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Photobiomodulation and Its Therapeutic Potential in Sleep Disturbances

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Photobiomodulation (PBM) is a non-invasive therapeutic technique employing specific wavelengths of red and near-infrared light to induce photochemical reactions in biological tissues without generating significant heat. PBM operates at low power densities, primarily acting through mitochondrial chromophores like cytochrome c oxidase to enhance cellular metabolism, energy production, and repair mechanisms. Based upon this foundational understanding, a critical evaluation was conducted to assess its impact on sleep-wake regulation. Current scientific evidence from both preclinical and clinical research suggests that PBM has the potential to influence sleep architecture, duration, and quality through complex interactions with cellular metabolic pathways and neurophysiological mechanisms governing the sleep-wake cycle. Despite growing scientific interest, significant research gaps persist; elucidating the precise cellular and molecular mechanisms by which PBM affects sleep physiology remains a primary challenge. There is an urgent need to standardize intervention protocols, including determining optimal wavelengths, dosage parameters, treatment durations, and delivery methods, to ensure consistent and reproducible results. Future research should focus on identifying predictive biomarkers for personalized treatment, examining transcranial PBM's effects on neural pathways involved in sleep regulation, and assessing long-term safety to address potential cumulative effects. In conclusion, while PBM shows promise as a non-invasive therapeutic approach for sleep regulation, rigorous research is needed to establish its clinical efficacy and understand its molecular mechanisms, ultimately advancing it from an experimental therapy to a standardized treatment for sleep disorders. **Sleep Med Res 2024;15(4):218-227**

Keywords Sleep; Photobiomodulation; Sleep disorders; Phototherapy; Low-level light therapy.

INTRODUCTION

Photobiomodulation

Photobiomodulation (PBM) represents a non-invasive phototherapeutic approach that employs non-ionizing light sources within the visible to infrared spectral range. It was also known as low-level light therapy and was recently recognized as an official Medical Subject Heading (MeSH) term by the U.S. National Library of Medicine in 2015. However, PBM has become the preferred term for this therapeutic approach [1]. PBM employs relatively low-power light between 5 mW and 500 mW, ensuring insignificant thermal impact on target tissues without significant structural alterations [2]. The therapeutic modality primarily focuses on red (620–700 nm) and near-infrared (NIR, 700–1100 nm) wavelengths, where specific light interactions with cellular chromophores elicit complex biological responses [3]. Although the precise mechanisms underlying PBM are still being elucidated, current research indicates that it affects mitochondrial function, cellular signaling pathways, and gene expression, ultimately contributing to improved cellular activity and resilience [4]. Spe-

cifically, PBM mediates critical cellular processes, including augmented adenosine triphosphate (ATP) production, modulation of reactive oxygen species (ROS), and intricate modifications of intracellular calcium dynamics. Its applications have been extensively explored across several medical domains, including wound healing, pain management, and neurorehabilitation [4-6]. As research progressively illuminates its multifaceted mechanisms, understanding the comprehensive therapeutic potentials, not only for the peripheral tissues but also for central nervous system, becomes increasingly imperative for clinical practitioners and researchers alike.

Unmet Needs in Treatment for Sleep Disturbances

In modern society, sleep problems have become increasingly prevalent, with insomnia being one of the most common issues affecting individuals across all age groups [7]. Despite the critical importance of sleep for overall health and well-being, many people struggle to find effective treatments for their sleep disorders. Conventional treatments, such as pharmacological interventions and cognitive-behavioral therapy, often have limited efficacy or come with unwanted side effects [8]. Furthermore, there is a significant unmet need for accessible and effective sleep interventions, as many individuals are hesitant to seek professional help due to fear, stigma, or misconceptions about sleep treatments in hospital settings [9]. This reluctance to engage with traditional medical approaches has led to a growing interest in alternative and complementary therapies for sleep management. However, the effectiveness of these alternatives is often not well-established, leaving many individuals with unresolved sleep issues and potentially compromising their cognitive, emotional, and physical health.

Aim of the Literature Review

The escalating global prevalence of sleep disorders necessitates innovative therapeutic approaches that can effectively modulate neurophysiological mechanisms underlying sleep regulation. This comprehensive literature review endeavors to synthesize the current knowledge concerning PBM's potential modulatory effects on homeostatic sleep mechanisms. By systematically examining the cellular and molecular mechanisms of PBM and their potential impact on sleep, we seek to elucidate the therapeutic potential of this non-invasive technique in sleep medicine. Furthermore, we will discuss safety and practical considerations, future research directions, and the potential implications of PBM in clinical practice. By synthesizing contemporary research and identifying emergent research trajectories, we aspire to provide a nuanced, evidence-based perspective on PBM's prospective role in advancing sleep therapeutic strategies.

MECHANISMS OF PHOTOBIOMODULATION

Light Sources and Wavelengths

PBM induces biomodulation processes through various light sources, including lasers and light-emitting diodes (LEDs), with its effects predominantly governed by key parameters, particularly wavelength [10,11]. Wavelength is a critical determinant of PBM's therapeutic efficacy, influencing tissue penetration depth and biological effects [12], with most PBM research concentrated within the 600−1100 nm spectral range [13,14]. Within this spectrum, red light (620−700 nm) and NIR (700−1100 nm) exhibit distinct tissue penetration characteristics. Red light is primarily effective for targeting superficial tissues, whereas NIR penetrates deeper tissues, making it therapeutically applicable to internal structures such as muscles, joints, and the nervous system [15].

The biological mechanism of NIR wavelengths is particularly significant, as these wavelengths penetrate tissues effectively and interact directly with cytochrome c oxidase (CCO), the primary photoreceptor in cellular mitochondria, to elicit the biological effects of PBM [16]. However, as wavelengths exceeding 900 nm are absorbed by both CCO and water molecules, diminishing tissue penetration efficiency, selecting an appropriate therapeutic wavelength range is crucial for optimizing treatment outcomes. Wavelengths exceeding 900 nm are absorbed by both CCO and water molecules, thereby diminishing tissue penetration efficiency. Therefore, the selection of an appropriate therapeutic wavelength range is critical to maximizing the efficacy of PBM treatments. Lasers and LEDs possess unique optical characteristics capable of generating narrow wavelength ranges from 1 to 20 nm, respectively. These characteristics provide significant advantages in PBM therapy, particularly by enabling precise wavelength selection and accurate energy output modulation, substantially enhancing treatment efficiency and reproducibility. Consequently, this technological precision has established lasers and LEDs as the preferred light sources widely utilized in PBM treatments [3].

Cellular and Molecular Mechanisms

Cytochrome c oxidase and ATP production

The most widely accepted mechanism of PBM is primarily mediated through its effects on CCO within mitochondria [17]. The primary target of PBM at the cellular level is the mitochondrial CCO, a critical enzyme in the cellular respiratory electron transport chain, which serves as the primary chromophore in cellular photobiological interactions. CCO selectively absorbs photons within the red and NIR spectrum, enhancing mitochondrial electron transport and consequently increasing ATP production [17,18]. The resultant augmentation of cellular energy metabolism cascades into physiological modulations, in-

cluding enhanced cell proliferation, migration, and differentiation mechanisms, ultimately facilitating tissue repair and regenerative processes [4].

Reactive oxygen species and antioxidants

PBM can modulate the production of ROS and antioxidants within cells [19]. At low level, ROS function as essential signaling molecules that trigger critical cellular adaptive responses, including activation of redox-sensitive transcription factors, enhancement of mitochondrial biogenesis, and stimulation of cellular repair mechanisms [20]. Conversely, excessive ROS generation can precipitate oxidative stress, potentially inducing cellular damage, mitochondrial dysfunction, and pro-inflammatory cascades [21]. The differential cellular response to ROS levels underscores the importance of precise PBM parameters, such as wavelength, power density, and exposure duration, in determining therapeutic outcomes.

PBM has been shown to enhance cellular antioxidant defense mechanisms, thereby mitigating oxidative stress and protecting cells from potential damage [19]. PBM exerts its protective effects by upregulating key antioxidant enzymes, modulating the Nrf2 signaling pathway to enhance cytoprotective gene expression, and reducing pro-inflammatory cytokine production, collectively contributing to improved cellular redox homeostasis and anti-inflammatory outcomes [22-24]. The interplay between these mechanisms creates a balanced cellular environment that effectively counters oxidative stress. This multifaceted approach to maintaining redox homeostasis underlies the therapeutic potential of PBM in various clinical applications.

Nitric oxide signaling

Another pivotal mechanism underlying the therapeutic efficacy of PBM involves its modulation of nitric oxide (NO) signaling pathways [25]. NO is a highly reactive free radical and signaling molecule involved in various physiological processes, including vasodilation, neurotransmission, and immune responses [26]. The interaction between PBM and NO signaling is particularly noteworthy, as light exposure can trigger the photodissociation of NO from its binding sites on CCO, thereby increasing local NO bioavailability. This enhanced NO release induces significant vasodilatory effects, leading to improved microcirculation, tissue oxygenation, and nutrient delivery [25,27]. Furthermore, NO acts as a crucial secondary messenger, orchestrating complex cellular signaling cascades that regulate inflammatory responses, apoptotic pathways, and mitochondrial bioenergetics. The modulation of these NO-dependent pathways synergistically contributes to PBM's broad therapeutic effects, including tissue repair, anti-inflammatory responses, and cellular protection [25].

Effects on Neural Activity and Brain Function

PBM exerts multifaceted effects on neural activity and brain function through various mechanisms. At the cellular level, PBM stimulates CCO in mitochondria, enhancing ATP production and metabolic function in neurons. This leads to improved cerebral oxygenation, increased blood flow, and upregulation of neuroprotective and anti-inflammatory processes [28]. Concurrently, PBM modulates neurotransmitter release and synaptic plasticity, influencing neural network dynamics [29]. These cellular and network-level changes manifest in alterations of brain activity, as evidenced by electroencephalography (EEG) studies showing shifts in power spectra across different frequency bands [30]. Functionally, PBM has demonstrated the potential to enhance cognitive performance, particularly in areas of executive function, memory, and attention, both in healthy individuals and those with neurological conditions [31-33]. Additionally, PBM has been investigated for its potential application in a range of neurological and psychiatric disorders, including traumatic brain injury (TBI), neurodegenerative diseases, and mood disorders [34,35]. Although the precise mechanisms of PBM are still under investigation, cumulative evidence indicates that its ability to modulate neural activity and restore functional connectivity contributes significantly to its effects on brain function and cognition.

SLEEP-WAKE CONTROL MECHANISM

Two-Process Model of Sleep Regulation

The two-process model of sleep regulation, initially proposed by Borbély (1982) [36], remains the most widely accepted framework for understanding the complex interplay of biological processes that govern sleep and wakefulness. The model comprises two complementary processes: the circadian process (Process C) and the homeostatic process (Process S) [36,37]. These processes work in concert to regulate sleep timing, duration, and quality, with Process C controlling the timing of sleep-wake cycles and Process S managing sleep pressure based on prior wake time. An intricate balance between these processes is essential for optimal sleep regulation and overall health. This theoretical framework has significant clinical implications, guiding the development and timing of therapeutic interventions, such as the strategic application of light therapy for circadian rhythm disorders or the optimal scheduling of sleep interventions based on individual sleep-wake patterns.

Circadian Process

The circadian process (Process C) is an endogenous biological clock that orchestrates the timing of sleep and wakefulness, ensuring synchronization with the external environment [37]. This 24-hour rhythm is regulated primarily by the suprachiasmatic nucleus of the hypothalamus, which receives light cues from the retina to align the internal clock with external light-dark cycles [38]. The circadian process influences various physi-

ological functions, such as body temperature, hormone secretion, and alertness, to promote optimal sleep timing and maintain overall health [39].

Homeostatic Process

The homeostatic process (Process S) represents the accumulating sleep pressure that builds up during wakefulness, driving the need for sleep to restore and recover various physiological and cognitive functions [36]. The homeostatic process is thought to be governed by the buildup of sleep-promoting molecules, such as adenosine, which accumulate in the brain during wakefulness and are cleared during sleep [40,41]. This process ensures that the duration and quality of sleep are sufficient to maintain optimal cognitive and physiological functioning [42]. Conversely, elevated adenosine level by sleep deprivation or pharmacological treatment increases sleep in animal model [40].

Factors Influencing Homeostatic Sleep Regulation

Homeostatic sleep regulation is influenced by a variety of factors, including genetic, environmental, and lifestyle factors [43]. Genetic factors can impact individual sleep patterns, with some individuals being predisposed to be "morning" or "evening" types [44]. Environmental factors, such as light exposure, ambient temperature, and noise levels, can also modulate the sleep-wake cycle [45]. Lifestyle factors, including work schedules, social activities, and electronic device usage, can impact sleep timing, duration, and quality, ultimately affecting homeostatic sleep regulation [46]. Understanding these factors is crucial for developing effective interventions to optimize sleep regulation and maintain well-being.

PHOTOBIOMODULATION EFFECTS ON SLEEP

Preclinical Studies

Despite significant advancements in understanding PBM across various physiological and neurological domains, its direct effects on sleep regulation remain largely unexplored. However, extensive neurobiological evidence provides a compelling theoretical framework for PBM's potential role in sleep modulation.

The established effects of PBM on mitochondrial activity, neurochemical signaling, and inflammatory modulation suggest its relevance to sleep regulation [47]. Enhanced mitochondrial bioenergetics, facilitated by PBM via CCO activation, plays a critical role in maintaining neuronal energy homeostasis essential for the sleep-wake cycle [12]. When cells are exposed to PBM, there is a marked increase in intracellular ATP production [48]. This elevated ATP undergoes distinct release mechanisms depending on the cell type: neurons release it through co-transmission, while astrocytes employ gliotransmission to expel ATP into the extracellular space [49,50]. Once in the extracellular environment, ATP rapidly breaks down into adenosine through enzymatic processes. The resulting elevation in extracellular adenosine levels can contribute to sleep pressure, suggesting a potential mechanism by which PBM may influence sleep-wake cycles. This pathway demonstrates how light-based therapy could modulate sleep regulation through biochemical signaling cascades. Furthermore, the anti-inflammatory and antioxidant properties of PBM, well-documented in preclinical studies, are particularly relevant given the strong association between systemic inflammation, oxidative stress, and sleep disturbances [24,29].

While the absence of direct preclinical evidence limits definitive conclusions, the alignment of PBM's systemic effects with core physiological processes underlying sleep underscores its potential as a therapeutic tool for sleep modulation. Future research employing animal models to investigate PBM's impact on sleep architecture, duration, and quality will be crucial for validating its application in sleep regulation.

Clinical Studies

Clinical evidence for sleep-improving effects of photobiomodulation

PBM has garnered increasing attention in clinical settings for its potential to address sleep-related disorders, including insomnia and disturbances in specific populations. Although clinical research on PBM and sleep remains in its early stages, emerging evidence highlights its promise as a non-invasive therapeutic option.

Recently, a randomized, sham-controlled study found that while actigraphy-measured sleep parameters remained unchanged between groups, the active treatment group reported significant improvements in perceived sleep quality, relaxation, and mood that were not observed in the sham group [51]. Further research has examined PBM's impact on specific patient populations. Using wearable devices based on the accelerometer, a study involving individuals with subjective cognitive decline (SCD) reported significant improvements in sleep efficiency alongside enhancements in cognitive performance, particularly in working memory tasks. Daily sleep measurements revealed a significant increase in sleep efficiency (total sleep time/total bedtime ×100%) in the active PBM treatment group by day 5 of the intervention. Furthermore, significant improvements were observed in the proportions of non-rapid eye movement (NREM) and rapid eye movement sleep phases [52]. This finding is particularly noteworthy given the association between SCD and increased risk of Alzheimer's disease, suggesting PBM's potential in addressing sleep disturbances in neurodegenerative conditions. Similarly, a post-Guillain-Barré syndrome case, who often experienced sleep disturbances due to chronic discomfort, demonstrated notable improvements in sleep duration, efficiency, and overall quality following intravascular PBM ther-

apy, with Pittsburgh Sleep Quality Index scores improving from 12 to 7 points post-treatment [53]. These findings suggest that PBM may alleviate sleep-related issues by addressing underlying physiological and neurological impairments. In addition, the sleep-improvement effects of PBM have also been demonstrated in studies involving patients with Parkinson's disease [54], xerostomia and hyposalivation [55], TBI [34,35,56], and athletes [57]. Additional studies on the sleep improvement effects of PBM are summarized in Table 1.

While these studies demonstrate PBM's potential for improving sleep outcomes, larger randomized controlled trials are necessary to validate these findings and optimize treatment protocols. Future research should focus on determining ideal parameters, including wavelength, dose, and frequency, to establish PBM as a reliable therapeutic modality for sleep disorders.

Potential Mechanisms Underlying Photobiomodulation Effects on Sleep

Neurometabolic mechanisms

PBM has shown the potential to improve sleep quality through various neurometabolic mechanisms, particularly by enhancing brain metabolic activity. PBM has been demonstrated to improve mitochondrial function and increase oxygen consumption in brain cells, thereby promoting energy production and overall brain function. This enhancement in cellular energy metabolism is primarily achieved through the stimulation of CCO, a key enzyme in the mitochondrial electron transport chain, leading to increased ATP production [17].

Interestingly, the increased ATP production resulting from PBM may have a dual effect on sleep regulation. While ATP is crucial for cellular energy and brain function, it is rapidly metabolized to adenosine in the brain [58,59]. Adenosine is a well-known sleep-promoting factor that accumulates during wakefulness and contributes to the buildup of sleep pressure [40]. Therefore, the PBM-induced increase in ATP production may indirectly lead to elevated adenosine levels, potentially enhancing sleep pressure and improving sleep quality. Indeed, our research team investigated the effects of transcranial PBM in mice. The experimental results demonstrated a significant increase in CCO activity in mouse brain tissue following PBM application. Furthermore, we observed that PBM treatment led to elevated adenosine concentrations in the brain, accompanied by a significant increase in NREM sleep duration (data not shown).

This potential mechanism supports that PBM might act as a non-pharmacological intervention to modulate sleep-wake cycles by influencing the energy metabolism in the brain. However, it is important to note that the exact pathways through which PBM affects sleep architecture and quality require further investigation. Future research should focus on elucidating the precise relationship between PBM-induced changes in brain energy metabolism, adenosine accumulation, and subsequent effects on sleep patterns and quality.

Effects on cerebral blood flow and brain activity

PBM's beneficial effects on sleep may be mediated through its ability to enhance cerebral blood flow and modulate brain activity. Studies have shown that transcranial PBM can significantly influence brain activity, particularly in the prefrontal cortex, as evidenced by changes in EEG patterns [60]. When applied during wakefulness, PBM induces considerable alterations in resting power spectrum of different brain waves, with observed increases in α, β, and γ waves, suggesting its capacity to influence neural oscillations critical for sleep regulation [61]. Additionally, PBM has been demonstrated to enhance cerebral blood flow through NO-dependent vasodilation, potentially improving tissue oxygenation and metabolic function in sleep-relevant brain regions [62]. This enhancement in cerebral hemodynamics may contribute to improved sleep quality by optimizing the brain's nighttime restorative processes, including the clearance of metabolic waste products through the glymphatic system [30]. The combination of modulated neural activity and enhanced cerebral blood flow suggests a mechanistic pathway through which PBM may improve sleep architecture and quality.

SAFETY AND PRACTICAL CONSIDERATIONS

Safety and Tolerability of Photobiomodulation

PBM has demonstrated a favorable safety profile across various therapeutic applications, with its light sources being classified as non-thermal lasers. This classification is particularly relevant when considering the safety parameters of PBM applications in neurological contexts.

Preclinical safety studies have provided substantial evidence supporting PBM's safety profile. When applied within therapeutic parameters, PBM produces only minimal and transient temperature changes in neural tissue, maintaining temperatures well below the neuronal damage threshold of 43°C [63,64]. Long-term safety studies have demonstrated no adverse neurological outcomes or histopathological changes in brain tissue, even with daily treatments extending up to 12 months and varying power densities [65,66]. Furthermore, investigations of supratherapeutic doses in rodent models have revealed no compromise to tissue integrity or behavioral function [67].

Clinical evidence has corroborated these preclinical findings. Multiple pilot studies investigating transcranial PBM across various neurological applications have reported no adverse effects with different wavelengths and power densities [35,68,69]. Notably, low-dose NIR transcranial PBM has maintained consistent safety profiles even with increased treatment frequency and extended protocols up to 12 weeks, showing no dose-dependent adverse events [70].

Table 1. Summary of studies on sleep improvement effects of photobiomodulation

Subjects	Target condition	Study design	Application method	Period	Stimulation parameters				Primary outcome	Secondary outcome	Reference
					Duration	Wavelength (nm)/ light souces	Power density (mW/cm^2)	Energy density (J/cm^2)			
PD (n=1)	Sleep disorders	Case report	Intraoral	33 sessions, 2 sessions per week	20 minutes	808 Laser	5000	6000	75% improvement in sleep quality after treatment (VAS score: 4 to 8) and maintained at 1-month follow-up (VAS score: 9)	Improvements in tremor and muscle stiffness (self-reported)	Panhoca et al. (2024) [54]
Healthy adults with sleep complaints (ISI>7, n=30)	Sleep and daytime function, mood	Randomized, sham-controlled trial	Cervical	3 weeks	25 minutes	Combined: 660, 740, 810 and 870 LED	NA	NA	Trend toward improved daytime performance in the active group (p=0.058)	Significant within-group improvements in sleepiness, sleep quality, and feeling refreshed	Kennedy et al. (2023) [51]
Patients with xerostomia and hyposalivation (n=60)	Xerostomia and hyposalivation	Single-blind randomized controlled trial	Extraoral	6 weekly sessions+ 1 year follow-up	1 or 2 minutes	810 Laser	NA	6	32.76% improvement in VAS xerostomia scores post-treatment (p<0.001) with stability at 1-year follow-up	Significant improvements in anxiety (HAD-A) and sleep quality (PSQI)	Ferrandez-Pujante et al. (2022) [55]
SCD (n=58)	Sleep and cognitive function	Randomized, double-blind, sham-controlled	Transcranial	6 days+ 4 weeks follow-up	12 minutes	1064 Laser	250	NA	Significant improvements in sleep efficiency, deep sleep%, and REM% were observed in the treatment group at Day 5	Improvement in working memory within the treatment group	Zhao et al. (2022) [52]
GBS (n=1)	Sleep disturbance	Case report	Intravascular	10 sessions	1 hour	632.8 Laser	NA	NA	Improvement in sleep quality (PSQI: 12 to 7)	NA	Chang and Chang (2022) [53]
Chronic TBI (n=10)	TBI	Retrospective case series	Transcranial	10–20 treatments over 2 months	8–12 minutes	810 or 810/980 dual wavelength Laser	14831.46 at 810 nm or 10112.36 at 810/980 nm	55–81	Improvements in depression scores (BDI, QIDS-SR) and sleep-related symptoms	Improved quality of life, return to work, and better relationships	Morries et al. (2015) [56]
Chronic mTBI (n=11)	Cognitive function	Pilot, open-protocol study	Transcranial	18 treatments +2 month follow-up	20 minutes	633/870 LED	22.2	13	Significant improvements observed in executive function and verbal learning and memory	Improvement in self-reported sleep with a trend toward significance in BDI	Naeser et al. (2014) [35]

Table 1. Summary of studies on sleep improvement effects of photobiomodulation (continued)

Subjects	Target condition	Study design	Application method	Period	Stimulation parameters				Primary outcome	Secondary outcome	Reference
					Duration	Wavelength (nm)/ light souces	Power density (mW/cm^2)	Energy density (J/cm^2)			
Athletes (n=20)	Sleep quality and endurance performance	Cohort study	Whole body irradiation	14 days	30 minutes	658 LED	NA	30	Significant improvement in PSQI and increased serum melatonin levels observed in the treatment group	Greater improvement in endurance performance observed in the treatment group ($p<0.05$)	Zhao et al. (2012) [57]
TBI (n=2)	Cognitive function	Case report	Transcranial	5 years or 9 months of treatment	5–12 minutes	633/870 LED	25.8 or 22.2	13.3	Significant improvements in sustained attention, executive function, and memory	Improvements observed in behavioral control, sleep quality, and PTSD symptoms	Naeser et al. (2011) [34]

PD, Parkinson's disease; VAS, visual analogue scale; ISI, Insomnia Severity Index; LED, light-emitting diode; NA, not available; HAD-A, Hospital Anxiety—Scale; PSQI, Pittsburgh Sleep Quality Index; SCD, subjective cognitive decline; GBS, Guillain-Barré syndrome; TBI, traumatic brain injury; BDI, Beck Depression Inventory; QIDS-SR, Quick Inventory of Depressive Symptomatology Self-Report; mTBI, mild traumatic brain injury.

While these findings strongly support PBM's safety profile in neurological applications, particularly at supratherapeutic doses, adherence to established treatment parameters remains crucial. Comprehensive safety evaluation through larger randomized clinical trials across diverse populations is essential to fully establish PBM as a standardized therapeutic intervention.

Potential Contraindications and Limitations

PBM is a promising therapeutic approach, but it is essential to consider its potential contraindications and limitations. Phototoxicity can occur when abnormal or excessive amounts of chromophores in the skin absorb photons, triggering molecular changes that lead to cell damage and localized inflammatory responses resembling severe sunburn. While ultraviolet light activates most phototoxic compounds, visible light can also cause minimal activation [71]. Therefore, when administering PBM therapy, especially using lower wavelengths with high red-light content, it is crucial to carefully assess and monitor patients with photosensitivity reactions due to the risk of adverse effects.

Another challenge in PBM is optimizing light dosimetry, as the effectiveness of the therapy depends on the amount of light reaching the target tissue depth. Factors such as skin color and the amount of subcutaneous fat can influence light penetration, making it difficult to establish standardized protocols [72,73]. Furthermore, the various irradiation parameters, including wavelength, power, irradiance, and pulse parameters, must fall within specific ranges and be applied for an appropriate duration to ensure effective treatment. Moreover, the potential influence of placebo effects in PBM studies necessitates careful consideration. Without proper control conditions, it can be difficult to differentiate between the physiological impact of PBM and psychological effects stemming from patient expectations. This makes it critical to design rigorously controlled sham trials when evaluating PBM outcomes to minimize bias and ensure reliable conclusions [74,75].

While PBM has shown promise in various applications, its effectiveness can be transient, requiring ongoing treatment. The lack of standardized protocols across different wavelengths, power outputs, and treatment durations also poses a challenge in establishing consistent clinical guidelines. Additionally, the limited penetration depth of certain wavelengths restricts PBM's effectiveness in treating deep-seated tissues.

FUTURE DIRECTIONS AND RESEARCH NEEDS

Identification of Potential Biomarkers for Photobiomodulation Response

Identifying potential biomarkers for PBM response could help personalize treatment and optimize outcomes for individuals with sleep disorders. Currently, the mechanisms through

which PBM affects sleep are not well understood, and individual responses to treatment may vary. By identifying biomarkers that predict treatment response, researchers could develop more targeted and effective PBM protocols for sleep improvement. Potential biomarkers could include genetic factors, neurotransmitter levels, or specific patterns of brain activity. Future research should focus on investigating these potential biomarkers and validating their utility in predicting PBM treatment outcomes for sleep disorders.

Combination Therapies Involving Photobiomodulation and Other Sleep Interventions

PBM, in conjunction with established sleep interventions, holds the potential to significantly enhance treatment outcomes by addressing both physiological and behavioral components of sleep regulation. PBM may modulate underlying neurophysiological mechanisms contributing to sleep disturbances, while its integration with evidence-based approaches such as cognitive-behavioral therapy for insomnia or pharmacological treatments may provide synergistic benefits, resulting in a more comprehensive management of sleep disorders. Moreover, light therapy is a well-established intervention for circadian rhythm sleep disorders, such as delayed sleep phase disorder. The administration of bright light exposure in the morning can facilitate the advancement of sleep phases, thereby enabling individuals to align their sleep patterns with societal norms. Incorporating transcranial PBM into such light therapy regimens may further enhance circadian entrainment by promoting a more efficient adjustment of sleep-wake cycles. Combination therapies involving PBM and traditional sleep treatments may offer a more holistic approach to improving sleep quality by effectively addressing the multifaceted nature of sleep disorders and promoting long-term sleep improvement.

Long-Term Effects of Photobiomodulation on Sleep and Overall Health

As PBM research in the context of sleep is still in its infancy, the long-term effects of PBM on sleep and overall health remain unclear. Understanding the long-term safety and efficacy of PBM is crucial for its adoption as a viable treatment option for sleep disorders. Future research should focus on longitudinal studies that assess the long-term outcomes of PBM treatment, including potential risks, benefits, and changes in sleep parameters over time. Additionally, exploring the impact of PBM on overall health, such as cognitive function, mood, and cardiovascular health, could provide valuable insights into the broader implications of PBM as a sleep intervention.

CONCLUSION

In conclusion, PBM presents a promising, non-invasive, and safe therapeutic approach for managing sleep disorders. By interacting with mitochondrial CCO, this technique enhances cellular ATP synthesis, antioxidant responses, and NO signaling. These pathways offer potential benefits for sleep regulation by influencing homeostatic and circadian processes. While emerging clinical evidence demonstrates improvements in sleep quality and related physiological outcomes, further research is essential to standardize treatment protocols and elucidate precise mechanisms. Addressing these gaps can help advance PBM into a widely accepted clinical solution for sleep medicine.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Author Contributions

Conceptualization: all authors. Data curation: Jieun Jung. Funding acquisition: Jieun Jung. Investigation: Jieun Jung. Project administration: Jieun Jung. Resources: Jieun Jung. Supervision: all authors. Visualization: Jieun Jung. Writing—original draft: Jieun Jung. Writing—review & editing: all authors.

Conflicts of Interest

Tae Kim, a contributing editor of the *Sleep Medicine Research*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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