 30 days post-baseline; nor was there any significant increase on the suggested minimum 4-h threshold compliance with CPAP at 7 days or 30 days for the reminder group ($p = 0.29$ and $p = 0.13$, respectively). There was limited information on biases inherent to the study in the commonest parameters assessed (Table 1).

Narcolepsy, Periodic Limb Movement (PLM) and Nightmare disorders post-TBI

At the time of this review, no RCTs had been published on the use of either pharmacological or non-pharmacological treatment in any of these sleep conditions. Of 8 studies investigating military personnel, no primary or secondary measures were included for any changes relating to dreams, nightmares or nightmare-related disorders.

Undefined post-TBI sleep disturbances

Pharmacological treatments

N-acetyl cysteine (NAC). Hoffer et al. [38] conducted a 7-day treatment period of NAC infusion compared to placebo in 81 service members suffering from mTBI. Participants had suffered head trauma less than 24–72 h prior to treatment. 'Abnormal sleep' (not defined in the study) was significantly less likely following NAC compared to placebo ($p = 0.029$), however the initial prevalence of abnormal sleep was low ($n = 3$). All biases were accounted for thoroughly (Table 1).

Non-Pharmacological treatments

Hyperbaric oxygen therapy (HBO_2)

Two well-conducted (Table 1) published trials examined the effects of HBO2 on sleep post-TBI [39,40]. Wolf et al. [39] did not show any significant differences in subjective sleep measures between HBO2 treatment and sham treatment. In fact, excessive daytime somnolence improved in the placebo group. By contrast, Walker et al. [40], using the PSQI recorded improvements in sleep quality ($p = 0.003$), sleep disturbances ($p = 0.002$), daytime dysfunction ($p = 0.002$) as well as global scores ($p = 0.02$). Sustained significant differences were found at follow-up for sleep quality ($p = 0.04$) and sleep disturbances ($p = 0.001$). However, objective measures of sleep quality did not change at all.

Light therapy

A RCT using blue and yellow light therapy and a no-treatment group showed a significant decrease in daytime sleepiness, as measured by the ESS, in those treated with blue light compared to no treatment ($p < 0.01$) [41].

Shane et al. [42], investigated the effect of blue light therapy (BLT) compared to sham placebo light therapy (SPLT) on 26 subjects presenting with co-morbid sleep difficulties following mild TBI in the previous 18 months. Daytime sleepiness ratings significantly decreased in the BLT group compared to a small increase in the SPLT group ($p = 0.015$).

Bogdanova et al. [43] conducted a transcranial plus intranasal red/near-infrared light-emitting diode (NIRS-LED) vs sham-LED pilot study on eight veterans over 8 weeks. PSQI total scores showed a significant improvement in sleep at one-week post-treatment with NIRS-LED ($p < 0.05$). It was difficult to ascertain risk of bias in the latter three studies from information provided and as such, caution should be exercised in interpreting the results (Table 1).

Acupuncture

Two studies have been conducted to date using two different types of acupuncture – Verum [44] and Traditional Chinese Acupuncture (TCA) [45]. Verum acupuncture led to significant improvement on the PSQI for sleep quality and sleep effectiveness but there was no difference between sham and treatment groups when it came to actigraphy. The TCA study [45], demonstrated no difference in sleep outcomes between sham and treatment groups at 6 weeks using the PSQI. Study quality was moderate with most biases accounted for (Table 1).

Problem-solving treatment

Vuletic et al. [46] conducted a telephone problem-solving treatment (PST) vs education only (EO) to 356 soldiers with combat-related mild-TBI. The study resulted in significant, subjective improvements in PSQI scores in the PST group at 6 months compared to baseline ($p = 0.001$) and compared to EO post-treatment ($p = 0.003$). Significant improvements were not maintained at follow-up at 12 months ($p = 0.65$ and $p = 0.4$, respectively). Unfortunately, the results need to be interpreted with some reservation due to difficulties in ascertaining bias (Table 1).

Methodological considerations of studies in this review

The GRADE criteria (Table 1) revealed that overall, the studies included in this analysis consistently failed to include clear and restrictive inclusion/exclusion criteria, consistent use of outcome measures and long-term follow-up. We did not formally assess publishing bias, but it is always a possibility in the context of any research.

Patient inclusion criteria in the studies

Mean time since injury was often unrecorded or comprised a wide range (e.g., 77 days to 20.47 years [24]). TBI severity across the RCTs in this review was broad and not controlled for statistically in any of the studies when it came to analysis. No power calculations were recorded. Furthermore, the distribution of mixed-severity samples tended to be heavily skewed towards mild injury.

Use of comparable outcome measures across studies

While symptom prevalence and severity in relation to sleep was well recorded, appropriate subjective and objective measures were not utilised to the same extent. On average per study, 0.58 objective sleep measures were used compared to 1.46 subjective sleep measures to record sleep changes. While most studies included subjective, standardised sleep measures such as the PSQI and ESS, only twelve studies used objective sleep measures such as actigraphy and the maintenance of wakefulness test (MSLT).Whilst subjective improvements were often significant, only six of the eleven studies demonstrated significant improvement in sleep using objective measures.

Treating sleep and its effect on co-morbidities

A few studies investigated treatment effects on sleep in relation to other conditions such as fatigue [23, 24 28, 29,(study quality good) and 42], depression [23, 24 (study quality good), 34, 41, 46], headaches [45], quality of life [25,45] and cognitive function [25,26,33,34,41]. Findings suggested that treatments specific to sleep can result in significant improvements to cognition [26, 33; study quality high], fatigue [23, 24 (study quality high), 28, 41], headaches [45] and depression [23, 24 (study quality high), 34, 46]. Two studies identified that there was a significant association between sleep and somatic symptoms, concussion, pain, depression and post traumatic stress disorder [32,46]. Unfortunately, risk of bias in both latter studies was high (Table 1). Apart from evaluating fatigue, no study used the same two methods of measurement for the co-morbities investigated.

Follow-up

Ten studies conducted post-trial follow-up of participants. Of these, only three studies found maintenance of significant improvements at 8 weeks and 6 months post-treatment respectively in those who had received the intervention [33,35,40].

Discussion

This systematic review differs from previous reviews of sleep interventions for post-TBI sleep-associated problems in that it has included both pharmacological and non-pharmacological treatment trials addressing a spectrum of sleep disorders. To our knowledge, no randomised clinical trials on sleep-apnoea, periodic limb movement disorder and parasomnias in the TBI population have been published. The majority of treatment trials included in this review investigated subjectively reported, dysregulated sleep and problematic sleep symptoms as opposed to specific sleep disorders. While the number of studies identified is somewhat low, the results of some of the studies suggest that commonly used interventions in the general population can be applied with success to a post-TBI population.

Sleep disturbances and disorders post-TBI are common and their prevalence is estimated to be even higher than in the general population [7]. On the basis of this review, however, the effectiveness of treating sleep disorders appears to be methodologically challenging and different types of TBI appear to have been studied in greater depth, compared to others e.g., no randomised, controlled treatment trials of sleep disturbances in sports-related TBI have been published to date [47].

The limitations encountered in the review with respect to study populations (often limited characterisation and small numbers) and the methods utilised for recording sleep may be a reflection of numerous obstacles encountered in integrating a sleep history into standard neurological, rehabilitation and psychiatric assessments of people post-TBI. In turn, this could be a reflection of the age at TBI, co-morbidities and aetiology of the trauma (e.g., sport vs war vs accident vs drug/alcohol related). One could also speculate that there is a lag in the education of health professionals working with people with TBI as well as overall lack of recognition of the importance of sleep and quality of sleep in their management, both acutely and chronically. This clearly also entails limited recognition of the importance of sleep and the role disordered sleep plays in increasing the risks of severe affective disorders [48], risk of suicide [49], and chronic neurodegeneration post-TBI [50]. Finally, there is some evidence that sleep disorders are dynamic post-TBI. For example, in a prospective study of consecutive patients with moderate to severe TBI, 84% had a circadian rhythm disorder (CRD) on commencing rehabilitation, 63% had a moderate to severe CRD during the following three weeks, which fell to 59% at four weeks [51]. In another study which surveyed over 300 patients with moderate-severe TBI, 11% had insomnia at one-year post-injury and 24% at two years post-injury [52].

Another consideration is that the pathophysiology of sleep disruption in TBI is poorly understood, making the choice of effective treatments difficult, reflected in the limitations in study design reviewed in this paper. Both sleep *per se* and the circadian rhythm can be affected to varying degrees as consequence of head injury. Circadian rhythm disruption is common in the acute phase of TBI; in the first 10 days after moderate to severe TBI, actigraphy recordings have demonstrated severe fragmentation of the sleep–wake cycle [53]. Lower melatonin production (measured in saliva) has been demonstrated up to one year post-TBI in association with lower sleep efficiency, increased wake after sleep onset as well as anxiety and depression [54]. Clearly, direct damage to the suprachiasmatic nucleus and hypothalamus will also disrupt circadian regulation of sleep–wake cycles.

Regardless of severity, 30–60% of patients post-TBI will suffer from insomnia, and the frequency will also change according to TBI aetiology [17]. Insomnia tends to be more common in mild TBI [17]. Interestingly, objective tests (e.g., polysomnography) do not necessarily correlate with subjective symptom reports based on clinical history or questionnaire [55]. The aetiology of insomnia is likely to be multifactorial and includes psychological sequelae of trauma, generalised anxiety, injury to the fronto-basal and antero-temporal regions of the brain and increased light and noise sensitivity.

On the opposite end of the spectrum, hypersomnia plagues about 32% of post-TBI patients [56]. The aetiology again is diverse and may include injury to the reticular activating system (RAS), a reduction in hypocretin producing cells (up to 30%) and direct damage to the tubero-mammillary neurones producing histamine and hypocretin in the lateral hypothalamus. Testing for hypersomnolence is generally undertaken in a sleep laboratory using strictly defined criteria as established by the AASM in 2005 including: actigraphy and sleep diary prior to overnight PSG followed the next day by the multiple sleep latency test (MSLT) [57]. Screening for drugs of abuse is crucial. However, in TBI, there may be issues with stopping pain medications, REM-suppressant drugs and additional problems in dealing with disability which may invalidate the test, making it difficult to establish a diagnosis and hence instigate correct management.

Finally, obstructive sleep apnoea appears to be more common in the post-TBI population than in the general population [7] and may arise as a consequence of weight gain due to immobility, depression, over-eating, damage to the hypothalamus and direct damage to the craniofacial complex and muscles of the upper airway and nerves controlling them.

With respect to the importance of sleep quality and sleep cycling *per se* in terms of recovery post-TBI, current speculation implicates the glymphatic system and meningeal lymphatics as integral to optimising brain function [58]. The glymphatic system, radically suppressed during wakefulness and 90% more active during sleep, particularly slow wave sleep, clears the brain parenchyma of excess fluid and macroscopic waste including beta-amyloid and tau, draining into the meningeal lymphatic system [59]. The latter regulates tissue homeostasis in the brain and maintains immune surveillance by draining fluid, macromolecules and immune cells from the CNS into the cervical lymph nodes [60,61]. Integral to the function of the glymphatic system is aquaporin-4 (AQP-4), playing a critical role in the maintenance of the efflux and influx pathways [61]. TBI has been to shown to result in mislocalization of AQP-4, resulting in the promotion and acceleration of neurodegeneration and increasing amyloid-beta and tau pathology [62].

Equally important is the hypocretin system. Hypocretin is not only central to the regulation of sleep and wakefulness, it is increasingly recognised as integral to the waste clearance function of the glymphatic system [63]. With any pathological shift in hypocretin levels, glymphatic flow appears to be compromised, leading to the development of neurodegeneration [64]. Thus, given the proposed heightened functionality of the glymphatic system during sleep, sleep becomes central to recovery from TBI.

Having established the importance of sleep duration and quality, as well as its appropriate timing in TBI as discussed above, it appears that it should be the primary focus of post-injury care and rehabilitation. However, treatment of sleep and circadian dysfunction and sleep disorders is not part of any guideline for post-TBI assessment or rehabilitation. This might

explain the poor recognition to date of the importance of longitudinal studies and adequately powered trials of treating sleep in TBI. Assessment of patients post-TBI should include routine questions about sleep quality and sleep disorders questionnaires, bearing in mind that the majority of instruments developed to assess sleep have only been validated in non-TBI populations. This might also explain the contrast between reported subjective measures and objective measures when it comes to sleep in patients post-TBI. Objective measurement tools should include polysomnography, particularly when sleep is to be recorded, actigraphy (when the focus is on circadian misalignment) and sleep diaries. Further investigation, using MSLT and the maintenance of wakefulness test as well as tests of attention/alertness (e.g., SAART, Osler test) [65] may also be appropriate. Instruments to measure fatigue, tiredness, sleepiness and the effect of mood, anxiety, pain and depression, injury severity, as well as premorbid personality or personality changes resulting from TBI need to be developed and validated. Large trials incorporating appropriate power calculations can now be planned based on some of the studies reported in this review. Time since injury, degree of injury and severity of the sleep disorder in the context of co-morbidities need to be adequately documented and controlled for in any interventional research. We would also propose collaboration across several specialties - sleep, rehabilitation, neurology, psychology and psychiatry in the first instance - when designing trials of treatment for sleep disorders in TBI.

Limitations of this review

The main limitation of this review has been the inability to undertake meta-analysis due to the heterogeneity in data across the studies. Not including unpublished studies on some common sleep disorders may also have introduced bias. We have addressed limitations in the interventions trialled for sleep disorders and sleep disturbances post-TBI in the studies included. We did not explore any reported effects of treating sleep disturbance on co-morbidities in the post-TBI population in detail; this was difficult in view of the inconsistency of the evaluation techniques utilised.

Notwithstanding these limitations, we believe that a few of the reported interventions have demonstrated some efficacy in the treatment of sleep problems post-TBI. Blue light therapy showed significant improvement in sleep in patients with mild TBI and may be useful in the treatment of hypersomnia, CRD and general sleep disturbance post-TBI. Other treatments that have shown promising findings are CBT for insomnia, modafinil for insomnia, HBO_2 for general sleep complaints and verum acupuncture. Finally, it is important to note that of 24 studies included in this review, 11 showed high risk of bias using GRADE criteria, five moderate risk of bias and only 7 were of high quality, namely one study trialling melatonin [23], one study demonstrating the effectiveness of CBT-I [24], two studies on the stimulants modafinil and armodafinil respectively [28,29], one study using blue light therapy [36], one study using a NAC infusion acutely post-TBI [38] and two studies on the effects of hyperbaric oxygen in treating TBI [39,40].

Based on this review, it is the authors' considered opinion that post-TBI sleep problems are vastly understudied. The reasons for this are likely multifactorial and may include lack of *routinely* incorporating a detailed sleep history in assessing TBI patients. Despite some interventions showing promising results, patient sample heterogeneity and lack of long-term efficacy data limits their uncontested application in clinical practice. Finally, like others before us [55] we have noted the complete absence of any studies documenting an evidence-base for managing restless legs syndrome, OSA and parasomnias in patients post-TBI.

Practice points

- Sleep disorders *frequently* described post-TBI include obstructive sleep apnoea (OSA), narcolepsy, insomnia, hypersomnia, and circadian-rhythm disorders.
- Promising treatments for these disorders include cognitive behavioural therapy, blue light therapy, melatonin and modafinil.
- Objective measures of sleep are infrequently used in studying sleep disruption post-TBI and when used, rarely support significant subjective improvements.
- Most randomised, controlled studies do not include longitudinal data on interventions reported as initially beneficial.
- Many randomised, controlled studies in this area fail to implement and control for inter-group variation such as severity of brain injury, time since injury, sleep symptom prevalence and sleep symptom severity and co-morbidities such as depression, pain and anxiety.

Research agenda

- There is significant scope for devising large, randomised, controlled trials in a variety of sleep disorders experienced by patients post-TBI.
- Future research must be founded on a robust methodological approach with sample sizes allowing for generalisability of the findings in the post-TBI group as well as comparison with the non-TBI population.
- Inter-disciplinary collaboration in designing treatment trials post-TBI is strongly recommended, incorporating expertise from across specialities (sleep, neurology, rehabilitation, psychology, psychiatry)
- An evidence-base for specific treatment modalities for restless legs syndrome, OSAS and parasomnias post-TBI is completely lacking and represents unique opportunities for research.
- There is tremendous opportunity for studying the glymphatic and hypocretin systems in TBI vis-à-vis sleep disruption and eventual targeting of various components in the pathway for future intervention

Conflicts of interest

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

References

[1] Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. Dis Model Mech 2013;6:1307–15.
[2] Humphreys I, Wood RL, Phillips CJ, Macey S. The costs of traumatic brain injury: a literature review. Clinicoecon Outcomes Res 2013;5:281–7.
[3] Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil 2006;21:375–8.
[4] Fazel S, Lichtenstein P, Grann M, Långström N. Risk of violent crime in individuals with epilepsy and traumatic brain injury: a 35-year Swedish population study. PLoS Med 2011;8:e1001150.

* The most important references are denoted by an asterisk.

[5] Arriola VD, Rozelle JW. Traumatic brain injury in United States operation enduring freedom/operation Iraqi freedom (OEF/OIF) hispanic veterans-A review using the PRISMA method. Behav Sci 2016;6:3.

*[6] Parsonage Michael. Traumatic brain injury and offending - an economic analysis. Retrieved from, https://www.centreformentalhealth.org.uk/traumatic-brain-injury; 2016.

*[7] Mathias JL, Alvaro PK. Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: a meta-analysis. Sleep Med 2012;13:898–905.

[8] Chaput G, Giguère JF, Chauny JM, Denis R, Lavigne G. Relationship among subjective sleep complaints, headaches, and mood alterations following a mild traumatic brain injury. Sleep Med 2009;10:713–6.

[9] Livingston WS, Rusch HL, Nersesian PV, Baxter T, Mysliwiec V, Gill JM. Improved sleep in military personnel is associated with changes in the expression of inflammatory genes and improvement in depression symptoms. Front Psychiatr 2015;6:59.

[10] Zeitzer JM, Friedman L, O'Hara R. Insomnia in the context of traumatic brain injury. J Rehabil Res Dev 2009;46:827–36.

[11] Sheng P, Hou L, Wang X, Wang X, Huang C, Yu M, et al. Efficacy of modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: a systematic review and meta-analysis. PLoS One 2013;8:e81802.

[12] Borghol A, Aucoin M, Onor I, Jamero D, Hawawini F. Modafinil for the improvement of patient outcomes following traumatic brain injury. Innov Clin Neurosci 2018;15:17–23.

*[13] Bhatnagar S, Iaccarino MA, Zafonte R. Pharmacotherapy in rehabilitation of post-acute traumatic brain injury. Brain Res 2016;1640(Pt A):164–79.

[14] Driver S, Stork R. Pharmacological management of sleep after traumatic brain injury. NeuroRehabilitation 2018;43:347–53.

[15] Thomas A, Greenwald BD. Nonpharmacological management of sleep disturbances after traumatic brain injury. NeuroRehabilitation 2018;43:355–60.

[16] Lowe A, Neligan A, Greenwood R. Sleep disturbance and recovery during rehabilitation after traumatic brain injury: a systematic review. Disabil Rehabil 2020;42:1041–54.

[17] Ouellet MC, Beaulieu-Bonneau S, Morin CM. Sleep-wake disturbances after traumatic brain injury. Lancet Neurol 2015;14:746–57.

[18] Orff HJ, Ayalon L, Drummond SP. Traumatic brain injury and sleep disturbance: a review of current research. J Head Trauma Rehabil 2009;24:155–65.

[19] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.

[20] Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. Sleep Med Rev 2016;25:52–73.

[21] Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011;34:601–8.

[22] Kemp S, Biswas R, Neumann V, Coughlan A. The value of melatonin for sleep disorders occurring post-head injury: a pilot RCT. Brain Inj 2004;18:911–9.

[23] Grima NA, Rajaratnam SMW, Mansfield D, Sletten TL, Spitz G, Ponsford JL. Efficacy of melatonin for sleep disturbance following traumatic brain injury: a randomised controlled trial. BMC Med 2018;16:8.

[24] Nguyen S, McKay A, Wong D, Rajaratnam SM, Spitz G, Williams G, et al. Cognitive behavior therapy to treat sleep disturbance and fatigue after traumatic brain injury: a pilot randomized controlled trial. Arch Phys Med Rehabil 2017;98:1508–17.e2. https://doi.org/10.1016/j.apmr.2017.02.031.

[25] Theadom A, Barker-Collo S, Jones K, Dudley M, Vincent N, Feigin V. A pilot randomized controlled trial of on-line interventions to improve sleep quality in adults after mild or moderate traumatic brain injury. Clin Rehabil 2018;32:619–29.

[26] Zollman FS, Larson EB, Wasek-Throm LK, Cyborski CM, Bode RK. Acupuncture for treatment of insomnia in patients with traumatic brain injury: a pilot intervention study. J Head Trauma Rehabil 2012;27:135–42.

[27] Chiu HY, Lin EY, Chiu HT, Chen PY. A feasibility randomized controlled crossover trial of home-based warm footbath to improve sleep in the chronic phase of traumatic brain injury. J Neurosci Nurs 2017;49:380–5.

[28] Jha A, Weintraub A, Allshouse A, Morey C, Cusick C, Kittelson J, et al. A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. J Head Trauma Rehabil 2008;23:52–63. https://doi.org/10.1097/01.HTR.0000308721.77911.ea.

[29] Kaiser PR, Valko PO, Werth E, Thomann J, Meier J, Stocker R, et al. Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury. Neurology 2010;75:1780–5. https://doi.org/10.1212/WNL.0b013e3181fd62a2.

[30] Menn SJ, Yang R, Lankford A. Armodafinil for the treatment of excessive sleepiness associated with mild or moderate closed traumatic brain injury: a 12-week, randomized, double-blind study followed by a 12-month open-label extension. J Clin Sleep Med 2014;10:1181–91.

[31] Weber M, Grandner MA, Killgore WD. Blue wavelength light therapy reduces daytime sleepiness following mild traumatic brain injury. Sleep 2016;39(SUPPL. 1):A54.

[32] Raikes. Daily blue light therapy reduces daytime sleepiness and post-concussion symptoms after mild traumatic brain injury. Sleep: journal of sleep and sleep disorders research 2019;42(Supplement 1):A376.

[33] Lequerica A, Jasey N, Portelli Tremont JN, Chiaravalloti ND. Pilot study on the effect of ramelteon on sleep disturbance after traumatic brain injury: preliminary evidence from a clinical trial. Arch Phys Med Rehabil 2015;96:1802–9.

[34] Lee H, Kim SW, Kim JM, Shin IS, Yang SJ, Yoon JS. Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. Hum Psychopharmacol 2005;20:97–104.

[35] Randler C. Validation of the full and reduced composite scale of morningness. Biol Rhythm Res 2009;40:413–23.

[36] Killgore WDS, Vanuk JR, Shane BR, Weber M, Bajaj S. A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury. Neurobiol Dis 2020;134:104679.

[37] Kataria LV, Sundahl CA, Skalina LM, Shah M, Pfeffer MH, Balish MS, et al. Annie: the veterans health administration's personalized text message application promotes compliance with positive airway pressure. Sleep:journal of sleep and sleep disorders research 2017;40(Supplement 1):A196.

[38] Hoffer ME, Balaban C, Slade MD, Tsao JW, Hoffer B. Amelioration of acute sequelae of blast induced mild traumatic brain injury by N-acetyl cysteine: a double-blind, placebo controlled study. PLoS One 2013;8:e54163.

[39] Wolf G, Cifu D, Baugh L, Carne W, Profenna L. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. J Neurotrauma 2012;29:2606–12.

[40] Walker JM, Mulatya C, Hebert D, Wilson SH, Lindblad AS, Weaver LK. Sleep assessment in a randomized trial of hyperbaric oxygen in U.S. service members with post concussive mild traumatic brain injury compared to normal controls. Sleep Med 2018;51:66–79.

[41] Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SM. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. Neurorehabilitation Neural Repair 2014;28:303–13.

[42] Shane BR, Alkozei A, Vanuk JR, Weber M, Killgore WD. The effect of bright light therapy for improving sleep among individuals with mild traumatic brain injury. Biol Psychiatr: a journal of psychiatric neuroscience 2015;77(9 SUPPL. 1):127S–8S.

[43] Bogdanova Y, Ho VT, Martin PI, Ho MD, Yee MK, Hamblin MR, et al. Transcranial LED treatment for cognitive dysfunction and sleep in chronic TBI: randomized controlled pilot trial. Arch Phys Med Rehabil 2017;98:e122–3.

[44] Geib J. Akupunktur bei Veteranen mit dauerhaften Schlafstörungen nach milder traumatischer Hirnschädigung. Dtsch Z Akupunkt 2019;62:172–5.

[45] Jonas WB, Bellanti DM, Paat CF, Boyd CC, Duncan A, Price A, et al. A randomized exploratory study to evaluate two acupuncture methods for the treatment of headaches associated with traumatic brain injury. Med Acupunct 2016;28:113–30. https://doi.org/10.1089/acu.2016.1183.

[46] Vuletic S, Bell KR, Jain S, Bush N, Temkin N, Fann JR, et al. Telephone problem-solving treatment improves sleep quality in service members with combat-related mild traumatic brain injury: results from a randomized clinical trial. J Head Trauma Rehabil 2016;31:147–57. https://doi.org/10.1097/HTR.0000000000000221.

[47] Stevens DJ, Alghwiri A, Appleton SL, Rogers JM, Plummer SL, Grant C, et al. Should we lose sleep over sleep disturbances after sports-related concussion? A scoping review of the literature. J Head Trauma Rehabil 2021. PMID: 34145161. https://doi.org/10.1097/HTR.0000000000000701. Epub ahead of print.

[48] Martindale SL, Lad SS, Ord AS, Nagy KA, Crawford CD, Taber KH, et al. Sleep moderates symptom experience in combat veterans. J Affect Disord 2021;282:236–41.

[49] McIntire KL, Crawford KM, Perrin PB, Sestak JL, Aman K, Walter LA, et al. Factors increasing risk of suicide after traumatic brain injury: a state-of-the-science review of military and civilian studies. Brain Inj 2021;35:151–63.

[50] Werner JK, Shahim P, Pucci JU, Lai C, Raiciulescu S, Gill JM, et al. Poor sleep correlates with biomarkers of neurodegeneration in mild traumatic brain injury patients: a CENC study. Sleep 2021;44:zsaa272.

[51] Nakase-Richardson R, Sherer M, Barnett SD, Yablon SA, Evans CC, Kretzmer T, et al. Prospective evaluation of the nature, course, and impact of acute sleep abnormality after traumatic brain injury. Arch Phys Med Rehabil 2013;94:875–82.

[52] Cantor JB, Bushnik T, Cicerone K, Dijkers MP, Gordon W, Hammond FM, et al. Insomnia, fatigue, and sleepiness in the first 2 years after traumatic brain injury: an NIDRR TBI model system module study. J Head Trauma Rehabil 2012;27:E1–14.

[53] Duclos C, Dumont M, Blais H, Paquet J, Laflamme E, de Beaumont L, et al. Rest-activity cycle disturbances in the acute phase of moderate to severe traumatic brain injury. Neurorehabilitation Neural Repair 2014;28:472–82.

[54] Shekleton JA, Parcell DL, Redman JR, Phipps-Nelson J, Ponsford JL, Rajaratnam SM. Sleep disturbance and melatonin levels following traumatic brain injury. Neurology 2010;74:1732–8.

[55] Paredes I, Navarro B, Lagares A. Sleep disorders in traumatic brain injury. Neurocirugia (Astur : Engl Ed). 2021;32:178–87.

[56] Valko PO, Gavrilov YV, Yamamoto M, Finn K, Reddy H, Haybaeck J, et al. Damage to histaminergic tuberomammillary neurons and other hypothalamic neurons with traumatic brain injury. Ann Neurol 2015;77:177–82.

[57] Littner MR, Kushida C, Wise M, Davila DG, Morgenthaler T, Lee-Chiong T, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep 2005;28:113–21. https://doi.org/10.1093/sleep/28.1.113.

[58] Christensen J, Yamakawa GR, Shultz SR, Mychasiuk R. Is the glymphatic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties. Prog Neurobiol 2021;198:101917.
*[59] Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science 2013;342:373–7.
[60] Da Mesquita S, Louveau A, Vaccari A, Smirnov I, Cornelison RC, Kingsmore KM, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. Nature 2018;560:185–91.
[61] Louveau A, Da Mesquita S, Kipnis J. Lymphatics in neurological disorders: a neuro-lympho-vascular component of multiple sclerosis and alzheimer's disease? Neuron 2016;91:957–73.
[62] Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M, Yang L, et al. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. J Neurosci 2014;34:16180–93.
[63] Liguori C, Romigi A, Nuccetelli M, Zannino S, Sancesario G, Martorana A, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. JAMA Neurol 2014;71:1498–505.
*[64] Baumann CR, Bassetti CL, Valko PO, Haybaeck J, Keller M, Clark E, et al. Loss of hypocretin (orexin) neurons with traumatic brain injury. Ann Neurol 2009;66:555–9.
[65] Riha RL. Diagnostic approaches to respiratory sleep disorders. J Thorac Dis 2015;7:1373–84.