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Review article

Photobiomodulation as a promising new tool in the management of psychological disorders: A systematic review

Alba Gutiérrez-Menéndez[a,b,*], Marta Marcos-Nistal[a], Marta Méndez[a,b], Jorge L. Arias[a,b]

[a] Laboratory of Neuroscience, Department of Psychology, University of Oviedo, Plaza Feijóo, s/n, E-33003, Oviedo, Spain
[b] Instituto de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain

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ABSTRACT

Photobiomodulation is a brain modulation technique that has become a promising treatment for multiple pathologies. This systematic review collects studies up to 2019 about the beneficial effects of photobiomodulation as a therapy for treating psychological disorders and a tool for modulating cognitive processes. This technique is mostly used for the treatment of depression and stress, as well as to study its effects on psychological variables in healthy subjects. Despite the lack of parameters used, photobiomodulation seems to achieve enough brain penetration to produce beneficial effects in healthy subjects and patients with multiple pathologies. The best parameters are the wavelengths of 810 nm for the treatment of depression and 1064 nm for cognitive enhancement, along with a scalp irradiance of 250 mW/cm^2 and a scalp yield of 60 J/cm^2. It weekly application on the bilateral prefrontal area and the default mode network seems to be ideal for the maintenance of the effects. Photobiomodulation could be used as an effective and safe therapy for the treatment of multiple psychological pathologies.

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1. Introduction

Currently, there is an increase in the use of non-invasive brain stimulation techniques that modulate the central nervous system's (CNS) activity using safe application mechanisms. These techniques include the use of faint electric flows, magnetic fields in the brain (Bravo-Esteban and López Larraz, 2016), and photobiomodulation therapy (PBMT) (Chan et al., 2019). The latter therapy, previously known as low-level laser therapy or low-level light therapy (Hamblin, 2019a,b), was first applied in 1967 by Endre Mester. He used a low-level laser to study its effects on cancer cells, achieving better healing and hair growth in the application area (Hamblin, 2016a). In recent years, this technique has evolved into a clinical tool in therapies designed to treat various pathologies (Mussttaf et al., 2019). In addition, it has obtained the recognition of academic journals, clinical professionals, and entities related to biomedical science, including the constitution of professional societies dedicated to photobiomodulation (WALT and NAALT) (Hamblin, 2016a).

Michael Hamblin defines photobiomodulation (PBM) as: "the use of red or near-infrared light to stimulate, heal, regenerate, and protect tissue that has either been injured, is degenerating, or else is at risk of dying" (Hamblin, 2016b). PBM modulates biological functions of our biosystems without damaging them (Liu et al., 2009). These effects are made possible by the absorption of photons by the cytochrome c oxidase (CCO), an enzyme located in the mitochondrial inner membrane that is responsible for catalysing the transformation of oxygen into water for the production of adenosine triphosphate (ATP), the main energy molecule in the body (Hamblin, 2018a). This direct increase in ATP improves reactive oxygen species (ROS) generation, in addition to producing nitric oxide dissociation by the CCO, leading to greater metabolic activity (Hamblin, 2019b,b), which enhances chronic brain and neurological functions (Kuffler, 2016). Moreover, PBM induces stem cell activation, triggering an increase in migration, differentiation, proliferation, and neuronal viability (de Freitas and Hamblin, 2016), and it is involved in the expression of more than 100 protector genes (Mathewson, 2015; Mitrofanis and Jeffery, 2018).

The application of PBMT has achieved optimal results in several medical fields, and it is widely used in dentistry (Prasad et al., 2019; Ross and Ross, 2009; Zúñiga et al., 2018), pain reduction, dermatology (Hamblin, 2017), wound healing by triggering the immune re-

Abbreviations: ABM, attention bias modification; ADHD, attention deficit hyperactivity disorder; ASLMS, American Society for Laser Medicine and Surgery; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CCO, cytochrome c oxidase; CNS, central nervous system; DMN, default mode network; LED, light-emitting diode; OCD, obsessive-compulsive disorder; PBM, photobiomodulation; PBMT, photobiomodulation therapy; ROS, reactive oxygen species; SAD, seasonal affective disorder; WOS, Web of Science.

* Corresponding author at: Laboratory of Neuroscience, Department of Psychology, University of Oviedo, Plaza Feijóo, s/n, E-33003, Oviedo, Spain.
E-mail address: gutierrezalba@uniovi.es (A. Gutiérrez-Menéndez)

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sponse (Kuffler, 2016; Landaeta et al., 2008), and the treatment of several inflammatory conditions (Gavish and Houreld, 2018). The mechanism of this therapy makes it optimal for application on energy availability sensitive systems, such as the nervous system (Kuffler, 2016). For this reason, PBM has become one of the most dynamic and promising fields in Neurotherapy (Rojas and Gonzalez-Lima, 2013). The use of PBM on the brain began after confirming its benefits in acute stroke (Hamblin, 2019b,b), and since then, numerous studies have confirmed its advantageous effects: repairing damaged nerves in the CNS and restoring brain blood flow, the stimulation of neuron and glial cell neurogenesis, synaptogenesis, and migration, as well as the secretion of nerve growth factors, such as the brain-derived neurotrophic factor (BDNF) (Hamblin, 2018b, 2019a,b; Mitrofanis and Jeffery, 2018). Likewise, it has been shown to be effective in the treatment of traumatic brain injury and neurodegenerative diseases (Hamblin, 2018b; Oron and Oron, 2016; Salehpour and Hamblin, 2020). In the psychological realm, it has displayed effects on learning and memory, attention, executive functions, and several psychiatric disorders (Cassano et al., 2016). Therefore, PBM can be considered an innovative and potential treatment for a wide range of neurological, psychological, and psychiatric disorders (Salehpour et al., 2018b) from a non-invasive, inexpensive, and safe perspective (Rojas and Gonzalez-Lima, 2013).

Near-infrared light has also been applied in many pathologies to examine whether deleterious effects are found after its use, or whether, in contrast, it can be considered a potential alternative treatment. The pathology mostly chosen for these studies has been depression. According to the World Health Organization, this pathology is the leading cause of worldwide disability, affecting more than 300 million people (World Health Organization (WHO), 2017). Depression has been found to display several brain changes, such as hippocampal atrophy and dentate gyrus apoptosis, changes in oxygenation and mitochondrial dysfunction, weakening of neuronal networks (Salehpour and Rasta, 2017), and deficits in prefrontal brain flow, with the latter dysfunction being a common alteration in other mental disorders (Schiffer et al., 2009). An increase in oxidative stress, neuroinflammation, apoptosis, and hypometabolism (Caldieraro and Cassano, 2019), and a decrease in BDNF, have also been found (Caruncho Michinel and Rivera Baltanás, 2010). The usual depression treatments are pharmacological (Caruncho Michinel and Rivera Baltanás, 2010) and psychological (Arrarás and Manrique, 2019). For this reason, PBMT is considered a strong alternative anti-depressive treatment because it acts on the dysfunctional brain mechanisms of this disorder (Cassano et al., 2018).

PBMT has not only shown beneficial effects on depressive disorders. It has also been regarded as a useful treatment for other disorders that exhibit prefrontal lobe dysfunctions, including autism, obsessive-compulsive disorder (OCD), schizophrenia, or attention deficit hyperactivity disorder (ADHD) (Hamblin, 2016b). Moreover, other pathologies such as bipolar disorder, seasonal affective disorder (SAD), or sleep disturbances that have been associated with circadian rhythm dysregulations (Ashkenazy et al., 2009) could be restored through the use of PBMT (Santana-Blank and Rodríguez-Santana, 2018), showing its evident neurobiological functionality.

PBMT, like other transcranial techniques, is questioned because its efficacy and reproducibility are unknown, even though satisfactory results have been noted in different applications and its technology has been verified by the Food and Drug Administration (USA) (Rojas and Gonzalez-Lima, 2013). These positive results, along with the minimum presence of secondary effects, have led to an increase in experimental studies whose objective is to achieve quality and methodological rigour of PBM as a therapeutic tool, resulting in a body of solid knowledge that makes it possible to go beyond basic studies and normalize its use in human treatments. Thus, it is important to carry out reviews that show the discrepancies and similarities of the studies, in order to determine the most appropriate methodology and dosimetry and establish application procedures in multiple psychological disorders. Therefore, the purpose of this systematic review is to compare the different parameters used in PBMT, analyse the beneficial effects of PBM as a potential therapy in the field of psychological disorders and a tool for modulating cognitive processes, and discuss its use as a restorative technique for brain function, by reviewing the scientific literature published until the year 2019.

2. Method

The present systematic review was carried out following the PRISMA Statement for reporting systematic reviews (Moher et al., 2014, 2009). Study selection included all types of documents whose main topic was the intervention in psychological disorders using PBM, excluding reviews.

2.1. Search strategy

First, the PubMed MeSH Database was used to define the keywords (MeSH terms) that would be used as a search index, selecting a total of 12 keywords: *Low Level Light Therapy; Low-Level Light Therapy; Photobiomodulation Therapy; Photobiomodulation Therapies; LLLT; Low Level Laser Therapy; Low Level Laser Therapies; Low-Level Laser Therapy; Low Power Laser Therapy; Low-Power Laser Therapy; Laser Biostimulation* and *Laser Phototherapy*. Then, PubMed, Scopus, Google Scholar, Web of Science (WOS), and ScienceDirect were searched on 1 January of 2020 for articles published in English or Spanish before this date, with no time deadline to gather relevant articles. For this purpose, the MeSH terms were combined with the following terms: "*psychology*", "*stress*", "*depression*", "*cognitive*", or "*brain*", and excluded articles that used PBMT to treat medical conditions by using the Boolean operator "NOT" with the keywords: "*diabetes*", "*cancer*", "*skin*", "*retinal*", "*wound*", "*muscle*", "*traumatic*"," *fibromyalgia*", "*dental*", "*weight*", "*pain*", and "*oral*".

2.2. Study selection

The PubMed, Scopus, and WOS databases were first searched, gathering 222, 242, and 275 articles, respectively. In the same way, ScienceDirect and Google Scholar databases yielded 136 and 236 publications, reaching a total of 1111 documents. A manual selection was carried out after reading the title and/or the abstract, and duplicated publications in the different databases were removed, obtaining 96 articles. Additionally, 11 articles extracted from other publications were added. Finally, 71 articles that did not meet the inclusion criteria were deleted, selecting a total of 36 studies (Fig. 1)

2.3. Data analysis

An exhaustive analysis of each article of interest was carried out to extract relevant information about PBMT functioning and application in the psychological field (Table 1). Because there is no administration protocol, the different application parameters: type of light-emitting device (laser or light-emitting diode (LED)), wavelength, irradiance, fluency, wave type, and the mode of application of the treatment (application area, number of sessions, time of each session, and duration of the treatment) were taken into account. The type of sample used (human/animal) in each study and the presence of pathologies were also taken into consideration.

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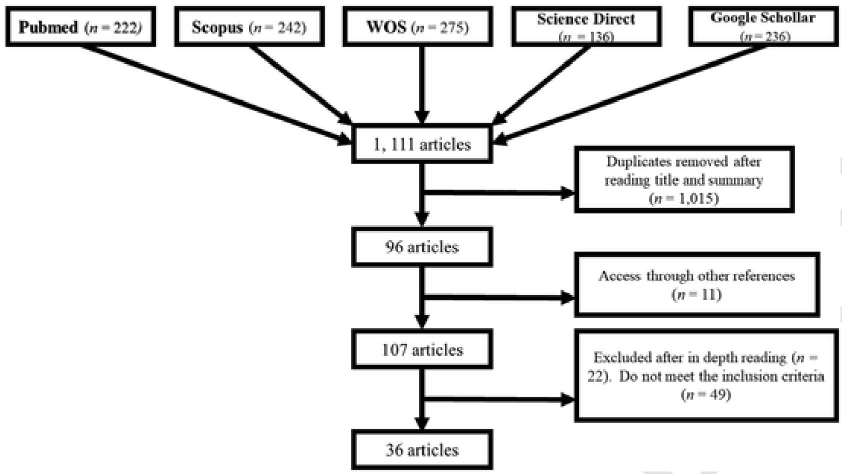

Fig. 1. Literature Flow diagram of the selection process in the different phases of the systematic review.

3. Results

3.1. Sample

Most of the articles ($n = 26$) used human populations, and the number of female participants ($n = 164$) was higher than the number of male participants ($n = 155$). More than half of these studies were carried out with healthy people with no pathologies ($n = 15$), and three of them used elderly participants. The rest of the publications included samples of patients diagnosed with depression ($n = 7$), bipolar disorder ($n = 1$), anxiety ($n = 1$), phobias ($n = 1$), and Gulf War syndrome ($n = 1$).

The remaining 10 articles used an animal sample, with the use of males ($n = 209$) prevailing over females ($n = 30$). Two of these articles chose healthy subjects with no pathologies, subjecting the animal, in one of these publications, to sleep deprivation. Most of the articles used subjects with depressive pathology ($n = 5$), and in the rest ($n = 3$), the animals were subjected to different stress protocols (early stress/ mild chronic stress).

3.2. Irradiation and light dose parameters

Most of the studies used a laser light ($n=23$) as opposed to the use of LEDs ($n = 13$). The prevailing wavelengths were 810 nm ($n = 12$) and 1064 nm ($n = 12$), followed by wavelengths of around 800 nm ($n = 11$). The shortest wavelength was 630 nm, and the longest was 1072 nm (Fig. 2).

The irradiance, also known as power density (power (W) divided by the area cm^2), shows greater variability in the values used. The 250 mW/cm^2 irradiance was the most frequently used value ($n = 10$), following by the values of 100 mW/cm^2 ($n = 3$) and 25 mW/cm^2 ($n = 3$) (Fig. 3).

Regarding the fluency or the energy density, as in the case mentioned above, there is great heterogeneity, with the fluency of 60 J/cm^2 being the most frequently used value ($n = 11$).

Finally, articles chose different types of waves. The majority of the studies used a continuous wave ($n = 17$) versus the use of 10 Hz pulse waves ($n = 7$). Two of the analysed articles chose a 40 Hz wave, and only one used a 100 Hz wave.

3.3. Area and mode of application

The majority of the analysed articles chose the prefrontal cortex as a point of application ($n=23$), with the right prefrontal cortex being the most predominant area ($n = 9$). In addition to this direct brain application, intranasal administration was also highlighted ($n = 5$).

Regarding the application mode, there is great diversity in the irradiation time in each session and the treatment interval. Thus, the irradiation time most widely used was eight minutes ($n = 9$), followed by 20 min ($n = 6$) and 30 min ($n = 5$). With regard to the treatment interval, three weeks ($n = 4$) and eight weeks ($n = 4$) were the most commonly used application times. The longest period of use was nine months ($n = 1$), and the shortest was only three days ($n = 1$).

3.4. Intervention effects

3.4.1. Depression

Schiffer et al. (2009) carried out the first study that analysed the effects of PBMT in depressed patients. The sample was composed of 10 patients who were resistant to common depression treatments. After two weeks of application, they achieved significant improvements in anxiety and depression symptoms and 60 % remission, a higher percentage than other treatments, accompanied by a cerebral blood flow increase in both hemispheres. After this research, Cassano et al. (2015) performed a pilot study where PBMT was applied to four patients diagnosed with treatment-resistant major depression, resulting in a reduction in depressive scores and great treatment tolerance after three weeks of application. Then, in 2018, this author, using 21 patients diagnosed with depression disorder, achieved a reduction in symptoms in 18 patients after four weeks of LED administration (Cassano et al., 2018). In addition, in the same year, together with Caldieraro et al. (2018), the author carried out a case study in which this technique was applied intranasally and transcranially to a 78-year-old woman with heart disease who had been diagnosed with anxiety depressive disorder for more than nine months. Results showed that intranasal application improved only the anxiety symptoms, but not the depressive ones, whereas transcranial administration improved both types of symptoms and enhanced quality of life. During the therapy, the patient reported headaches that increased with the administration of two daily doses of PBMT (Caldieraro et al., 2018). The same results were found by Henderson and Morries (2017), whose study achieved a decrease in depression scores and remission of suicidal ideation after laser administration. Recently, Cassano et al. (2019) examined PBM's effects on the blood pressure of depressed patients and found a slight increase in diastolic blood pressure in these patients, compared to untreated patients. Disner et al. (2016) combined PBMT with other techniques. In this case, they combined this therapy with Attention bias modification (ABM), a therapy used to avoid focusing on negative aspects. Both applications were carried out in 51 adults with

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Table 1
Description of the PBMT parameters used in the psychology field and main results of the review.

Source	Population/Sample	Pathological conditions	Light-emitting device	Wavelenght (nm)	Irradiancie (mW/cm ^{2})	Fluency (J/cm ^{2})	Wave type	Area	Treatment period	Results
Banqueri et al. (2019)	Animal (n = 41) Males	Early streess	Laser	1064	–	20	–	Prefrontal	One hour Once/day Five days	Cognitive flexibility and oxidative metabolism level restoration.
Barrett and Gonzalez-Lima (2013)	Human (n = 40) *Control:* 10 men 10 women *Treatment:* 10 men 10 women	Healthy subjects	Laser	1064	250	60	Continuous	Right prefrontal	Eight minutes	Cognitive and emotional functions enhancement: increase and maintenance of positive affective states and attentional improvement after two weeks.
Blanco et al. (2016)	Human (n = 118) 51 men 60 women	Healthy subjects	Laser	1064	250	60	Continuous	Right DLPFC and VLPFC [1]	Eight minutes	Cognitive enhancement: improvement of prefrontal rule-based learning and lack of effects on information-integration learning.
Blanco et al. (2017)	Human (n=30) 17 men 13 women	Healthy subjects	Laser	1064	250	60	Continuous	Right DLPFC and VLPFC [1]	Eight minutes	Executive function improvements evaluated by the Wisconsin Test.
Caldiedaro et al., (2018)	Human (n=1) Women	Heart disease Depression	LED	810	14'2	10'65	10 Hz	Intranasal. Transcranial	50–60 minutes Two/Seven times/week Over nine months	Intranasal application improved only anxiety symptoms, but not depressive symptoms. Transcranial administration improved both types of symptoms.
				830	33'2	49'8				
Cassano et al. (2015)	Human (n = 4) Three men One women	Depression	Laser	808	700	84	Continuous	Bilateral prefrontal	Six sessions Four minutes Twice/week Three weeks	Reduction in depressive scores and great treatment tolerance.
Cassano et al. (2018)	Human (n = 21)	Depression	LED	823	36'2	65'2	Continuous	Bilateral DLPFC [2]	16 sessions 20–30 minutes Twice/week Eight weeks	Medium antidepressant effect and great treatment tolerance

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Source	Population/Sample	Pathological conditions	Light-emitting device	Wavelenght (nm)	Irradiancie (mW/cm 2)	Fluency (J/cm 2)	Wave type	Area	Treatment period	Results
Cassano et al. (2019)	Human (n = 18) *Control*: nine subjects *Treatment:* nine subjects	Depression	LED	823	36'2	65'2	Continuous	Bilateral DLPFC [2]	16 sessions 20–30 minutes Twice/week Eight weeks	Absence of significant differences between groups in weight and systolic blood pressure and a slight increase in diastolic blood pressure in the treated group. Greater number of side effects in the treated group.
Chan et al. (2019)	Human (n = 30) *Control:* 15 subjects *Treatment:* 15 subjects	Elderly healthy subjects	LED	633 870	44'4	20	Continuous	Bilateral prefrontal. Posterior medial parietal	One session Seven and a half minutes	Improvements in selection actions, inhibition ability, and cognitive flexibility.
Chao (2019)	Human (n = 2)	Gulf War Syndrome	LED Vielight	810	100, 75 y 25	–	10 Hz	Intranasal. Intracranial	20 min 12 weeks	Decrease in Gulf War Syndrome symptoms: headaches, joint pain, gastrointestinal problems, etc.
Disner et al. (2016)	Human (n = 51) *Control:* 15 subjects*Treatment:* 36 subjects	Depression	Laser ABM	1064	250	60	–	Right or left medial and lateral prefrontal	Eight minutes	Improvements in attention and learning, and greater efficacy if the light emission was applied in the right prefrontal cortex and before the ABM session.
Eshaghi et al. (2019)	Animal (n = 55) *Control*: 11 subjects *Treatment:* 44 subjects.	Depression Anxiety	Laser	810	4'75	4, 8, and 16	10 Hz	Midline dorsal surface	Nine sessions Three times/week Three weeks	Reductions in anxiety, depression, cortisol, and nitric oxide levels in prefrontal cortex and hippocampus, and increase in serotonin. The 8 J/cm 2 fluency had the maximum behavioural and molecular effect.

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Source	Population/Sample	Pathological conditions	Light-emitting device	Wavelenght (nm)	Irradiancie (mW/cm ^{2})	Fluency (J/ cm ^{2})	Wave type	Area	Treatment period	Results
Gonzalez-Lima (2017)	Human (n = 328)	Healthy subjects	Laser	1064	250	60	–	Bilateral prefrontal	–	Improvement in CCO [3] activity and cerebral oxygenation in prefrontal cortex. Cognitive and emotional benefits after right prefrontal application in healthy and depressed subjects.
Gonzalez-Lima et al. (2019)	Human (n = 154)	Healthy subjects	Laser	1064	250	60	Continuous	Right prefrontal	–	Significant enhancement of cognitive performance in young adults and slight improvement in adults.
Heinrich et al. (2019)	Human	Healthy subjects	LED	810	100	–	40 Hz	Intranasal. Medial prefrontal and parietal	20 min	Lack of differences between treated and control groups.
Henderson and Morries (2017)	Human (n = 39)	Depression	Laser	810 980	–	55 81	–	Bilateral prefrontal and temporal	30 min Eight weeks	Depression scores decrease and remission of suicidal ideation.
Holmes et al. (2019)	Human (n = 34) *Control*: Seven men Nine women *Treatment:* Nine men Nine women	Healthy subjects	Laser	1064	250	120	–	Right prefrontal	One session Eight minutes	Cognitive performance enhancement on attentional and working memory tasks and brain oxygenation changes in prefrontal cortex.
Hwang et al. (2016)	Human (n = 60)	Healthy subjects	Laser Aerobic exercise	1064	250	60	Continuous	Right prefrontal	Eight minutes	Improvements in attention, working memory, and executive tasks after both PBMT and aerobic exercise.
Jahan et al. (2019)	Human (n = 30) 15 men 15 women	Healthy subjects	LED	850	285	60	–	Right prefrontal	150 s	Attentional performance improvement and electric brain activity modification.

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Source	Population/Sample	Pathological conditions	Light-emitting device	Wavelenght (nm)	Irradiancie (mW/cm ^{2})	Fluency (J/cm ^{2})	Wave type	Area	Treatment period	Results
Maiello et al. (2019)	Human (n = 15)	Anxiety	LED	830	30	36	Continuous	Prefrontal	20 min Once/day Eight weeks Autoadministration	Anxiety reduction and sleep improvement in the absence of significant adverse effects.
Mannu et al. (2019)	Human (n = 4) Two men Two women	Bipolar disorder	LED	830	33'2	40	Continuous	Bilateral dorsal prefrontal	20 min Twice/week Four weeks	Anhedonia reductions, libido increase, and improvements in sleep, anxiety, impulsivity, and irritability. Lithium levels increase.
Meynaghizadeh-Zargar et al. (2019)	Animal (n=60) Males	Mild chronic stress	Laser	810	4750	8	10 Hz	–	Three times/week Four weeks	Restoration of cognitive and molecular damages after the use of PBMT, methylene blue, and the combination of both treatments.
Michalikova et al., (2007)	Animal (n=30) Females	Healthy subjects	Laser	1072	–	–	Continuous	Full body	Six minutes 10 días	Lack of significant effects on exploratory activity and anxiety responses. Significant effects on working memory.
Moghadam et al. (2017)	Human (n = 34) *Control:* 17subjects *Treatment:* 17subjects	Healthy subjects	LED	850	285	60	Continuous	Right frontal	150 s	Attention improvement.
Mohammed (2016)	Animal (n = 48) *Control:* 24 subjects *Treatment:* 24 subjects	Depression	Laser	804	3'18	4'8; 12; 24	Continuous	Bilateral from the interaural line to the eyes	Six minutes One week	Lowest dose increases animal activity and improves depressive symptoms. Higher dose causes greater immobility.
Salehpour et al. (2016)	Animal (n = 50) Males	Depression	Laser	630	89	1'18	10 Hz	Midline of the dorsal surface in prefrontal	12 sessions Four times/week Three weeks	Immobility and anxious behaviour reductions. Decrease in cortisol levels and normalization of glucose levels. 810 nm laser more effective.
				810	562	14'4				

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Source	Population/Sample	Pathological conditions	Light-emitting device	Wavelenght (nm)	Irradiancie (mW/cm ^{2})	Fluency (J/cm ^{2})	Wave type	Area	Treatment period	Results
Salehpour et al. (2018a)	Animal (n = 40) Males	Healthy subjects Sleep deprivation	Laser	810	4'75	8	10 Hz	Midline of the dorsal surface between the eyes and ears	Three sessions Five seconds Once/day Three days	Prevention of cognitive damage induced after sleep deprivation. Improvement in antioxidant state and increase in hippocampal mitochondrial activity, reducing its oxidative damage.
Salehpour et al. (2019)	Animal (n = 27) Males	Depression	Laser Q_{10}	810	6'66	33'3	10 Hz	Midline of the dorsal surface between the eyes and ears	Five seconds Once/day Five days	Depressive behaviour improvement after PBMT, Q_{10}, and combination. Both treatments and the combination showed lipid peroxidation reduction and an improvement in antioxidant capacity in prefrontal cortex and hippocampus. In both areas, Neuroinflammatory activity, cortisol, corticosterone, TNF and IL levels, and apoptotic biomarkers were reduced.
Schiffer et al. (2009)	Human (n = 10) Five men Five women	Depression	LED	810	250	60	Continuous	Bilateral dorsal prefrontal	Eight minutes	Reduction in depressive and anxious scores in more than 50 % of patients and brain flow increase in both hemispheres.
Sinha et al. (2019)	Human (n = 23) 12 men 11 women	Elderly healthy subjects	LED	–	–	Intracranial52 and 26 Intranasal 44 and 22	–	Intranasal. Intracranial	30 min Once/day Six months	Functional connectivity increase in the posterior cingulate cortex using the lowest dose.
Vargas et al. (2017)	Human (n = 12) Five men Seven women	Elderly subjects with risk of cognitive impairment	Laser	1064	250	60	–	Right prefrontal	Eight minutes Once/week Five weeks	Improvement in cognitive measures, and alpha, beta, and gamma frequency increases in resting-state in prefrontal cortex.

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Source	Population/Sample	Pathological conditions	Light-emitting device	Wavelenght (nm)	Irradiancie (mW/cm [2])	Fluency (J/cm [2])	Wave type	Area	Treatment period	Results
Wang et al. (2017)	Human (n = 20)	Healthy subjects	Laser	1064	160	9'7	–	Right prefrontal	11 minutes	Changes in alpha frequency in the ipsilateral fronto-parieto-occipital network and in the contralateral parieto-occipital network.
Wu et al. (2012)	Animal (n = 32) Males *Control:* 8 subjects *Treatment:* 24 subjects	Mild chronic stress	Laser	810	15	120	100 Hz	Midline of the dorsal surface between the eyes and ears	Nine sessions Two minutes Three times/week Three weeks	Immobility reduction and maintenance of body-weight.
Xu et al. (2016)	Animal Males	Depression	Laser	808	23	–	Continuous	Medial surface	30 min 28 days	Depressive behaviour improvement, reducing immobility. ATP biosynthesis gain and increase in level of expression and activity of complex IV of the mitochondria in the prefrontal area.
Zaizar et al. (2018)	Human (n = 120)	Phobia extinction	Laser	1064	25	120	Continuous	Bilateral ventromedial prefrontal	Eight minutes	Fear reduction.
Zomorrodi et al. (2019)	Human (n = 20) Nine men 11 women	Healthy subjects	LED Vielight	810	75, 25, and 100	240	40 Hz	Intranasal DMN [4]	20 min Once/week Two weeks	Alpha, beta, and gamma frequency increments, and reductions in delta and theta frequencies.

[1] DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex.
[2] DLPFC, dorsolateral prefrontal cortex.
[3] CCO, cytochrome c oxidase.
[4] DMN, Default Mode Network.

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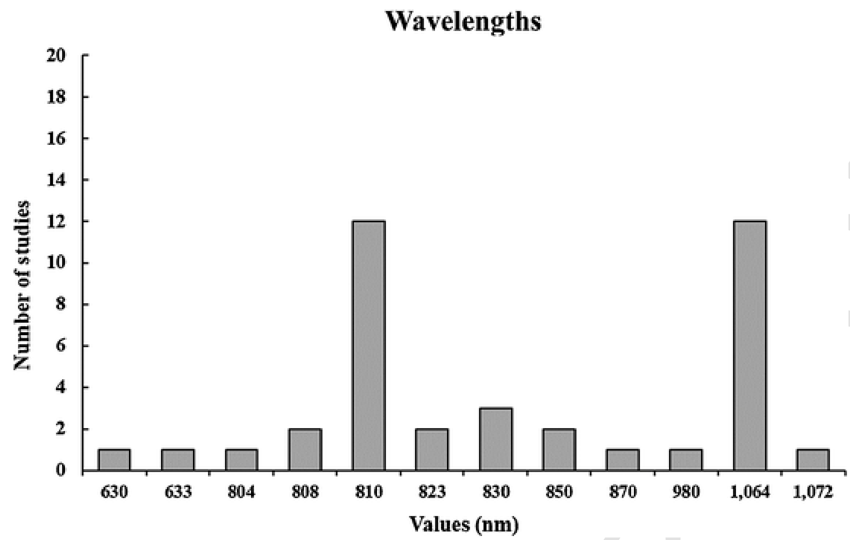

Fig. 2. Frequency of use of the different wavelengths (nm) in the selected articles.

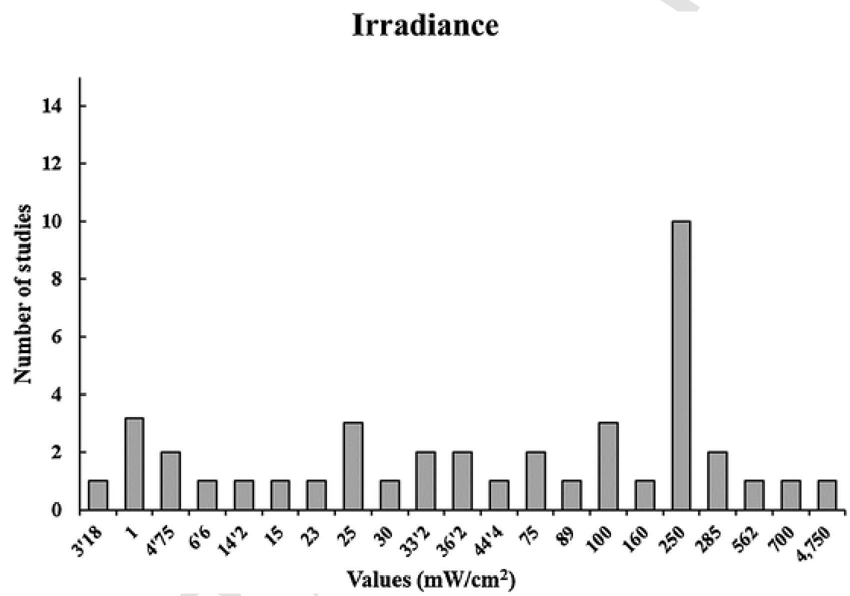

Fig. 3. Frequency of use of the different power densities (irradiance) (mW / cm^2) in the selected articles.

depression, and results showed improvements in attention and learning, with greater efficacy if the light emission was applied in the right prefrontal cortex and before the ABM session.

Basic research has shown similar results. Salehpour et al. (2016), using an experimental rat model of depression, found reductions in anxiety and depressive behaviours and cortisol and glucose levels, as well as body weight improvements, after PBMT. Recently, this author, considering PBMT's actions on inflammatory factors, combined coenzyme Q_{10}, an essential cofactor for mitochondrial complexes, with the emission of laser light in an induced depression rat model. Results showed a reduction in immobility and oxidative factors (Salehpour et al., 2019). In the same way, Mohammed (2016) achieved improvements in swimming and immobility and brain frequencies in rats with drug-induced depression.

Furthermore, Eshaghi et al. (2019), using a mouse animal model, achieved reductions in anxiety and depression levels, as well as reductions in cortisol and nitric oxide levels in the prefrontal cortex and hippocampus, along with an increase in serotonin. Likewise, Xu et al. (2017) showed an increase in ATP production and a decrease in depressive symptoms in induced depression mice.

3.4.2. Stress

Near-infrared light has also been used to treat multiple types of stress. Wu et al. (2012) applied laser light to animals with mild chronic stress, and they obtained a reduction in stress symptoms and body-weight maintenance after three weeks of treatment. Similarly, Meynaghizadeh-Zargar et al. (2019) used PBMT and the administration of methylene blue in animals with mild chronic stress. Both therapies, together and separately, restored cognitive and molecular damage that had been found. Finally, Banqueri et al. (2019) showed that the use of laser light re-established cognitive flexibility and oxidative metabolism levels, which had been altered in subjects subjected to early stress (Table 2).

3.4.3. Additional applications

Recently, Maiello et al. (2019) carried out a pilot study to evaluate the anxiolytic effects of PBMT, and their results showed anxiety reduction and sleep improvement. At the same time, Mannu et al.

Table 2
Summarize of the most used parameters in subjects subjected to different stress protocols.

Parameters	Choice	Several references
Light-emitting device	Laser	Banqueri et al. (2019) Meynaghizadeh-Zargar et al. (2019)
Wavelenght (nm)	810	Meynaghizadeh-Zargar et al. (2019) Wu et al. (2012)
Wave type	Pulse emission	Meynaghizadeh-Zargar et al. (2019) Wu et al. (2012)
Scalp irradiancie (mW/cm2)	4750	Meynaghizadeh-Zargar et al. (2019)
	15	Wu et al. (2012)
Scalp fluency (J/cm2)	20	Banqueri et al. (2019)
	8	Meynaghizadeh-Zargar et al. (2019)
	120	Wu et al. (2012)
Area	Prefrontal cortex Midline of dorsal surface	Banqueri et al. (2019)
Mode of administration	Three times/week	Meynaghizadeh-Zargar et al. (2019) Wu et al. (2012)

(2019) applied this therapy in patients diagnosed with bipolar disorder and found anhedonia reductions along with increases in libido and improvements in sleep, anxiety, impulsivity, and irritability. Chao (2019) used LEDs to treat two patients diagnosed with Gulf War Syndrome, characterized by the presence of multiple concurrent symptoms, including headaches, joint pain, gastrointestinal problems, fatigue, and even cognitive problems. Results showed a decrease in symptoms after 12 weeks of use. Moreover, Zaizar et al. (2018) described a randomized clinical design whose aim was to determine whether PBMT would be a useful technique for the extinction of phobias.

3.4.4. Application in healthy subjects

Studies designed to elucidate the effects of this technique have not only applied it to subjects diagnosed with several psychological disorders, but also to healthy subjects with no clinical symptoms. The first authors to use near-infrared light in healthy subjects were Barrett and Gonzalez-Lima (2013). In this study, they reported an increase in positive affective states and improvements in attention and memory that were maintained for two weeks after treatment. Subsequently, Gonzalez-Lima (2017) found an increase in CCO and oxygenated haemoglobin concentrations in the prefrontal cortex, along with an improvement in cognitive performance after the use of 1064 nm laser light on the subject's forehead. The same results were obtained by Blanco et al. (2016), who optimized prefrontal rule-based categorical learning. These previous results were confirmed by Blanco et al. (2017), who concluded that there were improvements in executive functions, evaluated by the Wisconsin Test, after the use of laser light in healthy subjects. Likewise, Moghadam et al. (2017) found improvements in attentional capacity. It should be noted that the study carried out by Hwang et al. (2016) combined aerobic exercise with laser emission and obtained improvements in attention, working memory, and executive tasks.

Brain wave modulation after the use of near-infrared light was achieved by Wang et al. (2017), who found changes in the alpha frequency in the ipsilateral fronto-parieto-occipital network and the contralateral parieto-occipital network. Moreover, Zomorrodi et al. (2019) showed similar results through the increase in alpha, beta, and gamma frequencies.

Currently, several groups continue their studies in healthy people. Thus, Gonzalez-Lima et al. (2019) describe a study in which they found improvements of up to 50 % in memory, learning, and attention, with a significantly higher effect on young adults after 1064 nm laser light. This cognitive achievement was also seen in the study by Jahan et al. (2019), where they obtained improvements in attention performance in addition to brain activity modification. Similarly, Holmes et al. (2019) found an improvement in cognitive performance, along with brain oxygenation changes, and Heinrich et al. (2019) showed no differences between treated and control groups after the application of LEDs in the prefrontal cortex (Table 3).

Several teams have tested the effects of this technique in elderly subjects. Thus, Chan et al. (2019) achieved improvements in selection actions, inhibition ability, and cognitive flexibility after seven and half minutes of the use of LED light in a single session. Sinha et al. (2019) also obtained an increase in functional connectivity in the cingulate cortex, and Vargas et al. (2017) found an improvement in cognitive measures and an increase in alpha, beta, and gamma frequencies in the resting-state of elderly subjects with risk of cognitive impairment.

Regarding the use of this therapy in animal models, Michalikova et al. (2008) found better spatial performance, memory improvement, and anxiety reduction after the use of lasers on female mice. Additionally, Salehpour et al. (2018a) found that PBM stops cognitive decline caused by sleep deprivation in mice, in addition to increasing hippocampal mitochondrial activity and reducing oxidative damage.

4. Discussion

This systematic review aimed to evaluate the effectiveness of near-infrared light as a modulator of cognitive processes and possible treatment for psychological disorders, in addition to analysing the different parameters in an attempt to unify the current methodology. The review included 36 articles in which this technique was applied in healthy subjects and subjects with psychological symptoms, and its analysis highlights the possible use of PBM as a promising future technique in the treatment of psychological disorders.

PBM is a technique that uses radiant energy with wavelengths ranging from red to near-infrared, administered by a laser or LED light, to modulate biological functions and /or induce a therapeutic effect in a non-invasive way (Rojas and Gonzalez-Lima, 2013). The studies compiled, as described above, chose mainly human samples, recruiting a low number of experimental subjects. The studies carried out by Blanco et al. (2016); Gonzalez-Lima (2017,2019), and Zaizar et al. (2018) have a broad sample of healthy subjects consisting of more than 100 participants. The target population is chosen in a non-random way, and, generally, there are no control groups for comparison. Moreover, there is a lack of adequate follow-up of the subjects to evaluate the long-term effects of this technique. Despite these limitations, the results show numerous beneficial effects, with no significant adverse effects. For this reason, authors such as Salehpour and Rasta (2017)

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Table 3
Summarize of the most used parameters in healthy subjects studies.

Parameters	Choice	Several references
Light-emitting device	Laser	Gonzalez-Lima et al. (2019) Blanco et al. (2016) Michalikova et al. (2008)
Wavelenght (nm)	1064	Wang et al. (2017) Blanco et al. (2016) Hwang et al. (2016)
Wave type	Continuous emission	Chan et al. (2019) Hwang et al. (2016) Barrett and Gonzalez-Lima (2013)
Scalp irradiancie (mW/cm2)	250	Gonzalez-Lima et al. (2019) Holmes et al. (2019) Blanco et al. (2016)
Scalp fluency (J/cm2)	60	Gonzalez-Lima et al. (2019) Blanco et al. (2017) Moghadam et al. (2017)
Area	Right prefrontal cortex	Holmes et al. (2019) Jahan et al. (2019) Blanco et al. (2016)

highlight the growing interest in the study and application of PBMT as a tool to enhance cognitive processes in healthy subjects.

Near-infrared light administration is usually carried out using a laser light source. This source supplies energy through a single wavelength with high penetration into small tissue areas. However, the large amount of supplied energy can produce tissue warming, which increases the risk of damage (Rojas and Gonzalez-Lima, 2013). Thus, LEDs are increasingly used because they emerge as a safer and less expensive alternative (Berman et al., 2017). This source can combine different wavelengths by emitting a non-coherent light beam, and it shows greater amplitude than the laser source, allowing its application on larger areas. However, it is less efficient and difficult to manipulate in terms of position, size, etc., limiting its use to superficial treatment (Mussttaf et al., 2019; Rojas and Gonzalez-Lima, 2013). Despite this, it has been described as a safe source because it generates a minimum amount of thermal energy, which leads to a reduction in the risk of tissue damage. Likewise, LED devices are programmable, rechargeable, low-cost, easy to use (Rojas and Gonzalez-Lima, 2013), and suitable for the treatment of acute and chronic conditions (Mussttaf et al., 2019). Thus, both sources, laser and LED, could be alternative treatments to the current ones because they provide beneficial effects with safe and affordable applications (Rojas and Gonzalez-Lima, 2013).

The importance of choosing an appropriate source lies in the biological effects they entail because it has been observed that the effects on the organism are completely different depending on the chosen source. Thus, some studies find that, although the light beams from lasers are limited to smaller areas, they are more effective and achieve deeper beneficial therapeutic effects (Mussttaf et al., 2019). In this regard, Tatmatsu-Rocha et al. (2018) found beneficial effects on the production of collagen in diabetic animals after the use of laser, but not after LEDs. These authors associate these differences with the type of wave used, pulsed in the case of the laser source and continuous in the case of LEDs. Therefore, the type of wave used, pulsed or continuous, also seems to be a relevant parameter that must be taken into account. Previous rodent studies have shown that the use of pulsed wave laser has been more effective than the continuous wave because it achieves improvements on behavioural tasks and a greater reduction in the amyloid protein in the hippocampus (Rojas and Gonzalez-Lima, 2013). Similarly, the administration of pulsed laser light could avoid the thermal effect, in addition to facilitating its coordination with different biological variables (Karu, 2014).

Wavelength is another relevant parameter whose variability is shown in the abundant bibliography analysed. The wavelength is chosen from the range of values where it has been verified that the CCO has greater absorption and there is adequate tissue penetration (Carroll, 2019). This range is between 600 and 1200 nm, except for an efficacy reduction between 700 and 780 nm, thus establishing the functional limit and the therapeutic window (Carroll, 2019; de Freitas and Hamblin, 2016; Henderson and Morries, 2017). For these reasons, most studies agree that the lengths of 810 and 1064 nm would be versatile and adequate values to achieve effects in the body. Likewise, several authors, such as Caldieraro et al. (2018); Chan et al. (2019); Henderson and Morries (2017), and Salehpour and Rasta (2017), combine different wavelengths to activate different biological mechanisms.

Irradiance is another significant parameter whose determination is complex because it depends on the emission watts and the size of the treatment area. The usual value employed in transcranial human studies is 250 mW/cm^2, and it descends to 10 and 30 mW/cm^2 in intranasal applications. Despite this, the value typically used in the medical field is usually lower, around 10–70 mW/cm^2 per session, to guarantee patient safety (Gavish and Houreld, 2018). Unfortunately, it is difficult to reach a consensus on the ideal value and develop a standardized protocol due to the heterogeneity of the data presented in the analysed articles.

Regarding fluency, the most commonly used values are situated in a range from 10 to 30 J/cm^2 for the treatment of neurological problems, from 12 to 84 J/cm^2 for psychological disorders, and from 15 to 60 J/cm^2 for use in healthy subjects (Gavish and Houreld, 2018; Salehpour and Rasta, 2017). Thus, recent research by Eshaghi et al. (2019) shows that the administration of 1.8 J/cm^2 on the cortical surface achieves an attenuation of depressive symptoms. Conversely, it has been verified that with the most commonly used value, 60 J/cm^2, only 2.1 J/cm^2 of this total fluency reaches the cortex (Schiffer et al., 2009). Despite this reduction, the supply from 1 to 3 J/cm^2 seems sufficient and ideal for triggering ATP production (Hamblin, 2018c).

The calibration and appropriate parameters seem to be highly relevant, taking into consideration the tissue properties, condition, amount of water, or type of receptors that absorb the light. Thus, studies have shown that the PBM response in our organism is biphasic, known as the Arndt-Schulz rule: the election of lower parameters does not produce effects in the organism; however, as these values increase, responses

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achieve a peak of maximum efficiency from which the effects are detrimental due to excessive product generation (de Freitas and Hamblin, 2016). Therefore, by choosing an adequate emission, a significant percentage will be able to pass through the external layers and reach the interested area, showing penetrations of 20 and 30 mm (Salehpour and Rasta, 2017) and even up to 50 mm and 2 cm (Hamblin, 2016b; Santos et al., 2019). Other authors such as Henderson and Morries (2017), however, find that transcranial emissions do not exceed 10 mm, and they prefer to choose a multi-watt emission combining different parameters, which can be up to 3 cm in human brains. In this regard, Mitrofanis and Jeffery (2018) mention that transcranial stimulation will not exceed 10 mm, but it will reach deeper structures through indirect pathways such as circulation. In contrast, Berman et al. (2017) opt for the intranasal application, due to the large number of capillaries that facilitate stimulation. Salehpour et al. (2018b) also describe exposure through the oral cavity or ears. Additionally, the implantation of LED fibres in macaques has also provided a safe long-term alternative with no damage (Moro et al., 2017). Regarding the application of the PBMT directly on the skin, the energy absorption will vary depending on the pigmentation, with some authors having to increase the emission force on dark skin and reduce it on lighter skin (Conde Quintero et al., 2011). For other authors, such as Barrett and Gonzalez-Lima (2013), this emission adjustment based on skin pigmentation is not important.

Regarding the treatment area, emission on the forehead is the most commonly chosen area due to the absence of hair, with the frontal area usually selected. Naeser et al. (2016), however, apply the laser on three specific brain networks: the default mode network (DMN), the central executive network, and the salience network. These interrelated networks play a key role in cognitive function and include the prefrontal, parietal, and even temporal areas (Naeser et al., 2016). Conversely, numerous authors focus these light applications on several distant points or bilaterally, which enhances the effect because the penetration can vary depending on the area. Thus, it has been verified that the application of light on a specific area of the body can have implications for other areas apart from the application site. This attribute is called systemic PBM, and it occurs due to the transmission of the biological effect (Caldieraro and Cassano, 2019). In this regard, a reduction in depressive symptoms has been found in patients with PBM treatment for back pain (Caldieraro and Cassano, 2019; Salehpour and Rasta, 2017). Ganeshan et al. (2019) also find that emission on the back of the rat produces a neuroprotective effect on dopaminergic neurons.

The emission distance also seems to be a variable to consider. Thus, Hamblin et al. (2015) show that light directly applied to the skin contact seems to be the most effective option because it presses on the tissues, modifying blood flow and achieving better penetration. Regarding the irradiation time and the treatment interval, it is difficult to reach a consensus that allows the standardization of this technique because there is high heterogeneity and a lack of specificity in the administration time. In humans, the administration time varies between two and 30 min, and authors such as Lapchak (2012) recommend the repetition of these applications to maintain the benefits. Thus, it should be acceptable to repeat the treatment to maintain its effect, due to the absence of long-term damage, but always taking into account the type of dysfunction and its severity.

Regarding questions related to the safety of the technique, the use of LED devices does not seem to produce harmful effects, but it always requires eye protection. In addition, the American Society for Laser Medicine and Surgery (ASLMS) recommends not using this therapy on visible skin lesions, pregnant woman, or people with haematological problems. Several studies have described transient side effects in humans, such as the presence of headaches (Caldieraro et al., 2018; Cassano et al., 2018). Other studies have also described harmful effects: Yang et al. (2017) showed the existence of apoptotic processes after 24 h of light emission in a non-photosensitive hippocampal cell culture. Additionally, Xuan et al. (2016) found a delay in the positive effects after 14 daily applications of PB on the mouse brain with traumatic injury, and, recently, a study carried out by Cassano et al. (2019) in patients diagnosed with depression found weight gain and increases in diastolic pressure in the treated group.

From a psychopathological point of view, this technique has been used as a possible therapeutic strategy to treat multiple psychological disorders. In the treatment of depression, Mathewson (2015) concludes that results reported after its use are greater than the results of electroconvulsive therapies or magnetic stimulation. Along these lines, Wu et al. (2012) and Salehpour et al. (2016) compare the effects of PBMT with those of fluoxetine and citalopram, drugs typically used in the treatment of depression symptoms, and they found similar effects of both treatments, but weight gain and a greater reduction in cortisol only occurred with the use of PBM. The combination of PBMT with other pharmacological, physical, or psychotherapeutic treatments is highly recommended because PBM is useful for optimizing states that enhance the action of other treatments (Disner et al., 2016). In this regard, the combination of light and antidepressants seems to accelerate the effectiveness and speed of pharmacological effects (Huang et al., 2009), in addition to achieving superior mitochondrial functions and higher neuronal protection when this technique is combined with metabolic products such as exogenous glucose (Dong et al., 2015) (Table 4).

There is evidence of the existence of mitochondrial dysfunction in many psychological disorders and the importance of oxygenation for the correct functioning of the organism. Duong et al. (2018) suggest the existence of alterations in genes related to oxidative phosphorylation and bioavailability of ATP, along with a deterioration in mitochondrial functioning, in bipolar disorder. These alterations make this disorder an ideal target for PBM application. In other ways, lack of sunlight and vitamin D deficiency are related to various disorders, such as depression, SAD, dementia, and schizophrenia (Mathewson, 2015), and so it is expected that the role of PBM will be taken into consideration in their treatment. Likewise, PBM could be used in cases of autism, OCD, ADHD, panic attacks, and claustrophobia (Hamblin, 2016b; Zaizar et al., 2018), and it even seems to produce beneficial effects in premenstrual syndrome, postpartum, and bulimia (Berman et al., 2017). The possible use of PBT in the treatment of all these disorders highlights the therapeutic role of this brain modulation. However, it would be necessary to develop new lines of research to evaluate the possible risks and benefits after their particular use.

5. Limitations

The articles included in this review describe a wide range of methodologies that are not very specific, and, in some cases, lack details about the parameters used. These disadvantages hinder the possibility of replicating studies and, therefore, developing standardized protocols for the correct, beneficial, and homogeneous use of this technique.

6. Conclusions

PBM achieves enough brain penetration to produce beneficial effects in healthy subjects and subjects with multiple pathologies. LED devices have reported higher safety and versatility than lasers, despite their lower penetration, and pulsed emission is more effective than continuous emission. Likewise, wavelengths of 810 nm and 1064 nm achieve the best results in depression treatment and cognitive enhancement, respectively, and there is a consensus about an scalp irradiance of 250 Wm/ cm^2 and a scalp fluency of 60 J/ cm^2 to improve cognitive functions. Anatomically, light projection is recommended in the bilat-

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Table 4
Summarize of the most used parameters in subjects diagnosed with depression.
Expand

Parameters	Choice	Several references
Light-emitting device	Laser	Cassano et al. (2018) Disner et al. (2016) Eshaghi et al. (2019)
Wavelenght (nm)	810	Salehpour et al. (2019) Caldieraro et al. (2018) Henderson and Morries (2017)
Wave type	Continuous emission	Cassano et al. (2019) Caldieraro et al. (2018) Mohammed (2016)
Scalp irradiancie (mW/cm2)	362	Cassano et al. (2018)
	250	Disner et al. (2016) Schiffer et al. (2009)
Scalp fluency (J/cm2)	Around 60	Cassano et al. (2019) Disner et al. (2016) Schiffer et al. (2009)
Area	Bilateral prefrontal cortex	Henderson and Morries (2017) Mohammed (2016) Cassano et al. (2015)
Mode of administration	Twice /week	Cassano et al. (2019) Eshaghi et al. (2019)

eral prefrontal cortex and the DMN, and weekly repetition seems ideal to maintain the effects (Table 5). The psychological benefits of light exposure are evident, and the preventive effect of this technique is an advantage in many clinical fields because it is able to reduce healthcare costs and become a possible sustainable, safe, and economical therapy that can easily be accessed and applied. Nevertheless, it will be necessary to overcome the lack of consensus administratively, in order to develop standardized protocols focused on the psychopathological characteristics of each patient. To achieve this goal, companies that produce the administration devices should provide concise and detailed information that allows the research team to adequately describe the parameters. This unification will allow the use of PBM as an effective and safe therapy for the treatment of multiple psychological disorders.

Table 5
Collection of the potential agreed parameters that could achieve better results in cognitive functions.
Expand

Parameters	Optimal choice	Several references
Light-emitting device	LED higher safety and versatility but, lower penetration	Chan et al. (2019)
		Jahan et al. (2019) Moghadam et al. (2017)
Wavelenght (nm)	1064	Zomorrodi et al. (2019)
	810	Blanco et al. (2016) Wang et al. (2017)
Wave type	Pulse emission	Zomorrodi et al. (2019) Heinrich et al. (2019) Salehpour et al. (2018a)
Scalp irradiancie (mW/cm2)	250	Gonzalez-Lima et al. (2019) Holmes et al. (2019) Blanco et al. (2016)
Scalp fluency (J/cm2)	60	Gonzalez-Lima et al. (2019) Blanco et al. (2017) Moghadam et al. (2017)
Recommended area	Bilateral prefrontal cortex DMN [1]	Zomorrodi et al. (2019)
		Gonzalez-Lima (2017) Blanco et al. (2016)
Mode of administration	Weekly repetition	

[1] DMN, Default Mode Network.

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Declaration of Competing Interest

The authors report no declarations of interest.

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