Current application and future directions of photobiomodulation in central nervous diseases

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Abstract
Photobiomodulation using light in the red or near-infrared region is an innovative treatment strategy for a wide range of neurological and psychological conditions. Photobiomodulation can promote neurogenesis and elicit anti-apoptotic, anti-inflammatory and antioxidative responses. Its therapeutic effects have been demonstrated in studies on neurological diseases, peripheral nerve injuries, pain relief and wound healing. We conducted a comprehensive literature review of the application of photobiomodulation in patients with central nervous system diseases in February 2019. The NCBI PubMed database, EMBASE database, Cochrane Library and ScienceDirect database were searched. We reviewed 95 papers and analyzed. Photobiomodulation has wide applicability in the treatment of stroke, traumatic brain injury, Parkinson’s disease, Alzheimer’s disease, major depressive disorder, and other diseases. Our analysis provides preliminary evidence that PBM is an effective therapeutic tool for the treatment of central nervous system diseases. However, additional studies with adequate sample size are needed to optimize treatment parameters.

Key Words: Alzheimer’s disease; central nervous system diseases; major depressive disorder; Parkinson’s disease; photobiomodulation; stroke; traumatic brain injury

Introduction
Photobiomodulation (PBM), an innovative therapeutic approach, utilizes light in the red (with wavelengths usually in the range of 600 to 700 nm) or near-infrared region (780 to 1100 nm), at a relatively low power density to minimize tissue damage (McGuff et al., 1965; Hennessy and Hamblin, 2017; Gordon and Johnstone, 2019). The photons can cause chemical changes within the cells and provoke various reactions, including the triggering of neuroprotective responses, improving blood flow, inducing metabolic changes and neurogenesis (Mitrofanis and Henderson, 2020). In 1967, Dr. Endre Mester first proposed the medical benefits of low-level laser therapy. Numerous studies thereafter investigated the medical application of low-level laser therapy and PBM. The therapeutic effects of PBM have been demonstrated in many studies on neurological diseases (McGuff et al., 1965), peripheral nerve injuries, pain relief (De Freitas and Hamblin, 2016) and wound healing (Houreld, 2014).

While the mechanisms underlying the therapeutic effects of PBM remain unclear, it has been thought that the photons induce the production of reactive oxygen species, increase electron transport, and trigger a series of downstream reactions. The resulting products, including nitric oxide (NO), reactive oxygen species, cyclic AMP and Ca2+, are second messengers that can activate transcription factors and impact the expression of genes related to cell proliferation and migration, inflammation and apoptosis (Avci et al. 2013; De Freitas and Hamblin, 2016). PBM can increase cerebral blood flow (CBF), enhance cellular metabolism, and prevent neurodegeneration (Rojas et al., 2012; Salehpour et al., 2018). Transcranial PBM refers to near-infrared light (NIR) applied to the head to treat neurological diseases. Research on transcranial PBM is still in infancy, but the limited studies in humans have shown encouraging outcomes in the treatment of stroke, traumatic brain injury (TBI), Parkinson’s disease (PD), Alzheimer’s disease (AD) and major depressive disorder (MDD). However, its clinical application still remains controversial. Overall, the results are not yet consistent as parameters has been continuously tested and optimized. Therefore, to assess the therapeutic potential of PBM, we conducted this review to summarize existing studies on PBM in the central nervous system (CNS) diseases.

Literature Search
To evaluate the current application of PBM in CNS diseases, we conducted a literature review of all published original research studies involving PBM in subjects with CNS diseases. Articles involving treatment for stroke, TBI, PD, AD and MDD were included.

The literature search was conducted up to January 2019 using the NCBI PubMed database, EMBASE database, Cochrane Library and ScienceDirect database using the following search terms: (“transcranial photobiomodulation”) OR ((photobiomodulation OR “low level laser therapy”) AND brain) OR ((photobiomodulation OR “low level laser therapy”) AND (brain injury OR stroke OR cerebrovascular disease OR depressive disorder OR neurodegenerative disease)). Only English language articles published in peer-reviewed journals were included. The details of the included studies are presented in Tables 1–6. In total, we identified 95 published papers relating to stroke, TBI, PD, AD and MDD.

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Photobiomodulation for Stroke

As summarized in Table 1, PBM has been evaluated in stroke animal models and patients. Lapchak et al. (2004) investigated the efficacy of laser therapy for stroke in a rabbit small clot embolic stroke model (RSCEM). They found that PBM improved behavioral performance and had long-term benefits. They also compared the effects of continuous wave (CW) or pulse wave (PW) PBM, and concluded that PW provides better outcome (Lapchak et al., 2007). In another study, 169 rats were irradiated ipsilaterally, contralaterally and on both sides, and all treated groups showed significant improvement (DeTaboada et al., 2006). The significant functional improvement provided by PBM may be associated with the induction of neurogenesis (Oron, 2006). Studies

### Table 1 | Photobiomodulation for stroke in animal and clinical studies

| Animal studies          | Animals Modeling method                                                                 | Wavelength (nm) | Irradiation parameters | Power density/energy density |
|-------------------------|----------------------------------------------------------------------------------------|-----------------|-------------------------|------------------------------|
| Lapchak et al. (2004)   | 14 Male New Zealand white rabbits Microclots were prepared from blood drawn from a donor rabbit and allowed to clot at 37°C | 808             | CW                      | 7 mW/cm² for 2 min (0.84 J/cm²) or 25 mW/cm² for 10 min (15 J/cm²) |
| Lapchak et al. (2007)   | Male New Zealand white rabbits Injection of clot particle suspension                    | 808             | PW at 100 Hz or 1000 Hz, or CW | 7.5 mW/cm², 0.9–1.2 J        |
| DeTaboada et al. (2006) | 169 Atherothrombotic model rats                                                         | 808             | /                       | 7.5 mW/cm² at brain tissue level, 0.9 J/cm² per site (in total 2 sites) |
| Oron et al. (2006)      | 43 Adult male Sprague-Dawley rats; 18 male Wistar rats (1) Permanent occlusion of the middle cerebral artery through a craniotomy or (2) insertion of a filament | 808             | PW at 70 Hz or CW       | 7.5 mW/cm² at brain tissue level, 0.9 J/cm² per site (in total 2 sites) |
| Yang et al. (2018)      | Male Sprague-Dawley rats /                                                           | 808±3.0         | CW                      | 25 mW/cm² at cerebral cortex tissue level, 350 mW/cm² on the scalp |
| Leung et al. (2002)     | Male Sprague-Dawley rats Unilateral occlusion of middle cerebral artery                | 660             | PW at 10 Hz             | 8.8 mW, 2.64, 13.2, or 26.4 J/cm² |
| Lapchak et al. (2008)   | Male New Zealand white rabbits Injection of emboli                                     | 808             | CW                      | 10 mW/cm²                     |
| Lapchak and De Taboada (2010) | 24 Male New Zealand white rabbits Injection of emboli                                    | 808             | PW at 100 Hz or CW     | 7.5, 37.5, or 262.5 mW/cm²; 0.9, 4.5, or 31.5 J/cm² |
| Yip et al. (2011)       | Male Sprague-Dawley rats Occlusion of right middle cerebral artery for 1 h              | 606             | PW at 10 Hz             | 8.8 mW, 2.64, 13.20, or 26.40 J/cm² |
| Choi et al. (2012)      | Male Wistar rats Occlusion of the right middle cerebral artery                          | 710             | CW                      | 0.042 mW/cm², 1.796 J/cm²     |
| Huisa et al. (2013)     | Male New Zealand white rabbits Injection of microemboli                                 | 808.5           | CW                      | 7.5, 10.8, or 20 mW/cm²       |
| Fukuzaki et al. (2015)  | Adult FVB mice Occlusion of bilateral common carotid artery                            | 532             | CW                      | 845 mW/cm², 30.4×10² J/cm²    |
| Lapchak and Boitano (2016) | 60 Male New Zealand white rabbits Injection of emboli                                   | 808             | CW                      | 7.5 mW/cm², 0.9 J/cm²         |
| Lee et al. (2016)       | Male mice (C57BL/6J) Photothrombosis of the cortical microvessels                       | 610             | CW                      | 1.7 mW/cm², 2 J/cm²           |
| Meyer et al. (2016)     | One male New Zealand white rabbits Injection of emboli                                 | 808.5           | CW or PW at 10 or 100 Hz | 7.5–333 mW/cm²                |
| Lee et al. (2017a)      | Mouse photothrombotic cerebral focal ischemia model                                     | 610             | CW                      | 1.7 mW/cm², 2 J/cm²           |
| Lee et al. (2017b)      | 17 Male CS7BL/6J wild-type and eNOS mice Occlusion of the right middle cerebral artery | 610             | CW                      | 1.7 mW/cm², 2 J/cm²           |
| Yun et al. (2017)       | 24 Male Sprague-Dawley rats Occlusion of the left middle cerebral artery                | 650             | PW at 100 Hz            | 30 mW                        |
| Argibay et al. (2019)   | Male Sprague-Dawley rats Occlusion of the middle cerebral artery                        | 830             | CW                      | 0.28 J/cm²                    |

| Clinical studies        | Subjects Wavelength (nm) Irradiation parameters | Power density/energy density |
|-------------------------|-----------------------------------------------|-------------------------------|
| Lampl et al. (2007)     | 120 Patients 808 CW 10 mW/cm², 1.2 J/cm²       |
| Zivin et al. (2009)     | 600 Patients 808 CW 10 mW/cm², 1.2 J/cm²       |
| Zivin et al. (2014)     | 630,316 Patients were allocated to treatment group versus 314 allocated to controls 808 CW 10 mW/cm², 1.2 J/cm² |
| Boonsong et al. (2012)  | A 29-year-old woman with brainstem stroke 660 and 850 CW 1400 mW, 2.95 J/cm² |
| das Neves et al. (2016) | 15 Subjects (6 males and 9 females) with cerebrovascular accident and spastic hemiparesis 808 CW 3.18 W/cm², 127.39 J/cm² |
| Jan et al. (2017)       | 38 Patients; LASER group (20 patients) and interventional current group (18 patients) 905 CW 400 mW, 6 J/cm² |

CW: Continuous wave; eNOS: endothelial nitric oxide synthase; PW: pulsed wave.
Table 2 | Photobiomodulation for traumatic brain injury in animal and clinical studies

| Animal studies | Animal models | Modeling method | Wavelength (nm) | Irradiation parameters | Power density/energy density |
|----------------|--------------|----------------|----------------|------------------------|-----------------------------|
| Oron et al. (2007) | 24 Mice | Weight-drop device | 808 | CW | 10 or 20 mW/cm², 1.2 or 2.4 J/cm² |
| Oron et al. (2012) | / | Weight-drop device | 808 | PW at 100Hz or CW | / |
| Ando et al. (2011) | 40 Mice | Controlled cortical impact | 810 | CW; PW at 10 Hz and 100 Hz | 50 mW/cm², 36 J/cm² |
| Wu et al. (2012) | 28 Adult male BALB/c mice | Controlled weight drop onto the skull | 665, 730, 810, or 980 | CW | 150 mW/cm², 36 J/cm² |
| Anders et al. (2014) | 22 New Zealand white rabbits | Controlled cortical impact | 810 and 980 | CW | 10 mW/cm²; 2–200 mW/cm² |
| Moreira et al. (2009) | 51 Adult male Wistar rats | Cryogenic brain injury | 660 or 780 | CW | 40 mW, 3 or 5 J/cm² per site (2 sites in total) |
| Moreira et al. (2011) | Forty adult male Wistar rats (Rattus norvegicus albinus) | Cryogenic brain injury | 780 | CW | 40 mW, 3 J/cm² |
| Khuman et al. (2012) | 239 Male C57BL/6 mice | Controlled cortical impact | 800 | CW | 500 mW/cm², 60 J/cm² |
| Quirk et al. (2012) | 104 Sprague-Dawley rats | Controlled cortical impact | 670 | CW | 50 mW/cm², 15 J/cm² |
| Xuan et al. (2013) | 144 Adult male BALB/c mice | Cortical impact; the bone flap was removed and mice were subjected to controlled cortical impact using a pneumatic impact device | 810 | CW | 25 mW/cm², 18 J/cm² |
| Xuan et al. (2014) | 64 Young adult male BALB/c mice | Controlled cortical impact | 810 | CW | 25 mW/cm², 18 J/cm² |
| Xuan et al. (2015) | 40 Male BALB/c mice | Controlled cortical impact | 810 | CW | 50 mW/cm², 36 J/cm² |
| Xuan et al. (2016) | 96 Male BALB/c mice | Cortical impact; the bone flap was removed and mice were subjected to controlled cortical impact using a pneumatic impact device | 810 | CW | 25 mW/cm², 18 J/cm² |
| Zhang et al. (2014) | Wild-type mice and IEX-1 knockout mice on 129sv/C57BL/6 background | Controlled cortical impact | 810 | PW at 10 Hz | 150 mW/cm², 36 J/cm² |
| Dong et al. (2015) | C57BL/6 mice | Controlled cortical impact | 810 | PW at 10Hz | 150 mW/cm²; 36 J/cm² |
| Clinical studies | Subjects | Wavelength (nm) | Irradiation parameters | Power density/energy density |
|----------------|----------|----------------|----------------|-----------------------------|
| Naeser et al. (2011) | Two chronic, traumatic brain injury cases | 633 and 870 | CW | 19.39 mW/cm² and 22.48 mW/cm², 13.3 J/cm² |
| Naeser et al. (2014) | Eleven chronic, mild traumatic brain injury participants | 633 and 870 | CW | 500 mW; 22.48 mW/cm², 13 J/cm² |
| Nawashiro et al. (2012) | Patients in a persistent vegetative state | 850 | CW | 11.4 mW/cm²; the energy density 20.5 J/cm² |
| Henson et al. (2015) | A patient with moderate traumatic brain injury | 810 and 980 | CW | 10–15 W |
| Hippskind et al. (2018) | Twelve symptomatic military veterans with chronic traumatic brain injury > 18 months post-trauma | 220 | CW | 6.4 mW/cm² for 20 min |
| Morries et al. (2015) | Ten patients with chronic traumatic brain injury | 810 and 980 | PW at 10 Hz | 10 and 15 W, 14.8–28.3 J/cm² |

CW: Continuous wave; PW: pulsed wave.

on C17.2 immortalized mouse neural progenitor cell lines show that PBM significantly increases cellular proliferation (Argibay et al., 2019). Yang et al. (2018) investigated the effect of PBM on neurogenesis. PBM promoted the proliferation and differentiation of neural progenitor cells in the peri-infarct zone and the switch from an M1 microglial phenotype to an anti-inflammatory M2 phenotype, thereby improving microenvironment and mitochondrial function.

Despite the encouraging results in animal stroke studies, laser therapy has limited success in humans. Early studies were not successful. A series of three clinical trials termed “NeuroThera Effectiveness and Safety Trials” (NEST-1 (Lamp, 2007), NEST-2 (Zivin, 2009), and NEST-3 (Zivin et al., 2014)) have evaluated the efficacy of PBM in stroke patients. Lampl et al. (2007) recruited 120 ischemic stroke patients, with 79 patients in the experimental group and 41 in the control group. More patients (70%) in the experimental group had favorable outcomes than controls (51%), as assessed with the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS). In NEST-2 with 660 patients, the group given transcranial laser therapy showed slightly, but not significantly better outcome than the control group. There were no significant differences in mortality rates or serious adverse events in term of safety data (Zivin, 2009). NEST-3 was prematurely terminated for futility (an expected lack of statistical significance) (Zivin et al., 2014). Researchers tend to attribute this failure to the violation of RIGOR guidelines (Lapchak and Boitano, 2016). In a case study, a 29-year-old woman who suffered a brainstem violation of RIGOR guidelines (Lapchak and Boitano, 2016). In a case study, a 29-year-old woman who suffered a brainstem violation of RIGOR guidelines, showed improvement in both cognitive state and motor recovery after 8 weeks of PBM (Boonsawang et al., 2012). The accelerated recovery in motor functions was also observed in a study of 15 patients with post-stroke spasticity (das Neves et al., 2016). After three consecutive phases, the group treated with PBM showed significant reduction in pain intensity. PBM was also effective in ameliorating post-stroke shoulder pain (Jan et al., 2017).

Photobiomodulation for Traumatic Brain Injury

We identified 21 papers reporting on PBM for TBI, including 15 animal studies and 6 clinical studies (Table 2). Oron et al. (2007) investigated the therapeutic effectiveness of PBM in mice with traumatic brain injury (TBI). They evaluated the

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parameters can be optimized with (Wu et al., 2012). Anders et al. (2014) proposed that the effectiveness of 810 nm is also supported by another study CW and 100-Hz mode with a wavelength of 810 nm. The found that 10-Hz pulse frequency was more effective than laser mode at 100 Hz (Oron et al., 2012). Ando et al. (2011) substantial improvement and better outcome with pulsed effects of two PBM modes (PW versus CW), and found a relationship in which the effect of PBM seemed to decline with increasing laser exposure. They designed another study with two groups given 3 or 14 sessions daily of PBM treatment, and found that the negative effect of excessive PBM was temporary and might be caused by temporary induction of reactive gliosis. With longer follow-up time, mice given 14 sessions started to show steady improvement (Xuan et al., 2016). Zhang et al. (2014) investigated the effect of PBM on secondary brain injury in mice lacking immediate early responsive gene X-1 (IEX-1). Laser therapy regulated proinflammatory mediators and increased ATP expression of IEX-1. Laser therapy reduced microgliosis and astroglial scar formation, thus promoting functional recovery in mice with MPTP-induced Parkinson’s disease (Salameh et al., 2015). Zhang et al. (2014) also observed an interesting biphasic dose-response relationship in which the effect of PBM seemed to decline with increasing laser exposure. They therefore conducted a study with two groups given 3 or 14 sessions daily of PBM treatment, and found that the negative effect of excessive PBM was temporary and might be caused by temporary induction of reactive gliosis. With longer follow-up time, mice given 14 sessions started to show steady improvement (Xuan et al., 2016). Zhang et al. (2014) investigated the effect of PBM on secondary brain injury in mice lacking immediate early responsive gene X-1 (IEX-1). Laser therapy regulated proinflammatory mediators and increased ATP levels, promoting brain recovery. The recovery of learning and memory function was associated with reduced loss of hippocampal tissue compared with the control group (Dong et al., 2015).

Several studies have investigated the underlying mechanisms. Moreira et al. (2009) found that PBM affected local and systemic immune functions following cryogenic brain injury by modulating tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β) and interleukin-6 (IL-6) levels. They also showed that PBM prevented neuronal death and severe astrogliosis, thereby promoting wound healing (Moreira et al., 2011). Reduced microgliosis was also observed in the PBM-treated group in another study (Khuman et al., 2012). In addition, PBM may exert neuroprotective effects by upregulating mitochondrial function and decreasing oxidative stress (Quirk et al., 2012). Xuan et al. (2013) found that mice in the treatment group had smaller lesion size at 28 days and fewer degenerating neurons, suggesting that PBM therapy may encourage neurogenesis. They further discovered that laser therapy promoted neurogenesis in the hippocampus and subventricular zone by upregulating brain-derived neurotrophic factor, which may stimulate synaptogenesis and at least partially account for the improved memory and learning function (Xuan et al., 2014, 2015). Xuan et al. (2014, 2015) observed an interesting biphasic dose-response relationship in which the effect of PBM seemed to decline with increasing laser exposure. They designed another study with two groups given 3 or 14 sessions daily of PBM treatment, and found that the negative effect of excessive PBM was temporary and might be caused by temporary induction of reactive gliosis. With longer follow-up time, mice given 14 sessions started to show steady improvement (Xuan et al., 2016). Zhang et al. (2014) investigated the effect of PBM on secondary brain injury in mice lacking immediate early responsive gene X-1 (IEX-1). Laser therapy regulated proinflammatory mediators and increased ATP levels, promoting brain recovery. The recovery of learning and memory function was associated with reduced loss of hippocampal tissue compared with the control group (Dong et al., 2015).

Six human studies, all case series, with 37 patients in total have been done in traumatic brain injury with various results. Naeser et al. (2011) reported two cases with closed-head TBI that showed significant cognitive improvement and reduced cost of treatment. They then conducted a study in eleven chronic TBI patients. They found improvement in learning ability, which was positively correlated with treatment duration (Naeser et al., 2014). In other case reports, clinical symptoms, including depression, anxiety, headache and insomnia, were reduced after laser therapy, which might be associated with increased regional cerebral blood flow (Nawashiro et al., 2012; Henderson and Morries, 2015). Hippskind et al. (2018) investigated its effect on cognitive

### Table 3 | Photobiomodulation for Parkinson’s disease in animal studies

| Animal studies | Animals | Modeling method | Wavelength (nm) | Irradiation parameters | Power density/energy density |
|----------------|---------|-----------------|-----------------|------------------------|-----------------------------|
| Peoples et al. (2012) | 80 Male albino BALB/c mice | Injection of MPTP | 670 | CW | 5 J/cm²; 90 s |
| Shaw et al. (2012) | 96 Male albino BALB/c mice | Injection of MPTP | 670 | CW | 0.5 J/cm² |
| Moro et al. (2013) | 40 Male BALB/c (albino) and 40 C57BL/6 (pigmented) mice | Injection of MPTP | 670 | PW, CW | 1.5 mW/cm² (PW) or 14.5 mW/cm² (CW) |
| Moro et al. (2014) | 36 Male BALB/c mice and 3 Sprague-Dawley rats | Injection of MPTP | 670 | PW with 5 s ON/60 s OFF | Lower doses (25 J or 35 J); higher dose (125 J) |
| Moro et al. (2016) | 15 Monkeys | Injection of MPTP | 670 | PW with 5 s ON/60 s OFF | 10 mW; 25 or 35 J |
| Darlot et al. (2015) | A monkey | Injection of MPTP | 670 | PW with 5 s ON/60 s OFF | 10 mW; 25 or 35 J |
| Shaw et al. (2014) | 12 Adult male macaque monkeys (Macaca fascicularis, Mauritius); 30 adult male albino BALB/c mice | Injection of MPTP | 670 | CW | / |
| Reinhart et al. (2015) | Male BALB/c mice | Injection of MPTP | 810 | / | 5.3 mW/cm² |
| Reinhart et al. (2016) | 147 Male BALB/c mice | Injection of MPTP | 670 | CW | 5.3 mW/cm²; 0.5 J/cm² |
| Reinhart et al. (2016) | 62 Male BALB/c mice | Injection of MPTP | 670 and/or 810 | CW | 15 or 30 mW |
| El Massri et al. (2014) | 130 Male BALB/c mice | Injection of MPTP | 670 | CW | 5.3 mW/cm² |
| Purushothuman et al. (2013) | K3 transgenic mouse model (K369I tau transgenic model (K3)) | Injection of MPTP | 670 | CW | 80 J/cm² |
| Vo et al. (2013) | Pink1 null mutants | Rotenone treatment | 808 | CW | 10–25 mW/cm² |
| Johnstone et al. (2014) | 143 Male BALB/c mice | Injection of MPTP | 670 | CW | 50 mW/cm²; 4 J/cm²; 90 s |
| El Massri et al. (2016) | 24 Adult Macaque monkeys (Macaca fascicularis) | Injection of MPTP | 670 | PW with 5 s ON/60 s OFF | 10 mW; 25 or 35 J over 7 days |
| El Massri et al. (2017) | 17 B alb/c mice, 15 Wistar rats and 16 macaque monkeys (Macaca fascicularis) | Injection of MPTP | 670 | CW | 0.16 mW for mouse and rat, and 10 mW for monkey |
| El Massri et al. (2018) | 12 Macaque monkeys (Macaca fascicularis) | Injection of MPTP | 670 | / | / |
| Kim et al. (2018) | 10 Male C57BL/6 mice/group | Injection of MPTP | 670 | CW | 50 mW/cm²; 3 min |
| Oueslati et al. (2015) | 23 Sprague-Dawley female rats (Charles River Laboratories) | Injection of 2 µL of viral suspension | 808 | / | 2.5 mW/cm² (n = 7) and 5 mW/cm² (n = 7) |
| Ganeshan et al. (2019) | 62 Male BALB/c mice | Injection of MPTP | 670 | CW | 50 mW/cm²; 4 J/cm² per day |
| Reinhart et al. (2016) | 61 Male Wistar rats | Injection of 6-OHDA | 670 | PW, CW | 333 mW or 0.16 mW, 634 mJ or 304 J |
| Shaw et al. (2010b) | BALB/c albino mice | Injection of MPTP | 670 | CW | 40 mW/cm² at scalp, 5.3 mW/cm² inside skull, 0.47 J/cm² |

CW: Continuous wave; PW: pulsed wave.
functional improvement and regional cerebral blood flow in 12 symptomatic military veterans diagnosed with chronic TBI.

**Photobiomodulation for Parkinson’s Disease**

*In vitro* studies have provided preliminarily support for a protective effect of PBM against 1-methyl-4-phenylpyridinium ion (MPTP)-induced neurotoxicity, supporting its application in *in vivo* studies (Dilworth et al., 1975; Liang et al., 2008; Ying et al., 2008; Trimmer et al., 2009). Peoples et al. (2012) found that laser therapy given concomitantly or after chronic MPTP administration protected dopaminergic cells from degeneration in the MPTP mouse model of PD (Table 3). The effect was long lasting, even after minimal exposure (Shaw et al., 2012). Moro et al. (2013) contributed greatly to the assessment of the efficacy and safety of laser treatment. They found higher numbers of tyrosine hydroxylase (TH)-positive cells in the laser-treated groups in both C57BL/6 (pigmented) and Balb/c (albino) mice. The albino mice showed better outcome because of greater penetration of NIR through the skin and fur. They then investigated its safety in MPTP-treated mice (Moro et al., 2014) and monkeys (Moro et al., 2016). NIR caused no observable behavioral deficits, nor was there evidence of tissue necrosis, suggesting NIR can be applied intracranially. Its effects on monkey PD models have also been investigated, and this primate model might be more suitable for pre-clinical studies (Shaw et al., 2010a; Darlot et al., 2016). Reinhart et al. (2015) evaluated the impact of different treatment parameters. They showed that 810 nm laser therapy had a more immediate therapeutic effect than 670 nm (Reinhart et al., 2015). They also investigated the effects of laser therapy before, at the same time, and after injection of MPTP. These investigators found that all three treatments produced similar outcomes in their PD model (Shaw et al., 2010a; Darlot et al., 2016). El Massri et al. (2016a) investigated the effect of different doses of NIR. The positive effect of PBM seemed to be dose-

### Table 4: Photobiomodulation for Alzheimer’s disease in animal and clinical studies

| Studies                  | Animals/Subjects                  | Modeling method            | Wavelength (nm) | Irradiation parameters                  | Power density/energy density |
|--------------------------|----------------------------------|----------------------------|-----------------|----------------------------------------|------------------------------|
| De Taboada et al. (2011) | One hundred male transgenic AP PP mice | Microinjection of human AP PP gene | 808             | PW at 100 Hz, or CW | 10 mW/cm²; 1.2, 6, or 12 J/cm² |
| Grillo et al. (2013)     | TASTPM mice                      | Transgenic mouse model     | 1072            | PW at 600 Hz                           | 5 mW/cm², 1.8 J/cm²         |
| Purushothuman et al. (2014) | 15 K3 mice or 18 APP/PS1 mice     | Transgenic mouse model     | 670             | CW                                      | 4 J/cm²; 90-second treatment equates to 4 J/cm²; a total of 80 J/cm² was delivered to the skull over the 4 weeks; 90 seconds |
| Purushothuman et al. (2015) | 10 K3 and 12 APP/PS1 transgenic mice | Transgenic mouse model     | 670             | CW                                      | 4 J/cm²                     |
| da Luz Eltchechem et al. (2017) | 60 Male Wistar rats (Rattus Norvegicus) | Transgenic mouse model     | 627             | /                                       | 7 J/cm², 70 mW |
| Farfara et al. (2015)    | 5Xfad transgenic male mice (Tg6799) | Transgenic mouse model     | /               | CW                                      | 400 mW, 1 J/cm²             |
| Lu et al. (2017)         | 12 Male Sprague-Dawley rats      | Transgenic mouse model     | 808             | CW                                      | 25 mW/cm², 3 J/cm²          |
| Saltmarche et al. (2017) | Five participants with dementia or Alzheimer’s disease | Transgenic mouse model     | 810             | PW at 10 Hz                            | 14.2 mW/cm²; 10.65 J/cm²    |
| Berman et al. (2017)     | 11 Participants                  | /                          | 1072            | PW at 10 Hz                            | /                           |
| Chao (2019)              | 8 Participants with dementia      | /                          | 810             | PW at 40 Hz                            | 75 mW/cm², 45 J/cm²         |

CW: Continuous wave; PW: pulsed wave.

### Table 5: Photobiomodulation for major depressive disorder in animal and clinical studies

| Animal studies      | Animals/Subjects          | Wavelength (nm) | Irradiation parameters                  |
|---------------------|---------------------------|-----------------|----------------------------------------|
| Ando et al. (2011)  | 40 Male BALB/c mice       | 810             | CW, PW at 10 Hz and 100 Hz              |
| Wu et al. (2012)    | 32 Adult male BALB/c mice | 810             | PW at 100 Hz                           |
| Salehpour and Rasta (2016) | 50 Adult male BALB/c mice | 630 or 810 | PW at 10 Hz                           |
| Mohammed (2016)     | 24 Adult male albino rats | 810             | CW                                      |
| Xu et al. (2016)    | /                         | 810             | CW                                      |
| Salehpour et al. (2018) | 75 Adult male BALB/c mice | 810             | PW at 10 Hz                            |

Clinical studies

| Subjects            | Wavelength (nm) | Irradiation parameters                  |
|---------------------|-----------------|----------------------------------------|
| Quah-Smith et al. (2005) | 30 Patients with elevated depressive symptoms | 804 | CW |
| Schiffer et al. (2009) | 10 Patients with treatment-resistant major depressive disorder | 810 | CW |
| Cassano et al. (2015) | 4 Patients with major depressive disorder | 808 | CW |
| Henderson et al. (2017) | 39 Patients with traumatic brain injury presenting with depressive symptoms | 810, 980 | 5 W, 700 mW/cm², 84 J/cm³ |
| Disner et al. (2016) | Fifty-one male adults with elevated symptoms of depression | 1064 | 8–15 W |
| Calderaro et al. (2018) | One patient with major depressive disorder with anxious distress | 830 | 250 mW/cm², 60 J/cm² |

CW: Continuous wave; KO: knock-out; PW: pulsed wave.
dependent—elevation to higher doses of NIR had a longer protective effect and was associated with reduced astroglial infiltration. Further studies are needed to optimize treatment parameters.

Several studies have investigated the mechanisms underlying the therapeutic effects of laser therapy. Purushothuman et al. (2013) found that NIR treatment reduced oxidative stress and inhibited neurodegeneration. Mitochondrial dysfunction has been observed in PD animal models and patients. PBM can improve mitochondrial function and cellular metabolism (Vos et al., 2013). Interestingly, it has been observed that unilateral exposure to NIR can have a bilateral effect. Indirect light may rescue TH+ cells in the substantia nigra pars compacta, possibly via unidentified mediators. This indirect effect is diminished by high-dose MPTP exposure (Johnstone et al., 2014).

El Massri et al. (2016b) discovered changes in the glial response, especially in astrocytes, after laser therapy in a monkey model of PD. These investigators further found that trophic factors, such as glial-derived neurotrophic factor, in the striatum may also play a role during NIR therapy (El Massri et al., 2017). In a subsequent study, their research group focused on encephalopsin, which is expressed by two populations of striatal interneurons constituting complex networks. Although PBM seemed to have no notable effect, external light seemed to exert an effect on the network of encephalopsin-expressing cells (El Massri et al., 2018).

A number of recent studies have examined the indirect effects of PBM. For example, PBM applied distally can trigger brain protective mechanisms, saving crucial neurons in PD (Kim et al., 2018). Consistent with previous studies (Purushothuman et al., 2013; Oueslati et al., 2015; Vos et al., 2016), remote PBM was demonstrated to modulate a variety of signaling pathways, thereby upregulating cell signaling and migration, including CXCR4+ stem cells, adipoctokine signaling and nuclear factor erythroid 2-related factor 2 expression, in turn modulating cellular oxidative stress response pathways. In addition, PBM affects the blood-brain barrier and might reduce damage to the brain (Ganeshan et al., 2019).

**Photobiomodulation for Alzheimer’s Disease**

Aβ plaques and hyperphosphorylated tau are observed in patients with AD. NIR was shown to reduce Aβ plaques in the brain of a transgenic AD mouse model in a dose-dependent manner (De Taboada et al., 2011; Grillo et al., 2013) (Table 4). Grillo et al. (2013) reported upregulation of heat shock proteins in an AD model; however, a significant downregulation of heat shock proteins was observed after treatment with 1072-nm NIR. Purushothuman et al. (2014) used two different mouse models of AD: the K369I tau transgenic model (K3) that develops neurofibrillary tangles, and the APPswe/PSEN1de9 transgenic model (APP/PS1) that develops Aβ plaques. Both of these characteristic features of AD were reduced after NIR treatment (Purushothuman et al., 2014). These investigators subsequently examined the therapeutic effects of NIR treatment on the cerebellum (Purushothuman et al., 2015). A recent study demonstrated that PBM improves spatial memory and behavioral performance (da Luz Eltchechem et al., 2017). As mentioned above, PBM can impact signaling pathways, and thereby regulate cell proliferation, migration and apoptosis. In an AD model, NIR induces proliferation of CD11b-positive monocytes, which appear to remove plaques by phagocytosis (Farfara et al., 2015). Because inflammatory responses and oxidative stress are associated with the development of AD (De Felice and Ferreira, 2014; Urrutia et al., 2014), PBM may ameliorate mitochondrial dysfunction in the disease. Indeed, Lu et al. (2017) showed that PBM inhibits G6PDH and NADPH oxidase activities, thereby reducing reactive oxygen species production and oxidative stress.

Human studies on the effects of PBM are still limited. Saltmarche et al. (2017) reported a case series of five patients given PBM therapy. The subjects showed cognitive improvement and better emotional control after a 4-week treatment period. No side effects were observed. In another controlled trial with 11 participants, no significant difference was found between the PBM group and controls, possibly because of small sample size (Berman et al., 2017). Chao et al. (2019) found increased cerebral perfusion in eight participants diagnosed with dementia after 12 weeks of PBM. Given the encouraging outcomes in animal studies, further well-designed clinical trials with larger sample size and long-term follow-up are warranted.

**Photobiomodulation for Major Depressive Disorder**

Major depressive disorder (MDD) is one of the most common psychiatric disorders. PBM has been found to be potentially effective in the treatment of MDD (Table 5). In studies investigating PBM for TBI, immobility time in the forced swim test was reported to be decreased in the treatment group, suggesting an anti-depressive effect of PBM (Ando et al., 2011; Wu et al., 2012). Salehpour and Rasta (2017) assessed the effects of low-level laser therapy (10 Hz PW, 810 nm) in the chronic mild stress model of depression, compared with citalopram. Immobility time was significantly decreased in both groups; however, no significant reduction in anxiety-like behavior was detected in the elevated plus maze test. An antidepressant-like effect of PBM was also observed in the model of reserpine-induced depression, as evaluated by forced swim test and electrocorticography (Mohammed, 2016). Xu et al. (2017) reported that the NIR-treated group showed better outcomes in behavioral despair tests, and found that this improvement was associated with the modulation of neurotransmitter levels and improved mitochondrial function in the prefrontal cortex. Furthermore, PBM has been shown to reduce oxidative stress and superoxide anion levels (Salehpour et al., 2019). In a randomized double-blind controlled study with 30 patients with depression, a significant difference was observed in Beck Depression Inventory scores between the laser therapy and control groups (Quah-Smith et al., 2005). Schiffer et al. (2009) used the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A)
to evaluate the efficacy of PBM in 10 patients. Cassano et al. (2015) investigated the safety of 700 mW/cm² NIR, and reported that no serious adverse events were observed. High power NIR provides persistent and better results compared with low power NIR (Henderson and Morries, 2017). In addition, PBM can be used in combination with other treatment modalities to enhance therapeutic effectiveness. For example, laser therapy combined with attention bias modification can enhance cognitive improvement (Disner et al., 2016). A case report of a 76-year-old white woman diagnosed with MDD with anxious distress showed steady improvement (Calderiero et al., 2018).

Other Applications

PBM has been shown to be effective in other CNS diseases as well (Table 6). Muili et al. (2012) found amelioration of symptoms in a mouse model of multiple sclerosis. A study reported improvement of autism spectrum disorder in children and adolescents of 5–17 years of age after PBM treatment (Leisman et al., 2018). PBM can also prevent ischemic injury to neurons after global cerebral ischemia caused by cardiac arrest and neonatal hypoxic-ischemic encephalopathy (HIE) (Tucker et al., 2018; Yang et al., 2019). PBM attenuates hypoxic-ischemic brain injury by maintaining mitochondrial function, decreasing oxidative stress and inhibiting neuronal apoptosis.

Discussion

PBM with NIR delivered noninvasively to the deep brain tissue has wide application in the treatment of neurological diseases. Numerous studies have demonstrated its efficacy in stroke, TBI, PD, AD, MDD and other disorders. The low power density laser, insufficient to burn or damage tissue, has no adverse effects on non-human primates (Moro et al., 2017). Notably, no adverse events have been reported in clinical trials.

The parameters of PBM, including wavelength, operation mode, power density and treatment duration, are critical factors to optimize therapeutic effectiveness (Salehpour et al., 2018). The wavelengths affect the absorption and penetration depth. Light has been employed in recent studies with wavelengths in the red including 606, 627, 630, 632.8, 640, 660 and 670 nm, and in the NIR regions including 785, 800, 804, 808, 810, 830 and 850 nm. NIR wavelengths produce more favorable outcomes. PBM has CW and PW modes. Studies have shown that PW mode at 10, 40 and 100 Hz provides better outcomes compared with CW. Pulsed light at 10 or 40 Hz may better affect brain activity. In addition, PBM with energy densities of 0.1–15 J/cm² is effective for neurons in animal models, whereas 10–84 J/cm² is effective in humans. PBM treatment appears to observe a biphasic dose-response relationship that follows the Arndt-Schulz Law. It has a stimulatory effect at low doses, but after the peak, stronger response relationship that follows the Arndt-Schulz Law. It has been demonstrated in non-human primates (Moro et al., 2017). Notably, no adverse events have been reported in clinical trials.

The application of 670 nm and 810 nm NIR together or sequentially provides better outcome than individually (Anders et al., 2015). Given favorable outcomes in pre-clinical and clinical studies, the application of PBM in CNS diseases has a promising future. However, studies with larger sample size are needed for a consensus on treatment parameters. An improved apparatus with optimal parameters could enhance the efficacy and safety of PBM, and allow its application to be standardized to minimize side effects.

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Remote tissue conditioning is a novel treatment strategy that has gained significant attention in the field of neuroregeneration. This approach involves the use of low-level light therapy, also known as photobiomodulation (PBM), to induce biological effects through the absorption of light by cellular structures. The rationale behind this approach is that PBM can modulate cellular processes, including mitochondrial function, cellular energy metabolism, and the immune system, which are all critical for tissue repair and regeneration.

**Key Findings**

- **Mitrofanis J, Stone J, Benabid AL (2014)**: The effects of different doses of near-infrared light on the monkey striatum. Exp Brain Res 236:955-961.
- **Moro C, El Massri N, Darlot F, Chabrol C, Benabid AL (2014)**: Photobiomodulation-induced changes in a monkey model of Parkinson's disease: changes in tyrosine hydroxylase cells and GDNF expression in neurons in the mouse neocortex. PLoS One 10:e0123833.
- **Ganeshan V, Skladnev NV, Kim JY, Mitrofanis J, Stone J, Johnstone DM (2019)**: Preconditioning with remote photobiomodulation modulates the brain transcriptome and protects against MPTP insult in mice. Neuroscience 400:85-97.

**Mechanisms of Action**

PBM works by engaging cellular photoreceptors, such as mitochondria and chromophores, which absorb light at specific wavelengths. This absorption triggers a cascade of intracellular events, including the production of reactive oxygen species (ROS), which can stimulate mitochondrial function, increase cellular energy production, and modulate the immune response. Additionally, PBM can influence gene expression through the activation of transcription factors and the modulation of epigenetic marks.

**Clinical Applications**

- **Transcranial near-infrared laser therapy (NILT)**: This modality is particularly promising for the treatment of traumatic brain injury (TBI), where it can improve neurological outcomes and reduce secondary damage.
- **Low-level light therapy for beta amyloid toxicity in rat hippocampus**: This study demonstrated the potential of PBM in reducing the effects of beta amyloid toxicity, a key factor in the development of Alzheimer's disease.

**Future Directions**

Despite the promising results of PBM in preclinical models, several challenges remain to be addressed before this approach can be translated into clinical practice. These include understanding the optimal parameters for treatment, developing novel phototherapeutic devices, and elucidating the long-term effects of PBM on the brain. Further research is needed to determine the safety and efficacy of PBM in various neurological disorders and to develop more targeted and specific applications of this technology.

In conclusion, PBM represents a promising emerging strategy for the treatment of neurological disorders. Continued research is essential to fully realize the therapeutic potential of this approach and to translate these findings into effective clinical interventions.
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