Review

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 therapeutical 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 Ca^{2+}, 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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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/cm^2 for 2 min (0.84 J/cm^2) or 25 mW/cm^2 for 10 min (15 J/cm^2)
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/cm^2, 0.9–1.2 J
DeTaboada et al. (2006)	169 Atherothrombotic model rats	/	808	/	7.5 mW/cm^2 at brain tissue level, 0.9 J/cm^2 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/cm^2 at brain tissue level, 0.9 J/cm^2 per site (in total 2 sites)
Yang et al. (2018)	Male Sprague-Dawley rats	/	808±3.0		25 mW/cm^2 at cerebral cortex tissue level, 350 mW/cm^2 on the scalp
Leung et al. (2002)	Male adult 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/cm^2
Lapchak et al. (2008)	89 Male New Zealand white rabbits	Injection of emboli	808	CW	10 mW/cm^2
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/cm^2; 0.9, 4.5, or 31.5 J/cm^2
Yip et al. (2011)	12 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/cm^2
Choi et al. (2012)	Male Wistar rats	Occlusion of the right middle cerebral artery	710	CW	0.042 mW/cm^2, 1.796 J/cm^2
Huisa et al. (2013)	Male New Zealand white rabbits	Injection of microemboli	808.5	CW	7.5, 10.8, or 20 mW/cm^2
Fukuzaki et al. (2015)	Adult FVB mice	Occlusion of bilateral common carotid artery	532	CW	845 mW/cm^2, 30.4×10^2 J/cm^2
Lapchak and Boitano (2016)	60 Male New Zealand white rabbits	Injection of emboli	808	CW	7.5 mW/cm^2, 0.9 J/cm^2
Lee et al. (2016)	Male mice (C57BL/6J)	Photothrombosis of the cortical microvessels	610	CW	1.7 mW/cm^2, 2 J/cm^2
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/cm^2
Lee et al. (2017a)	Mouse photothrombotic cerebral focal ischemia model	/	610	CW	1.7 mW/cm^2, 2 J/cm^2
Lee et al. (2017b)	17 Male C57BL/6J wild-type and eNOS mice	Occlusion of the right middle cerebral artery	610	CW	1.7 mW/cm^2, 2 J/cm^2
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 / cm^2

Clinical studies	Subjects	Wavelength (nm)	Irradiation parameters	Power density/energy density
Lampl et al. (2007)	120 Patients	808	CW	10 mW/cm^2, 1.2 J/cm^2
Zivin et al. (2009)	660 Patients	808	CW	10 mW/cm^2, 1.2 J/cm^2
Zivin et al. (2014)	630,316 Patients were allocated to treatment group *versus* 314 allocated to controls	808	CW	10 mW/cm^2, 1.2 J/cm^2
Boonswang et al. (2012)	A 29-year-old woman with brainstem stroke	660 and 850	CW	1400 mW, 2.95 J/cm^2
das Neves et al. (2016)	15 Subjects (6 males and 9 females) with cerebrovascular accident and spastic hemiparesis	808	CW	3.18 W/cm^2, 127.39 J/cm^2
Jan et al. (2017)	38 Patients; LASER group (20 patients) and interferential current group (18 patients).	905	CW	400 mW, 6 J/cm^2

CW: Continuous wave; eNOS: endothelial nitric oxide synthase; PW: pulsed wave.

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 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/cm^2, 1.2 or 2.4 J/cm^2
Oron et al. (2012)	/	Weight-drop device	808	PW at 100 Hz or CW	/
Ando et al. (2011)	40 Mice	Controlled cortical impact	810	CW; PW at 10 Hz and 100 Hz	50 mW/cm^2, 36 J/cm^2
Wu et al. (2012)	28 Adult male BALB/c mice	Controlled weight drop onto the skull	665, 730, 810, or 980	CW	150 mW/cm^2, 36 J/cm^2
Anders et al. (2014)	22 New Zealand white rabbits	Controlled cortical impact	810 and 980	CW	10 mW/cm^2; 2–200 mJ/cm^2
Moreira et al. (2009)	51 Adult male Wistar rats	Cryogenic brain injury	660 or 780	CW	40 mW, 3 or 5 J/cm^2 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/cm^2
Khuman et al. (2012)	239 Male C57BL/6 mice	Controlled cortical impact	800	CW	500 mW/cm^2, 60 J/cm^2
Quirk et al. (2012)	104 Sprague-Dawley rats	Controlled cortical impact	670	CW	50 mW/cm^2, 15 J/cm^2
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/cm^2, 18 J/cm^2
Xuan et al. (2014)	64 Young adult male BALB/c mice	Controlled cortical impact	810	CW	25 mW/cm^2, 18 J/cm^2
Xuan et al. (2015)	40 Male BALB/c mice	Controlled cortical impact	810	CW	50 mW/cm^2, 36 J/cm^2
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/cm^2, 18 J/cm^2
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/cm^2, 36 J/cm^2
Dong et al. (2015)	C57BL/6 mice	Controlled cortical impact	810	PW at 10 Hz	150 mW/cm^2; 36 J/cm^2

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/cm^2 and 22.48 mW/cm^2, 13.3 J/cm^2
Naeser et al. (2014)	Eleven chronic, mild traumatic brain injury participants	633 and 870	CW	500 mW, 22.48 mW/cm^2, 13 J/cm^2
Nawashiro et al. (2012)	Patients in a persistent vegetative state	850	CW	11.4 mW/cm^2; the energy density 20.5 J/cm^2
Henderson et al. (2015)	A patient with moderate traumatic brain injury	810 and 980	CW	10–15 W
Hipskind et al. (2018)	Twelve symptomatic military veterans with chronic traumatic brain injury > 18 months post-trauma	220	CW	6.4 mW/cm^2 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/cm^2

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 (Lampl, 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 stroke showed improvement in both cognitive state and motor recovery after 8 weeks of PBM (Boonswang 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

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/cm^2; 90 s
Shaw et al. (2012)	96 Male albino BALB/c mice	Injection of MPTP	670	CW	0.5 J/cm^2
Moro et al. (2013)	40 Male BALB/c (albino) and 40 C57BL/6 (pigmented) mice	Injection of MPTP		CW	/
Moro et al. (2014)	36 Male BALB/c mice and 3 Sprague-Dawley rats	Injection of MPTP	670	PW, CW	1.5 mW/cm^2 (PW) or 14.5 mW/cm^2 (CW)
Moro et al. (2016)	15 Monkeys	Injection of MPTP	670	PW with 5 s ON/60 s OFF	Lower doses (25 J or 35 J); higher dose (125 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		CW	/
Reinhart et al. (2015)	Male BALB/c mice	Injection of MPTP	810	/	5.3 mW/cm^3
Reinhart et al. (2016)	147 Male BALB/c mice	Injection of MPTP	670	CW	5.3 mW/cm^2, 0.5 J/cm^2
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/cm^2
Purushothuman et al. (2013)	K3 transgenic mouse model (K369I tau transgenic model (K3))	Transgenic mouse model	670	CW	80 J/cm^2
Vos et al. (2013)	Pink1 null mutants	Rotenone treatment	808	CW	10–25 mW/cm^2
Johnstone et al. (2014)	143 Male BALB/c mice	Injection of MPTP	670	CW	50 mW/cm^2, 4 J/cm^2; 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 Balb/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/cm^2, 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/cm^2 (n = 7) and 5 mW/cm^2 (n = 7)
Ganeshan et al. (2019)	62 Male BALB/c mice	Injection of MPTP	670	CW	50 mW/cm^2; 4 J/cm^2 per day
Reinhart et al. (2016)	61 Male Wistar rats	Injection of 6-OHDA	670	PW, CW	333 nW or 0.16 mW, 634 mJ or 304 J
Shaw et al. (2010b)	BALB/c albino mice	Injections of MPTP	670	CW	40 mW/cm^2 at scalp, 5.3 mW/cm^2 inside skull, 0.47 J/cm^2

CW: Continuous wave; PW: pulsed wave.

effects of two PBM modes (PW versus CW), and found a substantial improvement and better outcome with pulsed laser mode at 100 Hz (Oron et al., 2012). Ando et al. (2011) found that 10-Hz pulse frequency was more effective than CW and 100-Hz mode with a wavelength of 810 nm. The effectiveness of 810 nm is also supported by another study (Wu et al., 2012). Anders et al. (2014) proposed that the parameters can be optimized with *in vitro* models, and then followed by *in vivo* research and clinical application.

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). Hipskind et al. (2018) investigated its effect on cognitive

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 Aβ PP mice	Microinjection of human Aβ PP gene	808	PW at 100 Hz, or CW	10 mW/cm^2; 1.2, 6, or 12 J/cm^2
Grillo et al. (2013)	TASTPM mice	Transgenic mouse model	1072	PW at 600 Hz	5 mW/cm^2, 1.8 J/cm^2
Purushothuman et al. (2014)	15 K3 mice or 18 APP/PS1 mice	Transgenic mouse model	670	CW	4 J/cm^2; 90-second treatment equates to 4 J/cm^2; a total of 80 J/cm^2 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/cm^2
da Luz Eltchechem et al. (2017)	60 Male Wistar rats (Rattus Norvegicus)	Transgenic mouse model	627	/	7 J/cm^2, 70 mW
Farfara et al. (2015)	5XFAD transgenic male mice (Tg6799)	Transgenic mouse model	/	CW	400 mW, 1 J/cm^2
Lu et al. (2017)	12 Male Sprague-Dawley rats	Transgenic mouse model	808	CW	25 mW/cm^2, 3 J/cm^2
Saltmarche et al. (2017)	Five participants with dementia or Alzheimer's disease	/	810	PW at 10 Hz	14.2 mW/cm^2; 10.65 J/cm^2
Berman et al. (2017)	11 Participants	/	1072	PW at 10 Hz	/
Chao (2019)	8 Participants with dementia	/	810	PW at 40 Hz	75 mW/cm^2, 45 J/cm^2

CW: Continuous wave; PW: pulsed wave.

Table 5 | **Photobiomodulation for major depressive disorder in animal and clinical studies**

Animal studies	Animals		Wavelength (nm)	Irradiation parameters
Ando et al. (2011)	40 Male BALB/c mice	Depression following traumatic brain injury	810	CW; PW at 10 Hz and 100 Hz
Wu et al. (2012)	32 Adult male BALB/c mice	Chronic mild stress	810	PW at 100 Hz
Salehpour and Rasta (2016)	50 Adult male BALB/c mice	Chronic mild stress	630 or 810	PW at 10 Hz
Mohammed (2016)	24 Adult male albino rats	Reserpine induced depression	804	CW
Xu et al. (2016)	/	Depression induced by Ahi1 KO or space restriction	808	CW
Salehpour et al. (2018)	75 Adult male BALB/c mice	Sub-chronic restraint stress	810	PW at 10 Hz
Clinical studies	**Subjects**	**Wavelength (nm)**	**Irradiation parameters**	**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	250 mW/cm^2, 60 J/cm^2
Cassano et al. (2015)	4 Patients with major depressive disorder	808	CW	5 W, 700 mW/cm^2, 84 J/cm^2
Henderson et al. (2017)	39 Patients with traumatic brain injury presenting with depressive symptoms	810, 980	CW	8–15 W
Disner et al. (2016)	Fifty-one adult participants with elevated symptoms of depression	1064	CW	250 mW/cm^2, 60 J/cm^2
Caldieraro et al. (2018)	One patient with major depressive disorder with anxious distress	830	CW	36 mW/cm^2; 80 J/cm^2

CW: Continuous wave; KO: knock-out; 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 (Reinhart et al., 2016a). In addition, exposure to 670 nm and 810 nm NIR either together or sequentially produced better results than either alone, especially together (Reinhart et al., 2016b). El Massri et al. (2016a) investigated the effect of different doses of NIR. The positive effect of PBM seemed to be dose-

Table 6 | **Other applications of photobiomodulation in animal and clinical studies**

Studies	Animals/subjects	Modeling method	Wavelength (nm)	Irradiation parameters	Power density/energy density
Muili et al. (2012)	17 C57BL/6 mouse model of multiple sclerosis	Induction with myelin oligodendrocyte glycoprotein	670	CW	5 J/cm^2
Leisman et al. (2018)	40 Patients with autism spectrum disorder		635	CW	A power output of 15 mW
Yang et al. (2019)	Sprague-Dawley rats with neonatal hypoxic ischemic encephalopathy	Ligation of the right common carotid artery	808	CW	100 mW/cm^2; 12 J/cm^2

CW: Continuous wave.

dependent—exposure to higher doses of NIR had a longer protective effect and was associated with reduced astrogliosis. 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, adipocytokine 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 (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/cm^2 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 (Caldieraro 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/cm^2 is effective for neurons in animal models, whereas 10–84 J/cm^2 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 stimuli are inhibitory, leading to a negative response (Huang et al., 2011). Therefore, treatment dose and duration are of great importance. However, optimal parameters have not yet been determined.

The application of 670 nm and 810 nm NIR together or sequentially provides better outcome than individually (Reinhart et al., 2017). PBM combined with intranasal and/or transcranial light-emitting diodes has notable advantages for long-term therapy in that it can be performed at home for long-term use (Naeser et al., 2011).

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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