



Effects of Photobiomodulation on Nervous System Disorders: A Narrative Review

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Abstract

Introduction: Photobiomodulation (PBM), also known as low-level laser therapy (LLLT), has emerged as a potential therapeutic strategy for various nervous system disorders. Its biological effects on neural tissue are primarily mediated by the absorption of light by mitochondrial cytochrome c oxidase (CCO), leading to increased ATP synthesis and the production of reactive oxygen species (ROS). These upstream processes consequently activate kinases and release second messengers, ultimately influencing the structure and function of the nervous system. This narrative review aims to summarize the current understanding of the effects of PBM on nervous system disorders by assembling findings from both preclinical and clinical studies.

Methods: We conducted a comprehensive search of Google Scholar, PubMed, and Medline databases using keywords such as “low-level laser therapy,” “photobiomodulation,” and “nervous system diseases” to identify relevant studies.

Results: The review compiles findings on the application of PBM in a range of central and peripheral nervous system disorders, highlighting the diverse ways in which PBM has been explored for neural tissue stimulation and modulation.

Conclusion: The evidence we have compiled indicates that PBM is a non-invasive treatment option for nervous system disorders, showing its potential to bring about positive biological changes. Further research is required to optimize PBM protocols and clarify its long-term efficacy and safety in various neurological conditions.

Keywords: Photobiomodulation; Nervous system disorders; Low-level laser therapy; Animal models; Clinical studies, Neurodegeneration.

Introduction

Photobiomodulation (PBM) was discovered in 1967 by Endre Mester who delivered laser irradiation to cells and tissues. PBM uses low-level (low-power) radiation from lasers or light-emitting diodes (LEDs) with red and/or near-infrared wavelengths to induce changes in biological function. It is also known as low-level light therapy (LLLT).¹ According to many experimental, pre-clinical and clinical studies, this non-invasive process stimulates regeneration or healing in different kinds of nervous system disorders, including traumatic injuries, neurodegenerative diseases, psychiatric disorders, and peripheral nerve injuries.¹⁻⁴

Neurons require efficient mitochondrial aerobic metabolism for their proper neural function, cell survival, signal transmission, interneuronal communication, and motor, sensory, and cognitive functions. PBM targets photoreceptors such as myoglobin, cytochrome c oxidase (CCO), superoxide dismutase, cytochrome C, cytochromes

a & b, and NADH-dehydrogenase to promote neural protection.^{4,5} The application of PBMT in nervous system diseases has shown some promising results by enhancing ATP production and cerebral blood flow.^{4,6,7} PBMT affects various aspects of neurodegenerative diseases, including neuroinflammation, neurotoxicity, oxidative damage, neuronal loss, abnormal phosphorylation, and protein aggregation. The aim of this research is to offer a comprehensive overview of the cellular and behavioral reactions of the nervous system to PBM in both animal models and humans. This will aid scientists' perspectives in evaluating the potential of PBM for treating nervous system disorders. We prioritized neurodegenerative disorders that represent significant public health burdens and have a substantial body of preclinical and clinical PBMT research. These include stroke, multiple sclerosis (MS), age-related cognitive decline, traumatic brain injury (TBI), and peripheral nervous system disorders.

Developmental and mood disorders were not included.

Methods

A comprehensive literature search was conducted across Google Scholar, PubMed, and Medline databases. The search strategy employed keywords such as “photobiomodulation,” “low-level laser therapy,” “mechanisms of PBM at cellular and behavioral studies,” and specific terminology related to central and peripheral nervous system disorders. In this study, we concentrated on human studies that employed PBM on the scalp using specialized devices and animal models that were created with quantifiable symptoms of diseases. We reviewed more than 130 publications. The MeSH terms used were phototherapy, low-level laser therapy (LLLT) and nervous system diseases. Clinical studies were limited to those trials employing standard protocols and enough sample sizes.

Studies were included in this narrative review if they met the following criteria:

1. The studies that use LLLT as the primary therapeutic intervention.
2. The studies that examine the effects of PBM specifically on disorders of the central or peripheral nervous system. This encompassed studies on various neurological conditions such as stroke, MS, Alzheimer’s disease (AD), Parkinson’s disease (PD), and TBI, as discussed in this review.
3. Original research articles that comprise both preclinical studies (*in vivo* animal models that establish quantifiable disease symptoms) and clinical studies (involving human participants to whom PBM was applied, especially transcranially or using specialized devices).

Studies were excluded from this narrative review if they met any of the following criteria:

1. We excluded studies that focused on other forms of light-based therapies (e.g., high-intensity laser ablation and general phototherapy for non-neurological conditions) that are not named as low-level light/laser therapy.
2. Studies on the effects of PBM on healthy nervous systems without a disorder model, or on non-neurological diseases were excluded.
3. We did not include editorials, commentaries, conference abstracts without a subsequent full peer-reviewed publication, or book chapters that did not present original data.

Mechanisms of Action of PBMT

The light-dependent excitation of photoreceptors leads to changes in the redox status of respiratory chain components and activation of mitochondrial metabolism. Numerous studies have focused on the effects of PBM on CCO leading to increased consumption of oxygen and

changes in the mitochondrial membrane potential.⁸ The increased production of reactive oxygen species (ROS) in the mitochondria leads to secondary signal transduction processes.⁹

Light-responsive ion channels, such as transient receptor potential (TRP) channels which are permeable to calcium ions, can act as sensors for thermal stimuli and painful stimuli and can also be affected by 980 nm near-infrared (NIR),¹⁰ as well as longer IR wavelengths.¹¹ PBM can induce protective effects in the brain by increasing blood flow and stimulating mitochondrial activity. This in turn initiates cellular and molecular responses by the activation of signaling pathways promoting the synthesis of specific proteins.⁸ Cognitive enhancement by transcranial PBM is associated with increased cerebrovascular oxygenation of the prefrontal cortex.¹² The PI3K/Akt and SIRT1 pathways (involving the protein kinase enzymes PKA and PKC) are the key signaling cascades affected by PBM.

The production of cAMP after PBM leads to an increase in Ca^{2+} ions and the activation of signaling pathways that can inhibit or stimulate gene expression.^{12,13} The activation of the MAPK pathway by PBM prevents cellular damage mediated by oxidative stress and pro-inflammatory mediators. PBM activates the PI3K/Akt pathway by increasing Ca^{2+} influx and inhibits apoptotic cell death.¹⁴ The activation of PKC and Raf/MEK/ERK increases survival, while the activation of cAMP, PKA and SIRT1 suppresses inflammation and enhances cell viability.¹⁵

PBM for a Stroke

Animal Model Studies

One study employed the middle cerebral artery occlusion (MCAO) model of a stroke in rats. An 808 nm laser was used to deliver energy of 0.9 J/cm² over 2 minutes at two locations on the skull of rats. Improved neurological scores were observed from 14-28 days post-stroke, attributed to an increase in neurogenesis and neuroprotection.¹⁶ In another study, an 808 nm laser with a power density of 7.5 mW/cm² was applied for 2 minutes on the contralateral hemisphere of rats after the induction of a stroke. This treatment attenuated neurological deficits 24 hours post-stroke, but it was not effective at 4 hours post-stroke.¹⁷ When an 808 nm laser with a power density of 25 mW/cm² was delivered to the head in the rabbit small clot embolic stroke model (RSCM) for 10 minutes at 6 hours post-stroke, it was effective in enhancing functional recovery which lasted up to 21 days but was not effective when delivered at 24 hours post-stroke.¹⁸ Using the same RSCM model, the researchers applied an 808 nm laser for 2 minutes at different times post-stroke, that is, 2, 3, and 4 hours which led to improved functional behavior.¹⁹

In another experiment, LEDs emitting 904 nm infrared light with a power of 110 mW were used, delivering 7 J/cm² over 63 seconds on the frontal region of the brain in rats subjected to a cerebrovascular accident (CVA) model.

The experiment was conducted in three phases, acute 3 days, subacute 7 days, and chronic 21 days post-CVA. LED PBMT increased muscle resistance on 7 and 21 days and increased neurogenesis on days 7 and 21 post-CVA.²⁰ In an animal model of global ischemic brain injury, an 808 nm laser delivered at 6 hours after global cerebral ischemia (GCI) led to improved learning and memory, less apoptotic cell death in the CA1 hippocampus, mitochondrial preservation, increased antioxidant activity, and cell survival.²¹

In a photothrombotic (PT) model of ischemic stroke in rats, an 808 nm laser (25 mW/cm², 350 J/cm²) was used for 2 minutes daily for 7 days. This PBMT regimen attenuated the deficit in somatosensory activity in stroke animals, decreased the infarct zone and synaptic injury, enhanced neurogenesis, and increased ATP synthesis, while lessening pro-inflammatory cytokines and inhibiting reactive gliosis.²²

The effect of a 660 nm laser was studied in a MCAO stroke model in rats. PBMT with average power of 8.8 mW for 1, 5, or 10 minutes was delivered directly to the rat cerebrum. It showed increased neuroprotection after the ischemic stroke was mediated by the inhibition of NOS activity and the upregulation of TGF- β 1.²³

The neuroprotective effects of a 710 nm laser, with radiant power of 47 mW/cm² delivered on the whole body, were studied in a MCAO stroke model in rats. The circulating CD4+ T cells were lower after the stroke, but they increased after irradiation. They also found increased Treg cells and lower pro-inflammatory cytokines, increased IL-10 mRNA expression, and lower microglial activation along with functional recovery, suggesting the repair of the injury.²⁴

Clinical Studies

In one study in acute stroke patients, a transcranial 808 nm laser (NeuroThera Laser System) was applied to 20 specified locations on the scalp for 2 minutes each. This therapy showed good safety and 70 percent effectiveness when applied within 24 hours post-stroke. This neuroprotection was attributed to the stimulation of mitochondria.²⁵ The NeuroThera Effectiveness and Safety Trial-2 (NEST-2) tested the safety and efficacy of transcranial laser therapy (TLT) in an acute ischemic stroke and showed the safety and effectiveness, which was attributed to increased activity of mitochondria.²⁶ However, the NEST-3 phase three clinical trial carried out on 1000 patients was terminated early due to statistical futility.²⁷

Therefore, on the basis of current evidence, the application of PBMT for acute stroke patients has shown safety and some efficacy in early trials. However, the clinical paradigm requires modification to increase the success rate in patients.

PBM for Multiple Sclerosis

Animal Model Studies

The application of PBMT in a mouse model of autoimmune demyelinating inflammatory disease similar to MS was investigated with the purpose of ameliorating inflammation and increasing tissue repair. Two lasers with 660 nm and 904 nm wavelengths, a pulse duration of 60 ns, and mean power of 30 mW were applied for 20 seconds on the spinal cord of mice with experimental autoimmune encephalomyelitis (EAE) induced by immunization with MOG35–55 peptide. PBMT was applied to 6 points on the spinal cord daily for 30 days. Improved clinical scores, delayed disease onset, and fewer infiltrating immune cells were detected in the lumbar spinal cord. A smaller size of the demyelinated area, lower production of IL-17, IFN- γ , IL-1 β , and NO level in the CNS of EAE mice were observed after PBMT. However, lipid peroxidation and antioxidant capacity did not change. In this study, the beneficial effect of PBMT was proposed to be due to the suppression of neuroinflammation.²⁸

PBMT with 670 nm LEDs for 3 minutes daily for two weeks with an energy density of 5 J/cm² was delivered onto the entire dorsal surface of mice. Inducible nitrite oxide (iNOS) mRNA was downregulated in the spinal cord of MOG-induced EAE mice after exposure to 670 nm, along with diminished EAE disease severity. There was an increased BCL-2 to Bax ratio in the tissue samples, demonstrating that 670 nm PBMT reduced apoptosis. Therefore, PBMT reduced tissue damage and could prevent the progression of the disease.²⁹ In a previous study with the same treatment protocol, the effects of 670 nm PBMT on the production of cytokines in lymph node cells and on MOG-induced EAE mice were examined. The down-regulation of IFN- γ and the up-regulation of IL-10 in lymph node cells were observed. Moreover, light exposure led to the down-regulation of TNF- α and IFN- and the up-regulation of IL-4 and IL-10 in the spinal cord of EAE mice. This immunomodulatory effect of 670 nm PBMT contributed to the decreased severity of disease in EAE mice.³⁰

Another mouse model of MS was developed by feeding juvenile mice with the copper chelator called cuprizone. The study involved the delivery of an 808 nm laser with an energy density of 36 J/cm² to a single point between the eyes and ears of control laser (CTL) and cuprizone laser (CPZL) mice for 20 seconds for 6 sessions. LFB staining revealed less demyelination in CPZL mice than in CPZ mice. There was a greater amount of MBP labeling in the corpus callosum of the CPZL group. Moreover, the colocalization of PDGFR with Ki67 showed higher immunopositivity in the CPZL group. In the CTL group, fewer GFAP-positive cells were observed, and the intensity of Iba1-positive cells was less in the CPZL group. Therefore, PBMT could be a safe therapeutic option for demyelinating disease to improve motor recovery and reduce the demyelinated area.³¹

Clinical Studies

The effects of phototherapy were investigated using a combination therapy of both PBMT and broadband ultraviolet B-radiation (BB-UVBR) in patients with relapsing–remitting MS (RRMS). Ten minutes of PBMT with a near-infrared 850 nm laser with maximum power of 10W was applied on the cervical region and 20 minutes of BB-UVBR (280–320 nm) was delivered for 3 days a week for 4 weeks (12 sessions) in the study group, while another group received 850 nm PBMT alone. Both groups showed a significant improvement in the severity of disability and a positive effect on fatigue and cognitive dysfunction in these MS patients³².

In another trial, the effects of 10 minutes of PBMT using a 650 nm laser with a power of 50 mW on the cervical-thoracic segment (C5-Th1-2) and lumbosacral segment (Th12-S5) of the spinal cord in MS patients over 10 sessions were assessed. The authors tested PBMT alone, 10 minutes of magnetic stimulation alone, and a combination of the two treatments. The Expanded Disability Status Scale and the Kurtzke and Barthel Index showed an improvement in the functional status of MS patients with the combination of PBMT and magneto-stimulation therapy having a synergistic effect. Due to the functional improvements obtained by using two physical modalities in combination, this paradigm should be further investigated.³³

PBM for Age Related Cognitive Decline

Animal Model Studies

In one study, the effects of PBMT with an 810 nm laser on the head of aged rats (20 months old) at 100 mW power for 30 seconds daily for 58 days were examined. The cortical activation of STAT3, ERK, and JNK increased in aged rats treated with PBMT. PBMT activated intracellular signaling pathways related to memory, cell survival, and glucose metabolism.³⁴ In another study, same protocol was applied at each point on the head of aged animals. This prolonged PBMT treatment protocol led to the expression and upregulation of CCO in different areas of the aged brain and improved energy metabolism.³⁵

The same protocol (810 nm laser, 100 mW power for 30 seconds delivered over 58 consecutive daily sessions) was applied to young and aged rats for comparison. They observed improved cognitive function in both young and aged rats. PBMT increased the spatial learning and memory of young rats, and it also reversed the decrease in memory and learning seen in aged rats. PBMT did not affect anxiety in young and aged rats as assessed using the elevated plus maze. In young rats treated with PBMT, they found reduced cortical levels of GM-CSF, MCP1, LIX, and TNF- α , but in aged rats, the cortical expression of IL-6, TNF- α , and IL-10 increased. PBMT reduced the expression of IP-10 and fractalkine in the hippocampus of aged rats. Therefore, PBMT using this

protocol could improve cognitive function and reduce neuroinflammation in aged rats.³

In another study, they carried out PBMT using an 810 nm laser with 100 mW power for 30 seconds on the head of aged rats overlying different brain regions, including sensory-motor and limbic areas. The cortical metabolomics profiling of aged rats exposed to PBMT showed that the metabolite levels (adenine, creatine phosphate, and tryptophan) in aged rats reached the basal level found in young rats. The concentration of acetate and guanosine triphosphate (GTP) was higher in the hippocampus of PBM-treated aged rats. In young rats, cortical metabolic pathways were enhanced after PBMT. Therefore, PBM benefited both young and aged rats.³⁶

Clinical Studies

Transcranial infrared laser stimulation (TILS) at 1064 nm, 250 mW/cm², was applied to the prefrontal cortex once a week for 5 weeks. PBMT led to a cognitive improvement in older adults as shown by the sustained attention psychomotor vigilance task (PVT) for reaction time and the delayed match-to-sample (DMS) memory retrieval task for working memory³⁷.

In another clinical trial involving 30 older adults with cognitive deficits, researchers examined the effects of PBMT (using 633 nm and 870 nm LEDs at 44.4 mW/cm² for 7.5 minutes) applied to the frontal region on changes in executive functions. This single-session treatment with LEDs improved frontal cognitive functions such as inhibition ability as tested by the modified Eriksen flanker test and flexible thinking as tested by the category fluency test.³⁸

PBM for Traumatic Brain Injury

Animal Model Studies

Oron et al were the first to assess the effects of PBMT for TBI in mice. Closed-head TBI in mice was produced using a weight-drop device. Mice were exposed to an 808-nm laser with two energy densities (10 and 20 mW/cm² over 2 minutes giving 1.2 and 2.4 J/cm²) 4 hours after TBI. Improvement in neurobehavioral function was observed by the measurement of the neurological severity score (NSS).³⁹

Mice were subjected to TBI using a controlled cortical impact and exposed to transcranial PBMT using a continuous wave 810 nm laser with 25 mW/cm² power density for 12 minutes and a spot size of 1 cm diameter positioned centrally on the top of the mouse head at 4 hours post-injury. The number of exposures to PBMT was once, three times on consecutive days, and 14 times on consecutive days. The results showed that the 3-times PBMT had the best effect on significantly improving neural function, decreasing lesion volume, and increasing cell proliferation in the brain (neurogenesis).⁴⁰

In another study, a single exposure of the mouse head

to a NIR laser (808 nm) 4 hours after creating a TBI lesion improved neurological performance and reduced the size of the brain lesion. An 808 nm diode laser was applied to the head 4 hours after TBI, using two energy densities 1.2 and 2.4 J/cm² over 2 minutes at power densities of 10 and 20 mW/cm². A significant improvement in motor behavior was observed in the laser-treated group from 5 days to 4 weeks.³⁹ In another study, mice were subjected to a closed head weight-drop TBI and treated with different laser wavelengths (665, 730, 810, or 980 nm), all with the same fluence of 36 J/cm² onto the scalp at 4 hours after injury. The 665 nm and 810 nm groups showed a significant improvement in the NSS in comparison to the control group after 5 to 28 days. However, the 730 and 980 nm wavelengths did not show any marked improvement in NSS.⁴¹

TBI was induced in mice using a controlled cortical-impact device, and 4 hours after TBI, treatment groups were exposed to a single session of transcranial PBMT. An 810-nm Ga-Al-As diode laser with a 1 cm diameter spot, a power density of 50 mW/cm² for 12 minutes, and a fluence of 36 J/cm² was delivered to the head. The laser was either continuous wave (CW) or pulsed at 10 Hz or 100 Hz with a 50% duty cycle. The NSS was assessed for 4 weeks. Results showed the 810 nm laser pulsed at 10-Hz produced a more pronounced improvement in the NSS compared to the CW and 100 Hz pulse regimens. The brain lesion volume of mice was significantly lower from 15 days to 4 weeks.⁴² Results indicated that the expression of brain-derived neurotrophic factor (BDNF) also increased in the DG and SVZ at 7 days. Synapsin-1, a marker for synaptogenesis and neuroplasticity, increased in the cortex at 28 days.⁴²

TBI rats were exposed to an 808 nm laser onto the scalp with a power density of 350 mW/cm² for 2 minutes for 15 days. Neuroprotection was observed in the animals after laser treatment.⁴³ In this study, TBI was created in rats using the fluid percussion injury method. TBI rats were treated with an 808 nm wavelength and a power density of 1000 mW/cm² for 5 minutes. Neurogenesis and improved cognitive function were observed in the TBI rats.⁴⁴

TBI was induced in BALB/c male mice aged 6-8 weeks. TBI-injured mice were treated with 810 nm PBMT with a power density of 25-mW/cm² onto the injured head with a 1-cm spot size for 5 minutes. Neurogenesis and neuroprotection were demonstrated after exposure to PBMT.⁴⁵ TBI was induced in 6-8 week old BALB/c male mice, and they were treated with an 810 nm laser with a power density of 50 mW/cm² onto the injured head with a 1-cm spot size for 12 minutes. Synaptogenesis (the production of new connections between existing brain cells) was demonstrated after exposure to PBMT.⁴²

In another study, TBI was induced in 8-week-old C57BL/6 mice. They were treated with an 810 nm laser at a power density of 150 mW/cm² onto the injured head

with a spot size of 1 cm for 4 minutes. This PBMT was effective in mediating the neuroprotection of TBI-injured mice.⁴⁶ TBI was induced in C57BL/6 transgenic mice with a deficiency in immediate early responsive gene X-1 (IEX-1 ko). The TBI mice were treated with an 810 nm laser with a power density of 150 mW/cm² onto the injured head with a spot size of 1 cm for 4 minutes. The IEX-1 ko mice had worse damage than wild-type mice after TBI, but PBMT suppressed the secondary brain injury and produced a noticeable anti-inflammatory effect.⁴⁷ Another study in TBI mice showed that PBMT stimulated neurogenesis as shown by a BrdU incorporation assay.⁴⁸

An 800 nm laser was applied directly to the contused parenchyma through a craniotomy in TBI mice 60-80 minutes after injury. The mice were treated with 60 J/cm² (500 mW/cm² × 2 minutes) and showed anti-inflammatory effects (fewer activated microglia) and improved performance in the Morris water maze.⁴⁹

Clinical Studies

In a case series, eleven TBI patients were treated using the Cytonsys CytonPro-5000 1064 nm laser, with an output power of 10 W, a power density of 500 mW/cm², and a spot size of 4.5 cm². In 20-minute sessions of TILS, patients tolerated a dose of 250 mW/cm² CW laser to each hemisphere. There were no adverse events. After 5-8 sessions, nine out of eleven patients showed clinically significant improvements on the GRC self-reported symptom scale and objective tests of neuropsychological function.⁵⁰

Naeser et al assessed the effects of red and NIR LEDs in 11 patients with chronic, mild traumatic brain injury (mTBI) suffering from persistent cognitive dysfunction. LED clusters (5.25 cm in diameter, 500 mW, 22.2 mW/cm², 13 J/cm²) were used for about 10 minutes each session (5 or 6 LED placements in each session). After 18 sessions of PBMT, neuropsychological tests were performed on the patients who reported better social function and an ability to perform interpersonal and occupational activities.⁵¹

A randomized double-blinded trial was performed on 36 participants with moderate or severe TBI. They used a 632 nm LED device with a power of 830 mW over an area of 400 cm². The cranial region was irradiated for 30 minutes, providing a total dose of 3.74 J/cm² each session. After 18 sessions, PBMT was found to be safe and effective in improving memory and cognition in TBI patients.⁵²

In another study, transcranial PBMT was employed to promote alertness and awareness in TBI patients with severe disorders of consciousness. Five patients were exposed to PBMT (785 nm, 10 mW/cm², CW mode, 21 diodes) for 10 minutes every day for six weeks. After 4 weeks, an improvement in general alertness and awareness was observed.⁵³

All the clinical studies discussed above were carried out on chronic TBI patients, but Figueiro Longo et al carried

out a trial on acute moderate TBI patients.⁵⁴ A randomized double-blind sham-controlled trial included 68 patients who were recruited within 72 hours of a head injury. Real PBMT employed a custom-made helmet containing 0.036 W/cm² energy and 810 nm LEDs providing a power density of 36 mW/cm² and a fluence of 43 J/cm² per 20-minute session. Patients were scheduled to receive three daily treatments, and forty-three participants (19 real PBMT and 24 sham) completed the study up to the 3-month follow-up. Magnetic resonance imaging at 3 months showed that radial diffusivity, mean diffusivity, and fractional anisotropy improved significantly in PBMT compared to sham. Clinical assessment using the Rivermead Post-Concussion Questionnaire showed improvements in the PBMT group, but this was not significant compared to the sham group.

PBM for Alzheimer's Disease

Animal Model Studies

The most popular hypothesis to explain the cause of AD involves the aggregation of β -amyloid (A β) proteins in the brain, which increases pro-inflammatory cytokines and induces apoptosis. Many animal model studies have suggested that the application of PBMT can improve AD symptoms. For example, one study showed that transcranial PBMT at 1267 nm (32 J/cm²) may have contributed to the removal of A β plaques from the brain of AD transgenic mice. PBMT also improved memory and neurological deficits.⁵⁵ TLT at 808 nm was shown to reduce A β plaques in the brain of APP transgenic mice. After six months of TLT, there was an increase in mitochondrial function.⁵⁶ To explain the amyloid plaque removal mechanism, one study indicated that the treatment of the fibrosis β -amyloid (fA β) SH-SY5Y cell line with either 808 nm or 1064-nm lasers showed increased plaque phagocytosis by the downregulation of intracellular Ca²⁺ and IL-6 expression, resulting in increased viability.⁵⁷ Moreover, in 5XFAD transgenic mice that received PBMT with 610 nm LEDs for 14 weeks, there was improved cognitive performance accompanied by decreased amyloid plaque levels, possibly caused by the upregulation of insulin-degrading enzyme.⁵⁸ The treatment of AD mice with 1072 nm LEDs at 5 mW/cm² for 12 months decreased brain cell apoptosis by the upregulation of stress response protein expression.⁵⁹ Another study reported that the decreased apoptosis of neuronal cells after 632.8 nm He-Ne laser treatment was caused by AKT upregulation and increased activity in the Akt/GSK3 β / β -catenin pathway.⁶⁰

PBMT with an 808 nm diode laser led to the upregulation of antioxidant capacity in the rat hippocampus by regulating mtDNA oxidative metabolism and mitophagy, CCO activity, and ATP synthesis.⁶¹ Several studies reported that PBMT can increase ATP levels and mitochondrial

function in mouse models of AD.⁶² Moreover, transcranial PBMT using both red and NIR wavelengths could reduce age-induced mitochondrial dysfunction.⁶³

PBMT led to the upregulation of BDNF by the activation of CRE-binding protein (CREB) transcription factor and improved neuronal and dendritic function in the hippocampus of AD mice.⁶⁴ Another study reported that PBMT could mobilize mesenchymal stem cells (MSCs) from the bone marrow and promote their homing to the brain to increase amyloid phagocytosis.⁶⁵

Clinical Studies

In a clinical trial study, the effect of daily treatment for 28 consecutive days with 1060–1080 nm LEDs on AD patients was investigated. They showed that memory, visual attention, and executive function were improved by PBMT.⁶⁶ Maksimovich et al used an intravascular catheter to allow an optical fiber to be advanced into the brain, where a 633 nm laser with 20 mW power was used for 20–40 minutes. A single session of PBMT reduced dyscirculatory angiopathy of AD and improved cerebral microcirculation and metabolism, leading to the regression of dementia and cognitive improvement.⁶⁷

Saltmarche et al reported a case series of five dementia patients with mild to moderately severe cognitive impairment treated with PBMT.⁶⁸ A headset with 810 nm, 10 Hz pulsed LEDs plus intranasal PBM was used to treat the cortical nodes of the DMN (bilateral mesial prefrontal cortex, precuneus/posterior cingulate cortex, angular gyrus, and hippocampus). The protocol involved weekly, in-clinic use of a transcranial/intranasal PBMT device and daily at-home use of an intranasal-only device for 12 weeks. There was a significant improvement in MMSE and ADAS-cog scores after 12 weeks of PBMT, along with better sleep, fewer angry outbursts, less anxiety, and less wandering. There were no adverse effects, but declines were observed during the 4-week follow-up no-treatment period.

A trial of in-home PBMT in AD patients used the Vielicht Neuro-Gamma device with 810 nm 40 Hz pulsed LEDs with 100 mW power on the head plus an intranasal LED with three sessions per week for 12 weeks. These patients showed improvements in the ADAS-cog score, increased cerebral perfusion, and increased connectivity between the posterior cingulate cortex and lateral parietal nodes within the default-mode network in the PBM group.⁶⁹

In a prospective randomized controlled trial, AD patients would be treated with 630 nm LEDs included in a helmet and in an abdominal belt. The treatment was proposed to be 5 times per week continued for 24 weeks. At the end of the trial, cognitive function and behavioral performance in mild to moderate AD patients were expected to be improved.⁷⁰

PBM for Parkinson's disease

Animal model studies

Investigators have used several different animal models of PD to test the effects of PBMT. One study induced an electrode-mediated injury in the substantia nigra (SN) region of the brain in rats, followed by bilateral microinjections of 6-hydroxydopamine. The effects of two types of equipment, a 630 nm laser (4 J/cm², 45 mW) and 627 nm LEDs (4 J/cm², 70 mW), were compared. After 30 days, PBMT was administered daily for seven days using a laser or an LED. In the laser group but not the LED group, a significant increase in IL-2 was observed. An increase in anti-inflammatory cytokine IL-10 and lower levels of pro-inflammatory TNF- α were observed in both PBMT groups. The laser group showed the most pronounced improvement in motor performance in the open field test.⁷¹

Another study used a chronic MPTP-induced mouse model of PD. A 670 nm laser was used to deliver 5 J/cm² onto the substantia nigra pars compacta location on the head. PBMT improved the number of TH cells, suggesting that 670 nm PBMT could protect dopaminergic cells from degeneration.⁷² In another study, the effect of the time when PBMT was administered (before, at the same time, and after MPTP was injected) on the progression of PD was investigated. Male BALB/c mice were treated with MPTP and received two times PBMT with 670 nm LEDs at 5.3 mW/cm² over 6 days. The results showed that behavioral performance was improved in all conditions, showing that PBMT was both fast-acting and long-lasting.⁷³

In another study, 670 nm LEDs were used to deliver 4 J/cm² over 90 seconds at the substantia nigra pars compacta (SNc) region of the brain of 5-month-old K3 transgenic mice. K3 mice express the human tau protein carrying the FTD mutation K369I. When PBMT was delivered 8 times over 4 weeks, it reduced oxidative stress in the brain and protected dopaminergic cells in the SNc region from degeneration.⁷⁴ In another study, PD was induced by the supranigral injection of lipopolysaccharide in male Sprague-Dawley rats. Irradiation of the head with 670 nm LEDs at 50 mW/cm² was done twice a day for 6 days after surgery. The results confirmed that there was a protective effect of PBMT in the early stage of PD but not at the late stage disease.⁷⁵

Some animal models of PD produced by MPTP show evidence of leakage from the brain vasculature. In a study by Miguel et al, the effect of 670 nm LEDs at 50 mW/cm² on the leakage of brain vessels was investigated. PBMT was started 24 hours after the induction of PD and delivered for 3 minutes daily for 7 days. PBMT decreased labeled albumin in both brain regions (SNc and CPu), suggesting that PBMT may reduce brain vascular leakage.⁷⁶

Clinical Studies

In one study, platelets were isolated from normal or PD volunteers. Next, cybrid cell lines were created by fusing the platelets with mtDNA-free Rho0 cells created from the SH-SY5Y neuroblastoma cell line. The effect of PBM using an 810 nm laser with 50 W/cm² power was examined on the axonal transport process in these cybrids. The speed of mitochondrial movement along the axons in PD cybrid neurites was significantly increased after 40 seconds of irradiation.⁷⁷

In a proof-of-concept clinical study, patients with PD received PBMT with 904 nm LEDs for 12 weeks at 11 sites (9 on the abdomen, 2 on the neck). Patients then continued to self-administer PBMT 3 times per week for 25 or 40 weeks. Patients showed improved mobility, cognition, and dynamic balance.⁷⁸

The effects of simultaneous treatment with hydrogen water and PBMT on PD patients were investigated. 18 patients with PD at stages II-III received daily PBMT with a 940 nm laser and also drank hydrogen water. After two weeks, the patients showed improvements in the Unified Parkinson Disease Rating Scale and the clinical severity of the disease.⁷⁹

PBM for Amyotrophic Lateral Sclerosis

Animal Model Studies

Transgenic mice expressing multiple copies of the G93A mutant form of superoxide dismutase 1 (SOD1) develop motor neuron pathology and clinical symptoms similar to those seen in patients with amyotrophic lateral sclerosis (ALS). The effects of PBMT with an 810 nm diode laser, with 140 mW in a 1.4 cm² spot area, were studied in G93A SOD1 transgenic mice. The synergistic effects of PBMT combined with riboflavin on motor performance were investigated. Results showed that the 810 nm PBMT neither extended survival nor improved the outcomes of motor performance. However, the rotarod test showed a significant improvement in the PBMT group in the early stage of the disease.⁸⁰

Clinical Studies

In a case report study, the effect of PBMT using two lasers, one at 810 nm and the other at 890 nm, was reported. The 810 nm laser had a power density of 30 W/cm² in continuous mode and the 890 nm laser had 10 W/cm² in pulsed mode. A 69-year-old male with ALS was treated with PBMT at cervical, brachial plexus, sites along the vertebral column, mid sternum, umbilicus, and pelvis in 20 daily sessions and 3 cycles with a 40-day break. The result of the first cycle showed improved mobility of hands and better respiratory function. After the second cycle, the motor power of the upper and lower limbs increased. Additional improvement was still observed after the third cycle. However, the symptoms of ALS returned in the interval between the second and third cycles, and twenty

days after the end of the last cycle.⁸¹

In another study, the effects of PBMT using an intravenous 632.8 nm laser with power of 10 mW were investigated in ALS patients. The application of PBMT 8 times in two weeks reduced the respiratory rate and increased the peripheral oxygen saturation, while increasing the sympathetic tone by raising the LF/HF ratio of heart rate variability. These results were attributed to the stimulation of the sympathetic nervous system and the modulation of hyperkinetic hemodynamics.⁸²

PBM for Spinal Cord Injury

Animal Model Studies

A spinal cord injury (SCI) is typically caused by traumatic damage, initially leading to the death of neuronal and glial cells. Secondary stages of an SCI include uncontrolled inflammation, nerve irritability, edema, ischemia, free radical production, cell death (apoptosis), glutamate overstimulation, and chronic demyelination with glial scar formation which prevents any axonal regeneration and causes subsequent neuropathic pain.

Stem cell transplantation has been investigated as a treatment for an SCI. This approach could be made more effective by PBMT because it enhances the proliferation, homing, differentiation, and paracrine effects of the stem cells. The combination of transplanted human umbilical cord stem cells (hUCMSCs) and PBMT on the injured area using a 630 nm laser at 100 mW/cm² power for 20 minutes was investigated in a rat SCI model. This combination improved the rats' ability to move better than either of these treatments alone. Using the combination treatment reduced inflammation, increased the number of Nissl bodies, and helped repair nerve damage in the injured spinal cord. The expression of NF-200 and glial fibrillary acidic protein increased in the damaged area, and the structure and arrangement of neurofilament proteins were improved.⁸³

One study compared the effects of laser polarization on the efficacy of NIR PBMT for an SCI. The movement scores of SCI rats after 808-nm PBMT were remarkably higher than control SCI rats from day 5 after injury regardless of which way the light was delivered. Rats with an SCI that were treated with parallel polarization had better movement from day 10 after their injury compared to those treated with perpendicular polarization.⁸⁴

Another study treated SCI rats with an 810-nm laser at 150 mW. At 14 days, the cavity size in the spinal cord was smaller, showing that PBMT reduced glial scar formation and tissue loss. Tightening in the injured tissue was improved at 14 days after PBMT. An inter-group comparison semi-quantitatively measured changes in lipids, phosphatidic acid, CSPGs, and cholesterol in an SCI and after PBMT.⁸⁵

A similar report described the effects of PBMT administered every day after an SCI was created in rats.

A continuous 810 nm diode laser was used for 60 minutes per day for two consecutive weeks in the PBMT group. PBMT prevented the activation of neurotoxic microglia and astrocytes, reduced secondary inflammation and tissue apoptosis, increased the number of functional neurons, and improved the recovery of motor function after the SCI. The upregulation of Lcn2 and the activation of the JAK2-STAT3 pathway after the SCI were inhibited by PBMT.⁸⁶

A different animal model of SCI involved the creation of a lesion at the T9 spinal cord in Bama miniature pigs (*Sus scrofa domestica*). Then a diffusing optical fiber was embedded into the tissue and was used to deliver NIR light (810 nm) onto the spinal cord surface. Daily exposure to 200, 300, 500, or 1000 mW was investigated over a 14-day period. Results showed that directly exposing the spinal cord surface to 200 and 300 mW did not cause any notable changes in temperature, stress, inflammation, or nerve cell death. These factors increased slightly when the surface was exposed to 500 mW of irradiation. However, when it was exposed to 1000 mW of irradiation, there was a large increase in temperature, causing heat shock, inflammation, and apoptosis.⁸⁷

Sotoudeh et al asked whether PBMT could treat an SCI in rats caused by temporary induced ischemia-reperfusion in the spinal cord. The 810 nm laser used had a power of 150 mW and the skin in the area was exposed to 1,589 J/cm² per day (0.53 W/cm², 450 J). PBMT was given for 20 minutes four times a day for 3 consecutive days. The structure of the gray matter was preserved, with most of the neuroglial cells surviving the ischemic insult in the PBMT group and preventing apoptosis as shown by TUNEL staining.⁸⁸

The combination of PBMT and meloxicam for an SCI was investigated in an SCI rat model. A compression injury was induced at the T8-T9 segment of the rat spinal cord. PBMT (810 nm, 200 mW, 8 seconds, and 2 weeks) and meloxicam (1 mg/kg) were tested separately and in combination. All three treatment groups showed similar improvements in the BBB motor test scores.⁸⁹

Mojarad et al used a 660 nm laser at 30 mW/cm² for 30 minutes on 9 different points on the back of SCI rats. After 1 or 2 weeks of treatment with PBMT, there was an improvement in mechanical hyperalgesia and heat hyperalgesia. PBMT also helped to lower the high level of IL-6 that was caused by the compression SCI.⁹⁰

Medalha et al compared the effects of PBMT and electrical field stimulation (EFS) on bone loss in SCI rats. PBMT was delivered using an 830 nm laser (CW, 30 mW/cm², 250 J/cm²), while EFS was applied at 1.5 MHz with a 1:4 duty cycle (30 mW, 20-minute duration) in rats with an SCI. Both treatments helped to increase the inner diameter and internal and external areas of their leg bones. However, the treatments did not have any effect on the strength or density of the bones.⁹¹

Another study tested two treatments for pain after an SCI in male rats: chondroitinase ABC and PBMT. The rats received a 660 nm laser treatment for 2 weeks, starting 30 minutes after injury. The chondroitinase ABC injection was given one week later. The combination decreased allodynia and thermal hyperalgesia and improved functional recovery, but it did not affect mechanical hyperalgesia. Pain-related biochemical factors (BDNF and IL6) were reduced, while the anti-nociceptive factors (Gad65 and GDNF) were up-regulated.⁹²

An 810 nm wavelength laser, continuous wave, with a power of 150 mW for 3000 seconds per day, reduced inflammation and improved functional recovery.⁹³

Wu et al used PBMT in two SCI different models including a contusion model and a dorsal hemisection model. PBMT with an 810 nm laser was delivered transcutaneously at the lesion site immediately after injury and daily for 14 consecutive days. The laser diode had an output power of 150 mW and the daily fluence was 1589 J/cm² in a 0.3 cm² spot area. In both models, PBMT increased the average length of axonal regrowth and the total axon number.⁹⁴

Finally, various fluences of 808 nm laser PBMT, including 500 J/cm², 750 J/cm² and 1000 J/cm², were tested in SCI rats. PBMT was applied daily for 14 consecutive days. Functional behavior and tactile sensitivity were improved in all treatment groups, while the highest fluence produced the most pronounced decrease in the volume of injury. CD-68 expression was reduced, suggesting the inhibition of the inflammatory process in the spinal cord.⁹⁵

Clinical Studies

A clinical trial comparing PBMT plus physical therapy with placebo plus physical therapy was carried out in SCI patients.⁹⁶ Twenty-five subjects were split into two groups: one received placebo plus physiotherapy, while the other got active PBMT plus physiotherapy. Electromyographic evaluation was done before and after 12 PBMT sessions, and 30 days after the treatment ended. The injured area was exposed to an 808 nm diode laser. After 30 days, the average signal of the brachial biceps and femoral quadriceps muscles was higher when resting, and there were no significant findings relating to resting and isotonic contractions in the pre-PBMT or immediately post-PBMT when doing isotonic contractions.

Another study implanted a medical scattering optical fiber above the surgically exposed spinal cord in SCI patients.⁹⁷ Twelve patients with an acute SCI requiring posterior decompression surgery were recruited. The fiber was implanted above the spinal cord and delivered 810 nm light at 300 mW for 30 minutes daily over 7 consecutive days. Direct PBM at the SCI site did not result in any clinical alterations in the patient's vital signs. All patients showed increased WBC, The Neutrophil-Lymphocyte

Ratio (NEU), and high-sensitivity C-reactive protein (hs-CRP) at day 3 after irradiation compared to before surgery, but recovered to normal by day 7. Eosinophil and basophil levels, which are strongly connected with allergic responses, were within normal ranges throughout the irradiation protocol. Patients' coagulation functions (PT, APTT, and TT) were all within normal limits. The American Spinal Injury Association (ASIA) sensory and motor values of all patients remained unchanged throughout the irradiation treatment. Nevertheless, the ASIA sensory and motor scores were improved in the follow-up in all patients. The procedure was safe and practical, and it did not cause additional harm to the patient. This exploratory investigation may provide a novel paradigm for clinical PBMT of an acute SCI.

The effects of PBMT combined with physiotherapy on sensory-motor responses below the damage level and quality of life were evaluated in patients with SCI.⁹⁸ Thirty individuals were randomly assigned to either the PBMT (808 nm, 120 mW + physiotherapy) or the sham group (sham PBM + physiotherapy). The active PBM group showed improved sensation and perception of muscular contraction 30 days after treatment as compared to the sham group. The WHOQOL-BREF questionnaire showed that the active PBM group had a significantly higher overall quality of life than the sham group following treatment. Physiotherapy coupled with PBMT improved sensory-motor rehabilitation in individuals with an SCI, as well as their feeling of health and overall quality of life.

PBM for Epilepsy

Animal Model Studies

Convulsive status epilepticus (SE) is the most common neurological emergency in children. In 2020, Tsai et al evaluated the effects of transcranial PBMT on peripubertal Sprague Dawley rats with epilepsy induced by the injection of pentylenetetrazole (PTZ, a GABA receptor antagonist).⁹⁹ An 808 nm laser was applied transcranially to rats for 100 seconds prior to the PTZ injection. Behaviorally, Transcranial photobiomodulation (tPBM) attenuated the mean seizure score, reduced the incidence of SE, and lowered mortality. tPBM reduced dark neurons in the cortex, hippocampus, thalamus, and hypothalamus, while reducing apoptosis in the hippocampus.

Next, in the same group, the combination of 808 nm tPBM with valproic acid for treating SE in the same animal model was investigated¹⁰⁰. It was found that tPBM plus low-dose valproic acid could ameliorate SE severity and increase the latency to stage 2 seizures. However, the combination of tPBM with high-dose valproic acid exacerbated the severity of SE.

In a third study, Tsai et al investigated the effects of 808 nm tPBM on neuroinflammation in the PTZ peripubertal rat model of SE.¹⁰¹ It was found that tPBM could reduce neuron-specific enolase (NSE) and ionized calcium-

binding adapter molecule 1 (Iba-1) immunoreactivity in the CA3 region of the hippocampus. Moreover, GFAP immunoreactivity was reduced in the CA1 region. They concluded that tPBMT could improve SE by inhibiting neuroinflammation, astrogliosis, and microgliosis.

In an *in-vivo* study by Vogel et al, the effects of 780 nm tPBM on epilepsy in Wistar rats were compared with a diet rich in omega-3 fatty acids (Ω -3).¹⁰² Wistar rats were subjected to a stroke that caused epilepsy marked by long-term recurrent spontaneous abnormal electrical discharges. Rats received repetitive 780 nm laser PBMT on the scalp or an oral diet with Ω -3 for 2 months after the photothrombotic stroke. EEG recordings were performed 60 days after the treatment finished. PBM (but not Ω -3) reduced both electrographic seizure duration and spike numbers in the ipsilateral and contralateral cortex and ventral posteromedial thalamic nucleus.

An *in vitro* and *in vivo* study carried out in 2023 by Hong et al demonstrated that 825 nm tPBMT could improve seizures.¹⁰³ The *in vitro* study was performed on primary hippocampal neurons from embryonic (E17) rat pups, and the *in vivo* study was performed on male C57BL/6 mice injected with pilocarpine to induce temporal lobe epilepsy. It was found that tPBM could reduce seizures and improve hypoactivity, anxiety and impaired memory. PBMT reduced neuroinflammation, neuronal cell loss, and synaptic degeneration while simultaneously increasing synaptic connections via the regulation of Nlg3 (neuroligin-3) gene expression.

Clinical Studies

Although there have not yet been any published studies of PBMT for epilepsy in humans, there have been some publications suggesting that it should be tested in clinical trials^{104 103 105}. One reason that these trials have not yet been undertaken may be that epilepsy is frequently cited as a contraindication to PBMT by clinical practitioners, although there is no hard evidence that it has produced any seizures in susceptible subjects.

PBM in the Peripheral Nervous System

Animal Model Studies

PBMT has been tested as a therapy for enhancing the repair of peripheral nerve injuries. Rochkind et al reported that PBMT applied simultaneously to the injured sciatic nerve and the corresponding segment of the spinal cord in rats promoted the process of regeneration of the injured peripheral nerve. The CW 808 nm laser was used daily for 14 consecutive days (200 mW, 2997 seconds/day, 1,589 J/cm² per day, 0.53 W/cm², and 450 J). PBMT improved the nerve function and suppressed immune cell activation and cytokine/chemokine expression.^{106,107}

Another study assessed the regeneration effects of PBMT on the crushed facial nerve. A 4-mm crush injury was produced in a buccal branch of the facial nerve. PBMT

(980 nm; 70 mW; 16.71 J/cm²) was applied to the crush injury after surgery for 5 weeks. The results showed nerve regeneration, increased expression of growth factors, and improvement of facial movement.¹⁰⁸

In a pilot double-blind randomized study by Rochkind et al, a transverse section was created in the right sciatic nerve, and a 0.5-cm nerve segment was removed in 20 rats. Ten of the 20 rats were given post-operative, transcutaneous 780-nm laser PBMT (200 mW; 15 minutes) for 14 consecutive days to the corresponding segment of the spinal cord and to the injured nerve. At 3 months after treatment, they observed that PBMT promoted the regeneration and reconnection of the severed nerve and increased the total number of myelinated axon.¹⁰⁹

Barbosa et al carried out a study comparing the effects of PBMT with two different lasers in 27 Wistar rats subjected to a sciatic nerve crush injury.¹¹⁰ They used a 660 nm laser (10 J/cm², 30 mW, 0.06 cm² beam) and an 830 nm laser (10 J/cm², 30 mW and 0.116 cm²) daily for 21 days. The sciatic functional index (SFI) was measured before surgery and on days 7, 14, and 21 after surgery. The SFI was improved in the 660 nm laser group on the 14th day of PBMT.

Gigo-Benato et al carried out a study to investigate the effects of PBMT in a model of end-to-side neurorrhaphy in rats, an innovative technique for peripheral nerve repair.¹¹¹ After complete transection, the left median nerve was repaired by end-to-side neurorrhaphy on the ulnar "donor" nerve. They compared two different lasers used alone and in combination 3X/week for 3 weeks starting from postoperative day 1. A CW 808 nm laser and a pulsed 905 nm laser and the combination of the two were compared. Functional testing was carried out every 2 weeks after surgery by means of the grasping test. After 16 weeks, the recovery of muscle mass was assessed by weighing the muscles innervated by the median nerve. The repaired nerves were removed and analyzed by light and electron microscopy. The results showed that the combination of two lasers produced the best results in terms of nerve function, recovery of muscle mass, and faster myelination of the regenerated nerve fibers.

In another study, PBMT was investigated in rabbits subjected to sciatic nerve injury.¹¹² Six adult male rabbits received complete longitudinal and reverse sections of the nerve followed by crushing of the neural sheath. Treatment was carried out directly after the trauma using a 632.8 nm laser delivering 31.5 J/cm² once a day for 10 consecutive days. After two weeks, the PBMT group demonstrated nerve regeneration and repair, characterized by thicker nerve fibers and more regular myelin layers, which were not observed in controls.

Clinical Studies

In a randomized, double-blind, placebo-controlled trial, 18 patients with peripheral nerve injuries were

randomized to either placebo (non-activated LEDs) or PBMT (780 nm; 250 mW) groups. Twenty-one consecutive daily sessions of either laser or placebo were administered transcutaneously for three hours over the damaged peripheral nerve (delivering 450 J/mm²) and for two hours over the corresponding spinal cord segment (delivering 300 J/mm²). The results indicated that 780-nm PBMT could promote nerve motor function and functional recovery after six months.¹¹³

Esmaelinejad et al reported a randomized, double-blinded clinical trial of PBMT in 40 patients undergoing a surgical operation called sagittal split ramus osteotomy for orthognathic realignment.¹¹⁴ This surgical procedure often produces an injury to the trigeminal nerve. Patients in the active PBMT group received an 810 nm laser (70 mW; 140 mW/cm²; 8.4 J/cm²; 60 seconds) on four points on days 0 (immediately after the surgery), 1, 2, 3, 5, 7, 9, 11, 13, and 15 (10 sessions), with a placebo laser used in the control group. Patients in the active PBMT group demonstrated improved sensitivity to heat and pressure and reported higher satisfaction with the treatment.

Fuhrer-Valdivia et al carried out a similar clinical trial.¹¹⁵ In the active group, 17 patients received PBMT (810 nm, 100 mW, 0.283 cm², 90 sec, 3 points, 32 J/cm², 9J) on days 1, 2, 3, 5, 10, 14, 21 and 28, while the control group received a placebo laser. In the active group, 68% achieved normal sensitivity versus only 21% in the placebo group, and 87% of PBMT recovered directional discrimination at 6 months after surgery.

A systematic review and meta-analysis carried out by Firoozi et al on eight published papers concluded that PBMT for sagittal split ramus osteotomy showed a “striking” benefit one month post-surgery.¹¹⁶

PBM for Retinal and Optic Nerve Pathology

Animal Model Studies

Eells et al showed that PBMT could protect the retina after injury in a rodent model of methanol-induced toxicity, and they also carried out in vitro experiments.¹¹⁷ PBMT employing 670 nm LEDs with an energy density of 12 J/cm² was applied in three fractions at 5 minutes, 25 minutes, and 50 hours after systemic methanol administration. They reported that PBMT could help recovery from retinal injury and also induce the cell proliferation of visual neurons in culture.

The effectiveness of PBMT in the eye was assessed in models of traumatic optic nerve injury in rabbits and rats. The animals were exposed to the He-Ne laser (632.8 nm wavelength, 10.5 mW power, 1.1 mm beam diameter) for 2 minutes daily for 2 weeks. Results showed that PBMT was effective in repairing moderately injured nerves, whereas its benefits were not seen in severely injured nerves.¹¹⁸

An ophthalmic injury was induced by white light phototoxicity at 1800 lux for 3 hours, producing an injury

to the outer nuclear layer of the retina in pigmented rats. PBMT with 670 nm LEDs, 9 J/cm², and 60 mW/cm² was delivered in four fractions to rats after phototoxicity-induced retinal injury. After 1 month, significant retinoprotective effects of PBMT were observed in the injured rats.¹¹⁹

Another study used a rat model of retinitis pigmentosa caused by a rhodopsin mutation, which induced photoreceptor degeneration during early development. Rat pups were exposed to PBMT at 670 nm, 50 mW/cm², and 4 J/cm² for 5 days during the period of photoreceptor formation. PBMT led to an increase in the concentration of retinal cytochrome oxidase, superoxide dismutase and ciliary neurotrophic factor. Also, PBMTT reduced the rate of photoreceptor cell death.¹²⁰

Another study assessed the ability of PBMT to protect against retinal ganglion cell damage. Retinal degeneration was mediated by an intravitreal injection of the mitochondrial complex I inhibitor rotenone in rats. PBMT was delivered using 633 nm LEDs at 2 mW/cm², administering a total energy density of 21.6 J/cm² in six fractions (3.6 J/cm² per day). It was observed that PBMTT could ameliorate retinal neurodegeneration and visual dysfunction (Table 1).¹²¹

Clinical Studies

The clinical applications of PBMT in ophthalmology have mainly been in the treatment of dry age-related macular degeneration (AMD) and diabetic retinopathy (macular edema), which at present do not have any recommended treatments¹²².

The LIGHTSITE II randomized multicenter trial evaluated multiwavelength PBMT in dry AMD.¹²³ Forty-four patients and 53 eyes were treated with LEDs (590 nm, 4 mW/cm²; 660 nm, 65 mW/cm²; 850 nm 0.6 mW/cm²) or sham treatment for 5 minutes 3× per week over 3–4 weeks (9 treatments per series) with repeated series at 4 and 8 months. Approximately 35.3% of PBM-treated eyes showed ≥ 5-letter improvement at 9 months. Macular drusen volume did not increase over time in the PBM-treated group but did show increases in the sham-treated group.

Shen et al carried out an open-label, dose-escalation Phase IIa clinical trial involving 21 patients with central diabetic macular edema¹²⁴. Patients received 12 sessions of PBMT over 5 weeks for 90 seconds per treatment with a 670 nm laser at a setting of 25, 100 or 200 mW/cm² for the three sequential cohorts of 6–8 patients each. They found a significant reduction in central macular thickness at 2 months with 200 mW/cm², and significant reductions with all three settings at 6 months.

Conclusion

This review has highlighted the various PBM parameters and methods that have been used to treat each neurological

Table 1. Summary of Photobiomodulation Studies in Various Animal Models of Neurological Conditions

Animal Model	Wavelength	Power	Duration	Results
MCAO model of stroke	808 nm	0.9 J/cm ²	2 min	Improvement in functional performance, increase in neurogenesis and neuroprotection ¹⁶
RSCEM	808 nm	7.5-20 mW/cm ²	2 min	Improved functional behavior ¹⁹
RSCEM	808 nm	7.5 or 25 mW/cm ²	10 min	Enhanced functional recovery ¹⁸
Stroke rats	808nm	7.5 mW/cm ²	2 min	Attenuated neurological deficit ¹⁷
CVA model	904 nm	7 J/cm ²	63 s	Enhanced muscle resistance, Increase neurogenesis ²⁰
GCI	808 nm	8.0 mW/cm ²	2 min	Improved learning and memory, less apoptotic cell death in the CA1 hippocampus, mitochondria preservation and antioxidant activity increased cell survival ²¹
PT model of ischemic stroke	808 nm	350 mW/cm ²	2 min	Decreased infarct zone and synaptic injury, enhanced neurogenesis, and increase in ATP synthesis, lower pro-inflammatory cytokines and inhibition of reactive gliosis ²²
MCAO	660 nm	8.8 mW/cm ²	1, 5, 10 min	Promotes neuroprotection after ischemic stroke by inhibiting NOS activity and TGF- β 1 upregulation ²³
Multiple sclerosis	660 nm 904 nm	30 mW	20 s	Suppression of neuroinflammation and oxidative damage ²⁸
MOG-induced EAE	670 nm	28 mW/cm ²	3 min	Reduced tissue damage, reduced apoptosis ²⁹
Cuprizone	808	1.78 W/cm ²	20 s	Improved motor recovery and demyelinated area ³¹
Aged rats	810	100 mW power	30 s	Memory, cell survival, and glucose metabolism ³⁴
Young and aged rats	810	100 mW power	30 s	Improved cognition and neuroinflammatory response in aged rats ³
Aged rats	810	100 mW power	30 s	cortical metabolic pathways enhanced ³⁶
TBI	808 nm	10, 20 mW/cm ²	2 min	Improved neurobehavioural function ⁴¹
TBI	810 nm	25 mW/cm ²	12 min	Improved neural function, reduced lesion volume, neurogenesis ⁴⁰
TBI	810 nm	50 mW/cm ²	12 min	Lower brain lesion, neurogenesis, neuroprotection ⁴²
TBI	808 nm	350 mW/cm ²	2 min	Neuroprotection ⁴³
TBI	808 nm	1000 mW/cm ²	5 min	Neurogenesis, cognitive function ⁴⁴
TBI	810 nm	25 mW/cm ²	5 min	Neurogenesis, neuroprotection ⁴⁵
TBI	810 nm	150 mW/cm ²	4 min	Neuroprotection ⁴⁶
TBI	800 nm	500 mW/cm ²	2 min	Anti-inflammatory effect ⁴⁹
AD	1267 nm	32 J/cm ²	17 min	Improved memory and neurological deficit ⁵⁵
AD	808 nm	10 mW/cm ² Or 40 mW/cm ²	2 min Or 1 min	Increased mitochondrial function ⁵⁶
AD	610 nm	1.7 mW/cm ²	20 min	Increased cognitive performance, Decreased amyloid plaque ⁵⁸
AD	1072 nm	5 mW/cm ²	20 min	Upregulate stress response expression ⁵⁹
AD	808 nm	8.33 $\pm$ 0.27 mW/cm ²	2 min	Upregulation of anti-oxidant capacity, regulate mtDNA oxidative metabolism, mitophagy, cytochrome oxidase activity, ATP synthesis ⁶¹
AD	632.8 nm	12.74 mW/cm ²	0.7, 1.25, 2.5, and 5 min	Upregulation of BDNF, improve hippocampus function ⁶⁰
PD	630 nm	45 mW/cm ²	88 s	In laser group, increase in IL-2, Decrease TNF- α ⁷¹
PD	670 nm	5 J/cm ²	90 s	Protect dopaminergic cells from degeneration ⁷²
PD	670 nm	5.3 mW/cm ²	90 s	Improve in behavioural performance ⁷³
PD	670 nm	50 mW/cm ²	3 min	Decrease brain vascular leakage ⁷⁶
ALS	810 nm	140/1.4 mW/cm ²	2 min	Improve motor performance ⁸⁰
SCI	630 nm	100 mW/cm ²	20 min	Increase damaged area, Improve neurofilament proteins ⁸³
SCI	808 nm	25 mW/cm ²	20 min	Improved movement ⁸⁴
SCI	810 nm	150 mW/cm ²	50 min	Reduced glial scar ⁸⁵
SCI	810 nm	150 mW/cm ²	60 min	Decrease inflammation, prevent tissue apoptosis, increase functional neurons, improve recovery motor function ⁸⁶
SCI	810 nm	200, 300, 500 mW/cm ²	60 min	No change in inflammation and cell death ⁸⁷
SCI	810 nm	0.53 mW/cm ²	20 min	Prevent apoptosis ⁸⁸
SCI	810nm	200 mW/cm ²	8 s	Improvement in motor test score ⁸⁹
SCI	660 nm	100 mW/cm ²	45 s	Improvement in mechanical hyperalgesia and heat hyperalgesia ⁹⁰

Table 1. Continued.

Animal Model	Wavelength	Power	Duration	Results
SCI	830 nm	30 mW/cm ²	20 min	Increase in bone loss ⁹¹
SCI	660 nm	100 mW/cm ²	45 s	Decrease allodynia, thermal hyperalgesia, improve functional recovery ⁹²
SCI	810 nm	150 mW/cm ²	60 min	Decrease neuroinflammation ⁹³
SCI	810 nm	150 mW/cm ²	2997 s	Increase axonal regrowth ⁹⁴
SCI	808 nm	150 mW/cm ²	60 min	Decrease volume injury, decrease CD68, Inhibition of neuroinflammatory process ⁹⁵
Epilepsy	808 nm	1.333 W/cm ²	100 s	Decrease seizure score, decrease mortality, decrease apoptosis in hippocampus ⁹⁹
Epilepsy	780 nm	0.083 mW/cm ²	2 min	Decrease electro-graphical seizure, duration, and spike number ¹⁰²
Epilepsy	825 nm	40 mW/cm ²	380 s	Decrease seizure, improve hyperactivity and impaired memory, decrease neuroinflammation ¹⁰³
Peripheral nervous system	808 nm	0.53 mW/cm ²	2.997 s	Improve nerve function, Suppress immune cell activation and cytokine expression ¹⁰⁶
Peripheral nervous system	980 nm	70 mW/cm ²	30 s	Nerve regeneration, increased expression growth factors, Improve facial movement ¹⁰⁸
Peripheral nervous system	780 nm	200 mW/cm ²	15 min	Regeneration, Increase myelinated axon ¹⁰⁹
Peripheral nervous system	660 nm	30 mW/0.06 cm ²	20 s	Improve sciatic functional index ¹¹⁰
Peripheral nervous system	808 nm	200 mW/cm ²	9 min	Recovery of muscle mass, faster myelination of regenerated nerve fiber ¹¹¹
Peripheral nervous system	632.8 nm	25 mW/cm ²	15 min	Regeneration and repair of nerve fiber ¹¹²
Peripheral nervous system	670 nm	50 mW/cm ²	3 min	Recovery from retinal injury ¹¹⁷
Peripheral nervous system	632/8	10.5 mW/cm ²	2 min	Repair injured rats ¹¹⁸
Peripheral nervous system	670 nm	60 mW/cm ²	30 min	Renoprotective effects ¹¹⁹
Peripheral nervous system	670 nm	50 mW/cm ²	30 min	Reduced the rate of photoreceptor cell death ¹²⁰
Peripheral nervous system	633 nm	2 mW/cm ²	30 min	Ameliorate retinal neurodegeneration and visual dysfunction ¹²¹

MCAO: Middle cerebral artery occlusion, RSCM: Rabbit small clot embolic stroke model, CVA: Cerebrovascular Accident, GCI: Global cerebral ischemia, PT: Photothrombotic, TBI: Traumatic brain injury, ALS: Amyotrophic lateral sclerosis, SCI: Spinal cord injury.

condition, both in animal models and in human patients. However, authors generally did not compare different parameters and findings between preclinical and clinical studies. In addition, some studies lacked clear conclusions.

Tissue damage and functional deficits are major features of neurological disorders. The potential of PBMT to activate cellular processes involved in repair and tissue protection makes it a beneficial approach in the nervous system. According to the evidence obtained in animal models, PBMT can promote functional recovery and protect the nervous tissue against further damage.

Safety, non-pharmacological nature, and easy availability (especially of LED-based devices) suggest that the use of PBMT will continue to increase. The relatively low cost of PBMT compared to the cost of developing new drugs for nervous system disorders is another major advantage in its favor. The variability in PBM protocols across studies is a major limitation in the field. Therefore, it is difficult to directly compare results across studies and to establish optimal treatment parameters. There are limitations in clinical trial studies such as small sample sizes in early clinical trials, lack of blinding in some PBM studies, and lack of comprehensive safety concerns about adverse effects.

Future Directions

It is required to investigate the effects of PBM in a

large-scale, randomized, controlled trial with standard protocols. Treatment parameters should be optimized in terms of dose and response for certain nervous system disorders. Further research on the mechanisms of PBM in the nervous system, potentially using advanced neuroimaging and molecular techniques, will expand knowledge in the field to find the most effective cure.

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Competing Interests

There is no conflict of interest.

Ethical Approval

This research was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (reference number: IR.SBMU.LASER.REC.1401.006).

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