

UC Irvine

UC Irvine Previously Published Works

Title

Circadian therapy interventions for glymphatic dysfunction in concussions injuries: A narrative review.

Permalink

<https://escholarship.org/uc/item/5n68s9z4>

Journal

Science Progress: a review journal of current scientific advance, 106(3)

Authors

Kureshi, Sohaib
Stowe, Caroline
Francis, John
[et al.](#)

Publication Date

2023

DOI

10.1177/00368504231189536

Peer reviewed

Circadian therapy interventions for glymphatic dysfunction in concussions injuries: A narrative review

Science Progress

2023, Vol. 106(3) 1–14

© The Author(s) 2023

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/00368504231189536

journals.sagepub.com/home/sci

Sohaib Kureshi^{1,2}, Caroline Stowe²,
John Francis²  and Hamid Djalilian^{2,3}

¹Neurosurgical Medical Clinic, San Diego, CA, USA

²TBI Virtual, San Diego, CA, USA

³Department of Otolaryngology-Head and Neck Surgery, University of California, Irvine, CA, USA

Abstract

There are two primary threats to the brain after concussion. The first is a buildup of neurotoxic proteins in the brain. The second, a partial consequence of the first, is a sustained neuroinflammatory response that may lead to central sensitization and the development of persistent post-concussive symptoms. These threats make neurotoxin clearance a high clinical priority in the acute period after injury. The glymphatic system is the brain's primary mechanism for clearing neurotoxic waste. The glymphatic system is intimately tied to the sleep cycle and circadian dynamics. However, glymphatic dysfunction and sleep disturbances are nearly ubiquitous in the acute period after concussion injury. Because of this, sleep optimization via circadian therapy is a time-sensitive and critical tool in acute concussion management.

Keywords

sleep, glymphatic system, brain injuries, traumatic, brain concussion, melatonin, circadian rhythm

Introduction

Traumatic brain injury (TBI) cases in the United States approach 2 million annually.¹ Nearly 90% of TBIs are mild, injuries that are commonly referred to as “concussions.”² The two most concerning sequelae of concussion injuries are the possibility of early dementia (including manifestations such as chronic traumatic encephalopathy [CTE])³ and the development of persistent post-concussive symptoms (PPCS).⁴

Because of these concerns, tremendous efforts are being spent to address concussion injuries. Prevention efforts have advanced significantly, including the development of sports equipment

Corresponding author:

John Francis, TBI Virtual, San Diego, 515 N Hwy 101, Solana Beach, CA 92075, USA.

Email: john@tbivirtual.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>)

which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

technology⁵ and changes in the rules of contact sports.⁶ Significant resources are being spent increasing education about concussion.⁷ Return-to-play laws have been passed for youth athletes and the related protocols are being continually refined.⁸ Improved diagnosis via biological and clinical biomarkers is currently underway.⁹ Finally, progress is being made on determining who is at risk for PPCS and the optimal treatments for PPCS.⁴

Conspicuously lacking in this coordinated effort is elucidation of optimal acute treatment protocols. Increased attention is needed in acute care protocols, principally because the two primary pathophysiological forces that occur in the acute period after concussion, neurotoxin build-up and neuroinflammation, peak in the first week after injury.¹⁰ In this paper, we focus on the importance of glymphatic system dysfunction in acute concussion pathophysiology, its relationship to near-ubiquitous sleep disturbances in the acute period, and the importance of circadian therapy as a critical early intervention tool for acute concussion management (Table 1).

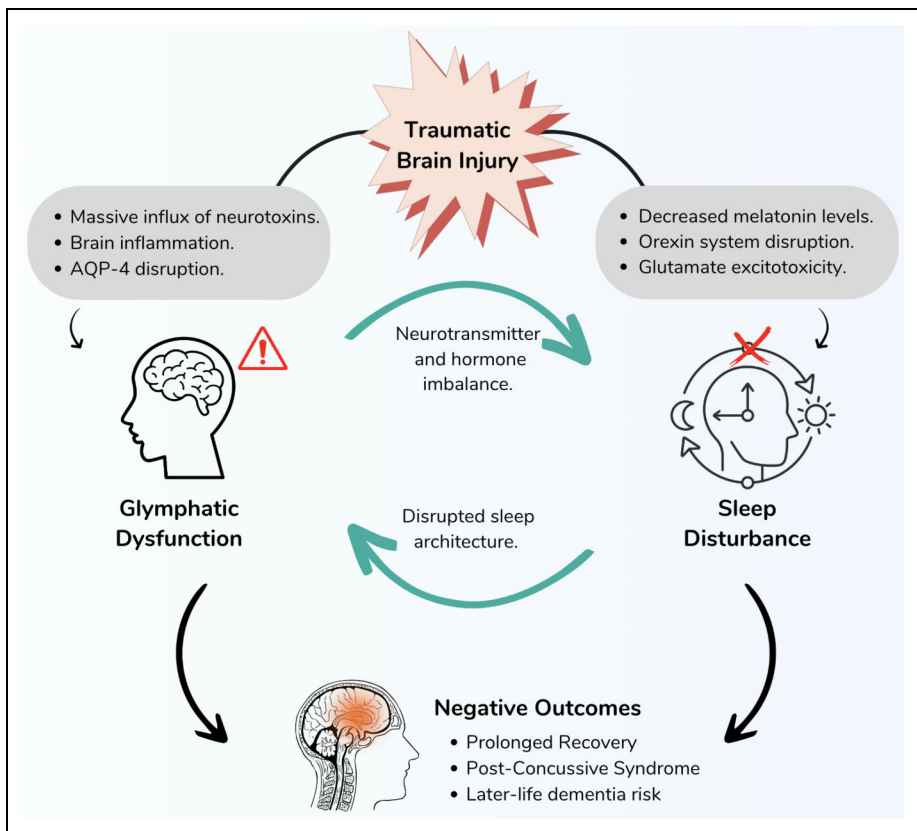


Figure 1. There is a reticulum of causation between TBI, glymphatic dysfunction, and sleep disturbances. The pathological consequences of TBI initiate a cascade of factors that disrupt both sleep and glymphatic clearance processes. These interconnected systems, once impaired, contribute to a cycle of dysfunction, exacerbating the negative outcomes following the injury. As a result, individuals may experience compromised recovery and suboptimal outcomes.

Neurotoxic proteins in concussion

After concussive injury, whether through axonal strain or tearing, there is a release of structural proteins into the interstitial fluid of the brain. These include tau proteins and beta-amyloid proteins, notorious for their role in neurodegenerative diseases. When these proteins are outside of their intracellular physiological context, they tend to propagate in a prion-like fashion, forming plaques and tangles.¹¹

Table 1. Selected studies that support circadian therapy for concussion management.

Author	Intervention	Study type	Summary points
Cassimatis (2022) ⁵⁰	Melatonin	Meta-analysis	Eight of nine studies reported positive outcomes after melatonin treatment, including improvements in subjective sleep quality, objective sleep efficiency, and total sleep time with reductions in self-reported fatigue, anxiety, and depressive symptoms.
Raikes (2020) ⁵⁶	MBLT	PC-RT	For the MBLT group, moderate to large improvements were found in multiple measures of sleep quality, mood disorder scores, and concussion symptom scores.
Kilgore (2020) ⁵⁷	MBLT	DB-PC-RT	For the MBLT group, there was improved measures in multiple sleep scores, improved executive functioning, and via MRI testing, greater thalamocortical functional connectivity, and increased axonal integrity.
Burkhart (2009) ⁷¹	EBLR	RT	The group that used blue-blocking glasses showed significant improvement in sleep quality and mood in adolescent subjects.
Macnow (2021) ⁶⁶	EBLR	RT	A screen-time-restricted group (limited screen time for the first 48 h after a concussion) had a significantly faster recovery from concussion than a screen-time-permitted group (3.5 vs. 8 days).
Wang (2023) ²⁶	OSA	Pre-Post	Patients with OSA showed glymphatic dysfunction via MRI versus controls. After CPAP treatment, this difference in glymphatic function resolved.
Zhang (2020) ⁷⁹	Omega Oils	Pre-Clinical	Omega oils attenuated TBI-induced neurological impairment, improved glymphatic clearance, reduced A β 42 accumulation, suppressed AQP4 expression and partially prevented loss of AQP4 polarity, and protected against blood-brain barrier disruption.
Yokoi-Shimizu (2022) ⁷⁷	Omega Oils	DB-PC-RT	Omega oil supplementation significantly improved several measures of sleep quality in healthy individuals.

MBLT, morning blue light therapy; EBLR, evening blue light restriction; RT, randomized trial; PC-RT, placebo-controlled randomized trial; DB-PC-RT, double-blind, placebo-controlled randomized trial.

The tau protein is of particular importance in concussion pathophysiology.¹² The tau protein is a microtubule associated protein. In pathological contexts, tau protein forms neurofibrillary tangles, one of the well-known hallmarks of neurodegenerative diseases. While intracellular tauopathy was initially thought to be causative of neuronal damage, new research suggests that extracellular tau is also a primary threat to brain health.¹³ Extracellular tau is not only directly toxic to neurons, it also triggers a sustained neuroinflammatory response via microglial activation.¹²

After concussion injury, there is a large release of tau proteins into the brain. This has been recorded in the interstitial fluid in animal models and in the cerebrospinal fluid and serum in human subjects.^{10,14,15} Beyond being a biomarker of acute neuronal injury, serum tau is an indicator of slower recovery and the development of neurobehavioral deficits.¹⁵ Several important findings were revealed regarding the relationship between serum tau levels in the acute period and clinical outcomes in a recent study of 229 TBI patients:

- Lower levels of acute period serum tau are associated with favorable outcomes.
- Early serum tau is negatively correlated with the presenting Glasgow Coma Score (GCS; i.e., high serum tau is positively correlated with injury severity).
- Tau protein levels at days 1, 3, and 5 after TBI are significantly correlated with cognitive dysfunction 6 months after injury.¹⁰

The fact that acute serum tau levels are predictive of poor outcomes is important because it highlights the importance of decreasing the burden of brain tau levels in the first week of recovery. As we will outline below, the primary mechanism for clearing extracellular tau proteins is the glymphatic system.

Importantly, tau accumulation after concussion is a precursor state to CTE. CTE is defined histologically as a perivascular accumulation of phosphorylated tau proteins (perivascular tauopathy).¹⁶ The proximate cause of CTE is the high extracellular burden of tau proteins after each concussive event. Regardless of whether a person develops PPCS, each concussive is a step closer to the development of CTE. This makes tau clearance in the acute period an important clinical priority.

The glymphatic system

In 2012, Maiken Nedergaard and colleagues first outlined the function of the glymphatic system in brain waste metabolism.^{17,18} The glymphatic system is now central to our understanding of brain physiology and neuropathology. In its essence, the glymphatic system cleans the interstitial space of brain waste products through the convective flow of water (interstitial and cerebral spinal fluids [CSFs]) from intracerebral arteries to veins. This waste transport is facilitated by water channels (specifically aquaporin-4) located in astrocyte processes that surround cerebral veins.¹⁹

Impairment of glymphatic function is central to neurodegenerative pathogenesis. In fact, some researchers now propose that neurodegenerative diseases such as Alzheimer's disease and CTE be recategorized as "interstitial fluidopathies."²⁰ When neurotoxic substances like amyloid and tau cannot be sufficiently cleared,

neuropathology ensues through a downward spiral; impaired perivascular clearance leads to tau accumulation, neurodegeneration, and neuroinflammation, all of which in turn further impair waste clearance.²¹

The glymphatic system is inexorably linked to sleep and the circadian cycle because the convective flow of CSF occurs during deep sleep. Importantly, glymphatic clearance is 80–90% higher during sleep relative to awake states.²² During slow wave sleep (SWS), the extracellular space expands in brain by more than 60%.²³ This is partially explained by the synchronous firing of brain waves during SWS, which may orchestrate ion-driven fluid influx into the interstitial space.²⁴ The transition to asynchronous firing in REM sleep then facilitates fluid efflux. Amazingly, the principal biological purpose of dreaming may be to facilitate this important brain-cleaning process.

Given that glymphatic function is so highly dependent on sleep, it is not surprising that sleep disturbances are causally linked to glymphatic dysfunction. For instance, people with obstructive sleep apnea have impaired glymphatic function as determined by diffusion tensor imaging,²⁵ and this dysfunction reverses with continuous positive airway pressure (CPAP) treatment.²⁶ In the case of dementia, the appearance of glymphatic dysfunction may coincide with the onset of sleep disturbances, acting in a bidirectional manner. On this point, Nedergaard and Goldman note that “the glymphatic system degrades with age, suggesting a causal relationship between sleep disturbance and symptomatic progression in the neurodegenerative dementias.”²⁷ In the case of TBI, the appearance of glymphatic dysfunction and sleep disturbances also coincides in a temporal fashion.

Overall, impaired glymphatic function is now considered the “missing link” between sleep disorders and multiple neurological disorders.²⁸ Many researchers now argue that neurotoxin clearance in the brain through glymphatic system optimization should be a central strategy to treat neurodegenerative diseases.²⁹ The principal way to do this is through optimization of deep sleep, as this is when the glymphatic system is most active. Sleep, not rest, is what is important.

The glymphatic system and concussion

As noted above, there is a flood of neurotoxic proteins into the interstitial space after concussion injuries. The glymphatic system is the primary mode of clearance for these toxic substances, yet experimental evidence suggests that in the acute phase, the glymphatic system experiences significant dysfunction. In animal models, the glymphatic system becomes impaired by up to 60% after experimental TBI.²¹ These deficits are detected in the acute period,³⁰ but can last for weeks after the injury.^{21,31}

Radiological studies provide evidence of glymphatic dysfunction after TBI in human subjects. Expansion of the perivascular space can be detected by MRI and is used as a proxy for glymphatic dysfunction. Several studies have documented a correlation between an expanded perivascular space and a history of TBI.^{32,33} Recent studies that employ diffusion tensor imaging also record glymphatic impairment in patients with a history of TBI.³⁴

Aquaporin-4 knock-out models also provide evidence of the centrality of the glymphatic system after TBI. Multiple studies show that genetic elimination of aquaporin-4

channels leads to glymphatic dysfunction, and subsequently to the accumulation of tau and other biomarkers of neurotrauma.^{35,36} This corresponds to preclinical studies that show that in the acute phase after TBI, fluid influx is intact but fluid efflux is impaired.³⁰ The expanded perivascular space studies mentioned above further demonstrate that the impairment is on the efflux, not influx, side of the system.³² Importantly, impaired efflux is permissive of the perivenous tauopathy seen in CTE.³⁷

Sleep disturbances and concussion

Sleep disturbances are exceedingly common after concussion injuries, with up to 70% of cases being affected.^{38,39} These disturbances can include hypersomnia, insomnia, sleep-wake disorders, and sleep apnea. Fatigue is also reported in up to 70% of cases.⁴⁰ There is strong clinical evidence that sleep disturbances are both a symptom of mTBI and a causative factor for poor clinical outcomes.⁴¹ Several studies document that sleep disturbance in the acute phase of concussion is predictive of both PPCS incidence and severity.^{42,43}

There are several mechanistic causes of sleep disturbances after concussion. Several recent reports implicate glymphatic disruption as the putative link between concussion and sleep disturbances.^{28,33} Additionally, neuroinflammation and sleep disorders appear to have a bi-directional relationship in the context of TBI, each reinforcing and propagating the other.⁴⁴ Finally, so-called “clock genes,” that is, genes directly connected to circadian physiology, are shown to be altered in preclinical mTBI models.³⁸ Interestingly, acute sleep disturbances after concussion appear to be worse in female patients.⁴⁵ This corresponds to preclinical findings that clock gene expression after mTBI is more significantly altered in females than males.³⁸

Melatonin regulation is also affected after concussion injury. In fact, the entire neuroendocrine and neuroimmune system becomes imbalanced in the acute phase after concussions, including melatonin regulation.⁴⁶ Cerebral melatonin levels are significantly decreased after acute concussion in animal models.⁴⁷ In humans, several studies document a decrease in salivary melatonin levels in acutely concussed patients.^{48,49} Hence, reduced melatonin levels, increased sleep disturbances, and glymphatic dysfunction are all convergent and interconnected phenomena in the acute phase of concussion.

Circadian therapy for acute concussion

Summarizing the information above, acute concussion results in a significant deposition of neurotoxic proteins into the extracellular space. The primary mechanism for bulk removal of these toxins is the glymphatic system. However, this system apparently becomes overwhelmed in the acute period. Simultaneously, sleep disturbances arise in the acute period, affecting the ability of the glymphatic system to clear toxins, presumably through a bidirectional dynamic. These forces induce neuroinflammation which in turn negatively reinforce the impaired waste clearance and sleep disturbances. In short, there is a reticulum of causation between TBI, glymphatic impairment, and sleep disturbances. These dynamics are illustrated in Figure 1.

Based on the above, it can be inferred that sleep optimization through circadian therapy will help restore glymphatic function, improve clearance of neurotoxins,

reduce neuroinflammation, and improve outcomes. We will now examine evidence that supports this inference.

The circadian system regulates various bodily functions, including sleep–wake cycles, hormone production, body temperature, metabolism, and cognitive performance. It helps optimize physiological processes to align with the demands of the external environment. Disruptions to the circadian system can lead to disturbances in sleep patterns, mood, alertness, and overall health. Given the significant impact of sleep on concussion recovery and considering that sleep is primarily regulated by the circadian system, it is reasonable to explore therapeutic interventions that support and reinstate healthy circadian rhythms.

Circadian therapy is a general term that describes tools that are used to optimize sleep. Melatonin and light therapy are typical interventions for circadian pathology. However, other treatments that optimize sleep can be considered circadian therapy as they help normalize circadian sleep architecture. Below is a list of interventions that we will discuss in more detail:

- Melatonin therapy
- Morning blue light therapy
- Evening blue light restriction
- Sleep apnea treatment
- Omega oil supplementation

Other important circadian therapy interventions include sleep hygiene education, cognitive behavioral therapy, adoption of a circadian diet, and prescribed physical activity.

Melatonin therapy

Because melatonin dynamics are acutely dysregulated in concussion, melatonin supplementation has become a well-studied treatment strategy in concussion management.⁴⁶ In a recent meta-analysis, eight out of nine studies showed that melatonin supplementation for concussed patients resulted in positive outcomes.⁵⁰ It is reasonable to infer that the positive effects of melatonin are due to its effect on glymphatic clearance, as melatonin improves glymphatic clearance of neurotoxins in preclinical models,^{51,52} and neurotoxin burden is directly related to clinical outcomes.¹⁵ Importantly, preclinical models show that early administration of melatonin is needed in order to see its beneficial actions.⁵³ Melatonin also has powerful antioxidant and cytoprotective effects.⁵³ Various dosages of melatonin have been studied, ranging from 1–10 mg, typically given 30 min to one hour before bedtime.⁵⁴ Interestingly, several studies found that a mid-range dose (around 3–5 mg) showed the most efficacy.⁵⁵

Morning blue light therapy

There have been a series of promising studies looking at the effect of morning blue light therapy on concussion patients. These studies show that morning blue light exposure can improve a range of sleep-related outcomes after concussion, including daytime sleepiness, sleep quality, and quality of life.⁵⁶ The typical prescription in these studies calls

for 30 min of exposure to an LED blue light panel within 2 hours of awakening, with the device at an arm's length.⁵⁷

To avoid exacerbating any underlying photophobia symptoms, patients are advised to not look directly into the light. Photophobia is common after TBIs, affecting around 40% of individuals by some estimates.⁵⁸ New research suggests that while bright light is commonly reported as a trigger for migraine attacks, this response is likely due to false attribution⁵⁹ and light therapy is actually being investigated as a treatment for migraines with photophobia.⁶⁰ Nevertheless, photophobia should be considered a relative contraindication to blue light therapy and patients should be advised to stop treatment if it is triggering adverse symptoms.

The effectiveness of blue light therapy has to do with mammalian physiology and how it responds to different light wavelengths. Melanopsin, a light-sensitive protein in human retinal ganglion cells, has its peak absorption around 480 nm, primarily responding to blue light.⁶¹ This maximal absorption influences non-visual responses, including circadian rhythm regulation, melatonin suppression, alertness modulation, and pupil size regulation. Understanding melanopsin's characteristics helps optimize lighting design, chronobiology research, and clinical interventions for improving sleep, circadian rhythms, and overall well-being, including morning blue light therapy.

As for clinical efficacy, morning blue light therapy reduced daytime sleepiness, increased cognitive functioning, and improved phase-advanced sleep timing in a randomized trial.⁵⁷ Beyond this, functional neuroimaging show that these clinical responses correspond to increases in grey matter volume,⁶² increased functional connectivity,⁶² increased white matter diffusion,⁶³ and increased resting state effective connectivity.⁶⁴ Together, these studies provide solid empirical evidence for the value of morning blue light therapy as treatment strategy for concussion.

Evening light restriction

Light restriction is important in acute concussion management, presumably through its effect on circadian physiology. The effects of screen time on concussion in the acute period have received considerable attention.⁶⁵ In a randomized clinical trial, screen time restriction in the first 2 days after injury resulted in a significant reduction in recovery times (3.5 vs. 8 days).⁶⁶ In fact, the global recommendation is that >2 h of evening use and all night-time use of screens should be avoided.⁶⁷ Incidentally, while the blue light component of screens is particularly implicated for causing sleep disturbances, studies show that when "night shift" mode (a blue light filter mode) is used during evening screen time, it has a negligible effect on sleep parameters versus normal mode.⁶⁸

Evening blue light is particularly disruptive of normal sleep architecture.⁶⁹ This is because evening blue light can disrupt the circadian rhythm by delaying the onset of melatonin secretion and shifting the timing of the biological clock. This can lead to difficulties falling asleep, reduced sleep quality, and overall disruption of the natural sleep-wake cycle.

Evening blue light restriction has proven effective in promoting circadian normalization.⁷⁰ In clinical studies, blue-blocking glasses improve subjective sleep quality,⁷¹ reduce sleep onset latency,⁷² and normalize melatonin levels.⁷³ To the best of our

knowledge, blue-blocking glasses have not been studied as an adjuvant treatment for acute concussion.

Sleep apnea treatment

As noted above, sleep apnea is a common finding in concussed patients, affecting 35–60% of patients.⁷⁴ The presence of sleep apnea is predictive of PPCS severity.⁷⁵ Sleep apnea also significantly alters circadian physiology.⁷⁶ Importantly, sleep apnea impairs glymphatic clearance, whereas positive airway pressure treatment improves glymphatic function.²⁶ For these reasons, sleep apnea screening and treatment should occur early after injury should be considered an integral part of circadian therapy in acute concussion management.

Omega oil supplementation

Omega oils are commonly prescribed supplements to help with concussion recovery. Relevant here is the impact of omega oils on the circadian system. Multiple studies show that omega oils have a positive effect on sleep quality.⁷⁷ Omega oils also influence circadian variations in blood pressure.⁷⁸ Putative mechanisms include a direct effect on melatonin release from the pineal gland and the regulation of norepinephrine.⁷⁷

Omega oils also have a direct effect on the glymphatic system. In a TBI animal model, researchers found that omega oils positively influenced glymphatic drainage and reduced neurological impairment after simulated TBI injury.⁷⁹ Interestingly, when the aquaporin-4 gene was knocked out, the positive neurological effect was eliminated, indicating that the beneficial effect of the omega oils on neurological outcomes was directly related to improved glymphatic clearance.

Conclusion

Circadian therapy is a non-obvious intervention for concussion, but the clinical and pre-clinical evidence supporting it is sound. If the clues about ubiquitous sleep disturbances after concussion are followed and the importance of impaired sleep on glymphatic function is understood, the argument for circadian therapy in acute concussion management becomes clear.

Circadian therapy can positively affect the two primary threats after concussion; neurotoxin buildup in the brain and the neuroinflammation that ensues. Further, circadian therapy is a non-toxic, conservative, and affordable intervention. We hope that this scoping review provides support for increased translation of circadian therapy science into the clinical management of acute concussion.

In conducting this review, it is crucial to acknowledge the inherent limitations that shape the scope and depth of our findings. Firstly, as this is a fairly new approach to treatment, identifying an ample number of studies specifically focusing on circadian therapy for concussions is challenging. Furthermore, the heterogeneity of study designs, participant populations, treatment protocols, and outcome measures across the existing

literature pose a challenge in drawing definitive conclusions or establishing standardized guidelines for circadian therapy in concussion management.

We recognize that our review represents a snapshot of the literature at a particular point in time, and it may not include the most recent developments in this rapidly evolving field. As the understanding of circadian therapy in concussion management continues to expand, it is essential to acknowledge that our findings may not encompass the most up-to-date research.

Despite these limitations, our review paper provides valuable insights, identifies knowledge gaps, and highlights the need for further research in the intersection of circadian therapy and concussion management. We hope that our work serves as a foundation for future investigations and stimulates discussions that ultimately contribute to advancements in the field, enhancing the effectiveness of circadian-based interventions for individuals recovering from concussions.

Acknowledgments

We would like to acknowledge Brian McGuire, Chief Operating Officer of TBI Virtual, for his general support and encouragement of the research team that put this review together.


Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors of this manuscript are affiliated with TBI Virtual, a for-profit telemedicine clinic whose primary focus is the treatment of concussion injuries. This manuscript reflects the treatment philosophy and practices of TBI Virtual and as such, represents for-profit services offered by the clinic.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

John Francis  <https://orcid.org/0009-0005-2202-0437>

References

1. Frost RB, Farrer TJ, Primosch M, et al. Prevalence of traumatic brain injury in the general adult population: a meta-analysis. *Neuroepidemiology* 2013; 40: 154–159.
2. Gao C, Nie M, Huang J, et al. Pharmacotherapy for mild traumatic brain injury: an overview of the current treatment options. *Expert Opin Pharmacother* 2022; 23: 805–813.
3. Graham A, Livingston G, Purnell L, et al. Mild traumatic brain injuries and future risk of developing Alzheimer's disease: systematic review and meta-analysis. *J Alzheimers Dis JAD* 2022; 87: 969–979.
4. Heslot C, Azouvi P, Perdrieau V, et al. A systematic review of treatments of post-concussion symptoms. *J Clin Med* 2022; 11: 6224.
5. Schmid W, Fan Y, Chi T, et al. Review of wearable technologies and machine learning methodologies for systematic detection of mild traumatic brain injuries. *J Neural Eng* 2021; 18

6. Kriz PK and Roberts WO. Prevention of sport-related concussion. *Clin Sports Med* 2021; 40: 159–171.
7. Gardner N and Heron N. A scoping review: mapping the evidence for undergraduate concussion education and proposing the content for medical student concussion teaching. *Int J Environ Res Public Health* 2022; 19: 4328.
8. Coenen J and Reinsberger C. Neurophysiological markers to guide return to sport after sport-related concussion. *J Clin Neurophysiol Off Publ Am Electroencephalogr Soc* 2023; 40: 391–397.
9. Hiskens MI, Mengistu TS, Li KM, et al. Systematic review of the diagnostic and clinical utility of salivary microRNAs in traumatic brain injury (TBI). *Int J Mol Sci* 2022; 23: 13160.
10. Ni P, Qiao Y, Tong W, et al. Associations between serum tau, neurological outcome, and cognition following traumatic brain injury. *Neurol India* 2020; 68: 462–467.
11. Kapoor M and Chinnathambi S. TGF- β 1 signalling in Alzheimer's pathology and cytoskeletal reorganization: a specialized tau perspective. *J Neuroinflammation* 2023; 20: 72.
12. Hossain I, Blennow K, Posti JP, et al. Tau as a fluid biomarker of concussion and neurodegeneration. *Concussion Lond Engl* 2022; 7: CNC98.
13. Sebastián-Serrano Á, de Diego-García L and Díaz-Hernández M. The neurotoxic role of extracellular tau protein. *Int J Mol Sci* 2018; 19: 98.
14. Holth JK, Fritschi SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* 2019; 363: 880–884.
15. Lange RT, Lippa S, Brickell TA, et al. Serum tau, neurofilament light chain, glial fibrillary acidic protein, and ubiquitin carboxyl-terminal hydrolase L1 are associated with the chronic deterioration of neurobehavioral symptoms after traumatic brain injury. *J Neurotrauma* 2022. doi:10.1089/neu.2022.0249
16. Ruchika FNU, Shah S, Neupane D, et al. Understanding the molecular progression of chronic traumatic encephalopathy in traumatic brain injury, aging and neurodegenerative disease. *Int J Mol Sci* 2023; 24
17. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci Transl Med* 2012; 4: 147ra111.
18. Nedergaard M. Neuroscience. Garbage truck of the brain. *Science* 2013; 340: 1529–1530.
19. Kecheliev V, Boss L, Maheshwari U, et al. Aquaporin 4 is differentially increased and dislocated in association with tau and amyloid-beta. *Life Sci* 2023; 121593. doi:10.1016/j.lfs.2023.121593
20. Taoka T, Ito R, Nakamichi R, et al. Interstitial fluidopathy of the central nervous system: an umbrella term for disorders with impaired neurofluid dynamics. *Magn Reson Med Sci MRMS Off J Jpn Soc Magn Reson Med* 2022. doi:10.2463/mrms.rev.2022-0012
21. Iliff JJ, Chen MJ, Plog BA, et al. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J Neurosci* 2014; 34: 16180–16193.
22. Reddy OC and van der Werf YD. The sleeping brain: harnessing the power of the glymphatic system through lifestyle choices. *Brain Sci* 2020; 10: 68.
23. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science* 2013; 342.
24. Hablitz LM, Plá V, Giannetto M, et al. Circadian control of brain glymphatic and lymphatic fluid flow. *Nat Commun* 2020; 11: 4411.
25. Lee HJ, Lee DA, Shin KJ, et al. Glymphatic system dysfunction in obstructive sleep apnea evidenced by DTI-ALPS. *Sleep Med* 2022; 89: 176–181.
26. Wang J, Tian Y, Qin C, et al. Impaired glymphatic drainage underlying obstructive sleep apnea is associated with cognitive dysfunction. *J Neurol* 2023; 270: 2204–2216.

27. Nedergaard M and Goldman SA. Glymphatic failure as a final common pathway to dementia. *Science* 2020; 370: 50–56.
28. Christensen J, Yamakawa GR, Shultz SR, et al. Is the glymphatic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties. *Prog Neurobiol* 2021; 198: 101917.
29. Verghese JP, Terry A, de Natale ER, et al. Research evidence of the role of the glymphatic system and its potential pharmacological modulation in neurodegenerative diseases. *J Clin Med* 2022; 11: 6964.
30. Christensen J, Wright DK, Yamakawa GR, et al. Repetitive mild traumatic brain injury alters glymphatic clearance rates in limbic structures of adolescent female rats. *Sci Rep* 2020; 10: 6254.
31. Li L, Chopp M, Ding G, et al. MRI Detection of impairment of glymphatic function in rat after mild traumatic brain injury. *Brain Res* 2020; 1747: 147062.
32. Opel RA, Christy A, Boespflug EL, et al. Effects of traumatic brain injury on sleep and enlarged perivascular spaces. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab* 2019; 39: 2258–2267.
33. Piantino J, Schwartz DL, Luther M, et al. Link between mild traumatic brain injury, poor sleep, and magnetic resonance imaging: visible perivascular spaces in veterans. *J Neurotrauma* 2021; 38: 2391–2399.
34. Park JH, Bae YJ, Kim JS, et al. Glymphatic system evaluation using diffusion tensor imaging in patients with traumatic brain injury. *Neuroradiology* 2023; 65: 551–557.
35. Ferrara M, Bertozzi G, Volonnino G, et al. Glymphatic system a window on TBI pathophysiology: a systematic review. *Int J Mol Sci* 2022; 23: 9138.
36. Peng S, Liu J, Liang C, et al. Aquaporin-4 in glymphatic system, and its implication for central nervous system disorders. *Neurobiol Dis* 2023; 179: 106035.
37. Sullan MJ, Asken BM, Jaffee MS, et al. Glymphatic system disruption as a mediator of brain trauma and chronic traumatic encephalopathy. *Neurosci Biobehav Rev* 2018; 84: 316–324.
38. Sgro M, Ellens S, Kodila ZN, et al. Repetitive mild traumatic brain injury alters central and peripheral clock gene expression in the adolescent rat. *Neurobiol Sleep Circadian Rhythms* 2023; 14: 100090.
39. Montgomery MC, Baylan S and Gardani M. Prevalence of insomnia and insomnia symptoms following mild-traumatic brain injury: a systematic review and meta-analysis. *Sleep Med Rev* 2022; 61: 101563.
40. Mosti C, Spiers MV and Kloss JD. A practical guide to evaluating sleep disturbance in concussion patients. *Neurol Clin Pract* 2016; 6: 129–137.
41. Hughes C, Hunt K, Cox B, et al. Sleep dysfunction in adolescents with prolonged postconcussion symptoms: a reciprocal coupling of traumatic brain injury and sleep-related problems. *J Sport Rehabil* 2022; 31: 809–814.
42. Ludwig R, D’Silva L, Vaduvathirayan P, et al. Sleep disturbances in the acute stage of concussion are associated with poorer long-term recovery: a systematic review. *PM&R* 2020; 12: 500–511.
43. Hoffman NL, Weber ML, Broglio SP, et al. Influence of postconcussion sleep duration on concussion recovery in collegiate athletes. *Clin J Sport Med Off J Can Acad Sport Med* 2020; 30: S29–S35.
44. Herrero Babiloni A, Baril AA, Charlebois-Plante C, et al. The putative role of neuroinflammation in the interaction between traumatic brain injuries, sleep, pain and other neuropsychiatric outcomes: a state-of-the-art review. *J Clin Med* 2023; 12: 1793.
45. Wiseman-Hakes C, Foster E, Langer L, et al. Characterizing sleep and wakefulness in the acute phase of concussion in the general population: a naturalistic cohort from the Toronto concussion study. *J Neurotrauma* 2022; 39: 172–180.

46. Kvetnoy I, Ivanov D, Mironova E, et al. Melatonin as the cornerstone of neuroimmunoendocrinology. *Int J Mol Sci* 2022; 23: 1835.
47. Govindarajulu M, Patel MY, Wilder DM, et al. Blast exposure dysregulates nighttime melatonin synthesis and signaling in the pineal gland: a potential mechanism of blast-induced sleep disruptions. *Brain Sci* 2022; 12: 1340.
48. Maerlender A, Masterson C, Calvi JL, et al. Sleep and stress in the acute phase of concussion in youth. *Sports Med Health Sci* 2020; 2: 109–114.
49. Shekleton JA, Parcell DL, Redman JR, et al. Sleep disturbance and melatonin levels following traumatic brain injury. *Neurology* 2010; 74: 1732–1738.
50. Cassimatis M, Browne G and Orr R. The utility of melatonin for the treatment of sleep disturbance after traumatic brain injury: a scoping review. *Arch Phys Med Rehabil* 2022; 104: 340–349.
51. Pappolla MA, Matsubara E, Vidal R, et al. Melatonin treatment enhances β lymphatic clearance in a transgenic mouse model of amyloidosis. *Curr Alzheimer Res* 2018; 15: 637–642.
52. Reiter RJ, Sharma R, Cuciolo MS, et al. Brain washing and neural health: role of age, sleep, and the cerebrospinal fluid melatonin rhythm. *Cell Mol Life Sci CMLS* 2023; 80: 88.
53. Cao R, Li L, Zhang W, et al. Melatonin attenuates repeated mild traumatic brain injury-induced cognitive deficits by inhibiting astrocyte reactivation. *Biochem Biophys Res Commun* 2021; 580: 20–27.
54. Bell A, Hewins B, Bishop C, et al. Traumatic brain injury, sleep, and melatonin—intrinsic changes with therapeutic potential. *Clocks Sleep* 2023; 5: 177–203.
55. Osier N, McGreevy E, Pham L, et al. Melatonin as a therapy for traumatic brain injury: a review of published evidence. *Int J Mol Sci* 2018; 19: 1539.
56. Raikes AC, Dailey NS, Shane BR, et al. Daily morning blue light therapy improves daytime sleepiness, sleep quality, and quality of life following a mild traumatic brain injury. *J Head Trauma Rehabil* 2020; 35: E405–E421.
57. Killgore WDS, Vanuk JR, Shane BR, et al. 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.
58. Abusamak M and Alrawashdeh HM. Post-concussion syndrome light sensitivity: a case report and review of the literature. *Neuro-Ophthalmol Aeolus Press* 2022; 46: 85–90.
59. Artemenko AR, Filatova E, Vorobyeva YD, et al. Migraine and light: a narrative review. *Headache* 2022; 62: 4–10.
60. Matt E, Aslan T, Amini A, et al. Avoid or seek light - a randomized crossover fMRI study investigating opposing treatment strategies for photophobia in migraine. *J Headache Pain* 2022; 23: 99.
61. Wahl S, Engelhardt M, Schaupp P, et al. The inner clock—blue light sets the human rhythm. *J Biophotonics* 2019; 12: e201900102.
62. Raikes AC, Dailey NS, Forbeck B, et al. Daily morning blue light therapy for post-mTBI sleep disruption: effects on brain structure and function. *Front Neurol* 2021; 12: 625431.
63. Bajaj S, Vanuk JR, Smith R, et al. Blue-Light therapy following mild traumatic brain injury: effects on white matter water diffusion in the brain. *Front Neurol* 2017; 8: 16.
64. Bajaj S, Raikes AC, Razi A, et al. Blue-Light therapy strengthens resting-state effective connectivity within default-mode network after mild TBI. *J Cent Nerv Syst Dis* 2021; 13: 11795735211015076.
65. Cairncross M, Yeates KO, Tang K, et al. Early postinjury screen time and concussion recovery. *Pediatrics* 2022; 150: e2022056835.
66. Macnow T, Curran T, Tolliday C, et al. Effect of screen time on recovery from concussion: a randomized clinical trial. *JAMA Pediatr* 2021; 175: 1124–1131.

67. Hartley S, Royant-Parola S, Zayoud A, et al. Do both timing and duration of screen use affect sleep patterns in adolescents? *PLoS One* 2022; 17: e0276226.
68. Driller MW, Jacobson G and Uiga L. Hunger hormone and sleep responses to the built-in blue-light filter on an electronic device: a pilot study. *Sleep Sci Sao Paulo Braz* 2019; 12: 171–177.
69. Münch M, Kobińska S, Steiner R, et al. Wavelength-dependent effects of evening light exposure on sleep architecture and sleep EEG power density in men. *Am J Physiol-Regul Integr Comp Physiol* 2006; 290: R1421–R1428.
70. Vethe D, Drews HJ, Scott J, et al. Evening light environments can be designed to consolidate and increase the duration of REM-sleep. *Sci Rep* 2022; 12: 8719.
71. Burkhart K and Phelps JR. Amber lenses to block blue light and improve sleep: a randomized trial. *Chronobiol Int* 2009; 26: 1602–1612.
72. Hester L, Dang D, Barker CJ, et al. Evening wear of blue-blocking glasses for sleep and mood disorders: a systematic review. *Chronobiol Int* 2021; 38: 1375–1383.
73. Liset R, Grønli J, Henriksen RE, et al. A randomized controlled trial on the effect of blue-blocking glasses compared to partial blue-blockers on melatonin profile among nulliparous women in third trimester of the pregnancy. *Neurobiol Sleep Circadian Rhythms* 2022; 12: 100074.
74. Wickwire EM, Williams SG, Roth T, et al. Sleep, sleep disorders, and mild traumatic brain injury. What we know and what we need to know: findings from a national working group. *Neurother J Am Soc Exp Neurother* 2016; 13: 403–417.
75. Santos A, Walsh H, Anssari N, et al. Post-concussion syndrome and sleep apnea: a retrospective study. *J Clin Med* 2020; 9: 91.
76. Koritala BSC, Conroy Z and Smith DF. Circadian biology in obstructive sleep apnea. *Diagnostics* 2021; 11: 1082.
77. Yokoi-Shimizu K, Yanagimoto K and Hayamizu K. Effect of docosahexaenoic acid and eicosapentaenoic acid supplementation on sleep quality in healthy subjects: a randomized, double-blinded, placebo-controlled trial. *Nutrients* 2022; 14: 4136.
78. Bhardwaj K, Verma N, Trivedi R, et al. Effect of essential fatty acid blend on circadian variations of ambulatory blood pressure in patients with essential hypertension and coronary artery disease risk markers. *J Hum Hypertens* 2022; 36: 289–298.
79. Zhang E, Wan X, Yang L, et al. Omega-3 polyunsaturated fatty acids alleviate traumatic brain injury by regulating the glymphatic pathway in mice. *Front Neurol* 2020; 11: 7.

Author biographies

Sohaib Kureshi is a practicing Neurosurgeon. His clinical practice includes the treatment of traumatic brain injuries and their sequelae.

Caroline Stowe holds a Doctorate of Nursing Practice (DNP) with additional qualifications in headache medicine (AQH). She specializes in the evaluation and treatment of migraine disorders.

John Francis is a medically trained business consultant (MD, MBA). His consulting focuses on translational medicine, applied clinical research, and organizational management.

Hamid Djalilian is a Professor of Otolaryngology/Neurotology. His clinical research focuses on chronic brain sensitivity disorders, such as migraines, vestibular disorders, tinnitus, and post-concussion syndrome.