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REVIEW ARTICLE

Photobiomodulation therapy in mood disorders: a systematic review

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Abstract

Mood disorders are common, debilitating and impose a high-cost burden on society. Side effects and resistance to psychiatric drugs justify finding new treatment methods. Photobiomodulation therapy (PBMT) uses photons of light to repair, modulate and improve the function of target tissue. The purpose of this study is to systematically review the use of PBMT for the treatment of mood disorders and to identify the useful parameters of PBMT, the level of evidence of its effectiveness, and the degree of its practical recommendation. "Google scholar," "Pub Med," "Scopus," and "Science direct" online databases were searched based on Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) guidelines. The human or animal studies written in English and published from January 2009 to August 2021 were included. Sixteen studies, which included four randomized controlled trials (RCTs), met the inclusion criteria. Infrared wavelength ranges from 800 to 830 nm, power density of 250 mW/cm^2 and energy density of 60 to 120 J/ cm^2 were the most used PBMT parameters. Bias risk assessment was performed to evaluate the quality of RCTs in which 2 out of 4 RCTs were evaluated as high quality. Based on grade practice recommendations, PBMT can be classified as strongly recommended for moderate grade of major depressive disorder (MDD) and recommended for anxiety disorder. In bipolar disorder, further studies are needed to recommend this therapeutic method.

Keywords Low-level laser therapy · Low-level light therapy · Photobiomodulation therapy · Laser therapy · Low power laser therapy · Mood disorders

Highlights
- PBMT has the ability to reduce neuroinflammation in mood disorders.
- PBMT has the ability to modulate imbalance between neurotransmitters.
- PBMT is strongly recommended for moderate grade of major depressive disorder.
- PBMT is recommended for treatment of anxiety disorder.

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Introduction

Mood disorders simultaneously affect emotion, energy, and motivation, and their lifetime prevalence in the general population is estimated at 9%. Their complications include impaired quality of life, reduced productivity, the cost of treatment, unemployment, and mortality. The mortality rate of patients with mood disorders is higher than the general population and also the risk of death due to suicide is 15 to 30% higher than healthy people [1, 2]. Major depressive disorder (MDD), anxiety, and bipolar disorders are the most prominent examples of mood disorders. Characteristic of MDD is persistent low mood, which is often associated with cognitive impairment and social and physical dysfunction. Ten to twenty percent of patients referred to the general practice offices are depressed and 40 to 80% of suicides are caused by depression. Pathological changes due to depression include prefrontal cortex abnormalities, neuroinflammation, mitochondrial dysfunction, and an imbalance of noradrenergic and monoaminergic neurotransmitters [2–5]. Bipolar disorder is characterized by recurrent episodes of

mania or hypomania alternating with periods of depression. The prevalence of this disorder has been estimated at 0.5 to 5% in various studies. Mania is manifested with irritability, overconfidence, talkativeness, extreme disinhibition, grandiosity, decreased need for sleep, elevated mood, and, in some cases, there are symptoms of psychosis [6, 7]. Anxiety refers to the psychological and physiological changes that result from encountering situations that confuse, frighten, annoy, or threaten a person. The most common symptoms of anxiety disorders are excessive worry, unproductive, and debilitating fear and excessive arousal. The body's response to anxiety includes impaired homeostasis and emotional and physical imbalances. Anxiety disorder has been shown to be a risk factor for other mood disorders and substance abuse [8, 9]. The most commonly used antidepressants are selective serotonin reuptake inhibitors (SSRIs), norepinephrine and dopamine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors. Lithium and antipsychotics are mood stabilizers commonly used to treat bipolar disorder. SSRIs and benzodiazepines are used to treat anxiety disorders. Available medications reduce symptoms and improve patients' quality of life, but may take weeks or months to produce the desired response and not be effective in all patients. Drug side effects and drug resistance are important barriers to effective treatment [10, 11]. Therefore, there is a need for new treatment methods with fewer side effects and more effectiveness.

Photobiomodulation therapy (PBMT), formerly known as low-level laser therapy, uses laser light or light-emitting diodes (LEDs). Its effects include stimulation of mitochondrial metabolism, increased production of adenosine triphosphate (ATP), repair of damaged hypoxic cells, and modulation of target tissue function. PBMT is safe and studies have not reported any significant side effects from its use [12, 13]. In cells, the cytochrome c oxidase (CCO) enzyme in the mitochondria and calcium ion channels are the primary chromophores that absorb the photons. Photon uptake by the CCO catalyzes the conversion of oxygen to water to produce ATP, the body's main source of energy. Increased ATP leads to the production of reactive oxygen species (ROS) as well as the separation of nitric oxide (NO) from CCO. In general, in photobiomodulation, an increase in ATP and free NO, a brief burst of ROS and regulation of calcium levels, occurs, leading to increased metabolic activity and neuronal function. PBMT has the ability to activate stem cells and increase migration, differentiation, proliferation, and survival of neurons, as well as regulate antioxidant defense, reduce oxidative stress, and reduce overall inflammation. In addition, PBMT has been shown to modulate neurotransmitter imbalances by releasing glutamate and gamma aminobutyric acid (GABA) into the cortex and hippocampus [14, 15]. Transcranial photobiomodulation (tPBM) is a novel modality in which visible or non-visible light penetrates into the skull. In humans, the penetration of red and NIR (630 to 810 nm) irradiated transcranially into the skull is estimated to be between 0.2 and 10%. [16] tPBM increases brain metabolism and brain perfusion by releasing NO and stimulating neurogenesis and synaptogenesis. It also reduces oxidative stress, neuroinflammation, and neuronal death, and modulates brain oscillations, brain networks, and cortical excitability [17–19]. PBMT has been used to treat mood disorders in animal models and humans and has been shown to alter neuroinflammatory profile in the brains of young and aged rats [20–22]. We have previously reviewed the use of PBMT in four common brain disorders including stroke, traumatic brain injury, Alzheimer's, and Parkinson's disease [23]. Here, the use of PBMT in mood disorders is reviewed and its useful parameters, level of evidence of effectiveness, and the grade of its recommendation in each experimental field are determined.

Methods

This systematic review was performed based on the guidelines of Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) [24]. Initial search was conducted by two review authors (K. M., S. C. H.) in August 2021 using "Google scholar," "Pub Med," "Scopus," and "science direct" online databases. Keywords were the followings: (Photobiomodulation therapy OR Low-Level Light Therapy OR Low-Level laser Therapy OR Low Power Laser Therapy OR Laser Therapy) AND (mood disorders). The human or animal researches written in English and published from January 2009 to August 2021 were included. The reviews, book chapters, patents, laser acupuncture studies, citations, unpublished articles, non-English papers, non-related articles and were excluded. The research papers were visually checked at first and then by Endnote software for finding duplicates. Finally, the full texts of the remaining articles were reviewed. The PICOS table is one of the features of the PRISMA method and includes participants (P), intervention (I), comparison (C), outcomes (O), and study design (S). According to PICOS, the required information was extracted from the articles. "Assessment tools" have been added to the table, which includes tools that evaluate findings of the studies. In mood disorders, assessment tools include a variety of questionnaires, behavioral tests, laboratory tests, and imaging techniques. Afterwards, the useful parameters of PBMT in each experimental field were determined. Bias risk assessments were then performed to determine the quality of RCTs using the Cochrane bias risk tool for randomized trials (RoB 2) [25]. The included articles were then classified based on "evidence-base medicine" and the degree of PBMT recommendation was determined using "Grade Practice Recommendations" [26].

Results

The initial search consisted of 6346 articles (Fig. 1). The utilization of "Google scholar" resulted in 6069 articles, "Pub Med" in 37 articles, "Scopus" in 33 articles, and "science direct" in 207 articles. In the initial screening, 762 duplicates were removed. Then, reviews, patents, citations, unpublished articles, non-English, and unrelated articles were removed. Unrelated articles refer to articles that have used PBMT in other brain disorders. Finally, the full text of 171 articles was reviewed and 155 articles that did not meet the inclusion criteria were excluded The final number of records was 16 articles which were divided into 2 groups of animals ($n=7$) and human studies ($n=9$).

Animal studies (Table 1)

Seven animal studies meeting the review criteria have been performed that all have confirmed the effectiveness of PBMT (Table 1). All of the studies had control groups. Six studies were performed on the treatment of depression and one study on depression and anxiety in the early stages of Alzheimer's disease (AD). In 5 studies, comparisons in terms of wavelength, power, energy density, and the effectiveness of a drug and PBMT were performed. Pulse mode (PM) of radiation was used in 3 studies.

Human studies (Table 2)

Nine human studies meeting the review criteria including 4 RCTs have been performed which all have confirmed the effectiveness of PBMT (Table 2). Areas of study included depression and/or anxiety and bipolar disorders. No comparisons were made, the radiation mode was continuous in all studies. In all studies, the location of radiation was the forehead, except for one in which the temporal region was also irradiated [33].

Useful parameters of PBMT (Table 3)

Determining useful parameters helps to select the most effective parameters and in special cases to select alternative options. With the exception of two animal studies that used red wavelength, the rest of the human and animal studies used infrared wavelength. Five human studies have used LED instead of laser, shown to be just as successful. Regardless of the case, wavelengths between 800 and 830 nm, power densities of 250 mW/cm^2 (0.25 W/cm^2), and energy densities between 60 and 120 J/cm^2 were most commonly used in human studies.

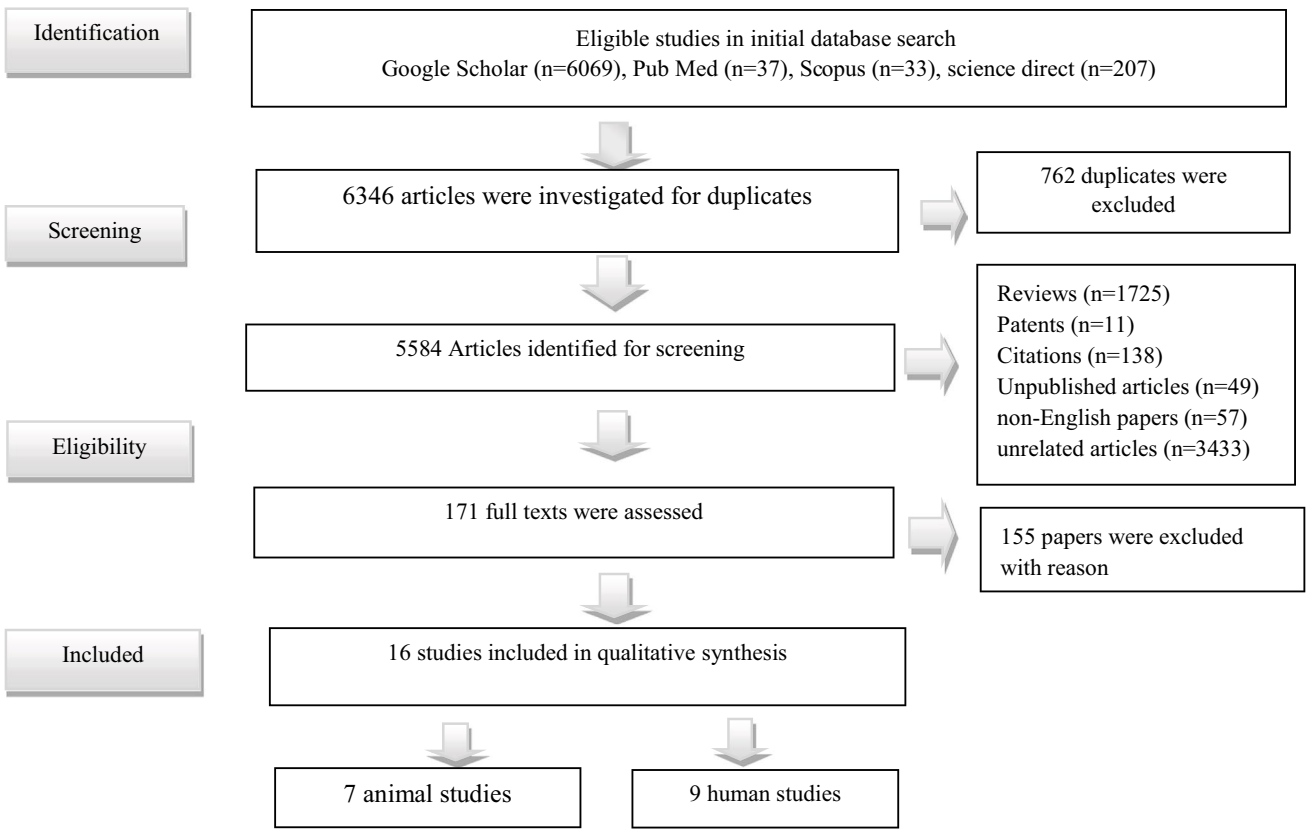

Fig. 1 Flow diagram of studies assessed in the systematic review

Table 1 Animal studies of PBMT in mood disorders

	Participants	Intervention (parameters of PBMT)	Assessment tools, comparison (if any)	Outcomes
1. Wu 2012 Depression [27]	32 Rats	810-nm laser, PM, 10 Hz, 15 mW/cm^2, 120 J/cm^2, midline of the dorsal surface of the head, 9 S. total dose: 1080 J/cm^2	FST, body weight, comparison fluoxetine and PBMT	The effects of PBMT on improving behavioral outcomes after mild chronic stress were comparable to fluoxetine
2. Salehpour 2016 epression [28]	50 rats	810 nm, 562 mw/cm^2 630 nm, 89 mW/cm^2, laser PM, 10 Hz, 1.18 ± 0.01 J/cm^2/S. 12 S., the midline of the dorsal surface of the shaved scalp, total: 14.4 J/ cm^2	FST, elevated plus maze test, serum cortisol and glucose, body weight, comparison NIR, red, and citalopram	The effect of PBMT with NIR on depression was comparable to citalopram and more effective than red light
3. Mohammed 2018 Depression [29]	48 rats	804-nm laser, CM, 0.64, 1.60, 3.18 W/cm^2, 4.8 12, 24 J/point, on the skull on six points, single S., total: 28.8, 72, 144 J/session	FST, ECoG, comparison different radiation powers	The antidepressant effect of PBMT was particularly significant at low doses
4. Salehpour 2019 Depression, [19]	75 mice	810-nm laser, CM, 6.66 W/cm^2, 33.3 J/cm^2, fiber on midline of the dorsal surface of the head in the region between the eyes and ears, 3 s, 5 S., total: 166.5 J/cm^2	Behavioral and biochemical assessments, WB, comparison the effects of PBMT and CoQ10	PBMT& CoQ10 may be effective in prevention of psychopathological and behavioral symptoms of stress
4. Eshaghi Depression, 2019 [30]	55 mice	810-nm laser, PM, 10 Hz, 4.75 W/cm^2, 4, 8, 16 J/cm^2, midline of the dorsal surface of the head in the region between the ears and eyes, 9 S., total: 36, 72, 144 J/cm^2	Behavioral tests, Serum cortisol, 5-HT, NO levels in hippocampus & PFC, comparison: 4, 8, 16 J/cm^2	PBMT and CoQ10 can be used to treat stress-induced depression
5. Yang 2021 Anxiety & Depression [31]	32 rats	808-nm laser, CM, 25 mW/cm^2, 3 J/cm^2, on top of the rat's head, 96 S. total: 288 J/cm^2	Behavioral tests, apoptosis, neural degeneration, mitochondrial function, and oxidative stress were measured	PBMT may improve the symptoms of depression and anxiety in the early stage of AD
6. Zhang, 2021 Depression [32]	94 mice	635-nm laser, CM, 12.74 mW/cm^2, 2 J/cm^2, the fiber was placed above the head, 30 S. total: 60 J/cm^2	SPT, FST, TST, ELISA for glutamate detection, cell culture & CORT, IHC exposures, cell viability assay, WB, semi quantitative reverse transcription-PCR	PBMT has the ability to control the progression of depression

nitric oxide (NO), pulse mode (PM), continuous mode (CM), sessions (S), forced swimming test (FST), Sucrose Preference Test1080 (SPT), forced swimming test (FST), tail suspension test (TST), enzyme-linked immunosorbent assay (ELISA), Western Blot (WB), prefrontal cortex (PFC), electrocorticography (ECoG), near infra-red (NIR), Alzheimer disease (AD), immunohistochemistry (IHC), coenzyme Q10 (CoQ10), corticosterone (CORT)

Table 2 human studies of PBMT on mood disorders.

	Participants study design	Intervention	Evaluation test	Outcomes
1. Schiffer, 2009 Dep/Anx. [34]	10 P, pilot study	808-nm LED, CM, 250 mW/cm^2, 60 J/cm^2/site, single site exposure, Single S., total dose: 120 J/cm^2	SCID, HAM-D, HAM-A, PANAS	PBMT can be useful in treatment of depression and other psychiatric disorders
2. Cassano, MDD, 2015 [35]	4P, *RCT*	808-nm laser, CM, 700 mW/ cm^2, 84 J/cm^2, 6 S. forehead bilaterally, total dose: 504 J/cm^2	HAM-D17	PBMT can be effective in treating MDD
3. Disner, 2016 Depression [36]	51 P, *RCT*	1064-nm laser, CM, 250 mW/cm^2, 60 J/ cm^2, forehead, single S., total dose of 60 J/cm^2	CES-D	Neuroenhancement using low-level laser could increase the benefits of bias modification techniques such as ABM in depression
4. Henderson 2017 Depression [33]	39 P, case series	810, 980-nm lasers, CM, 8–15 W, 55 to 81 J/cm^2, 8–34 S., forehead & temporal regions, total: 440–2754 J/ cm^2	HAM-D, QIDS	Multi-Watt near infrared-light therapy had more efficacy and persistent positive effects compared to low power
5. Cassano 2018, MDD [37]	21P, double-blind *RCT*	823-nm LED, CM, 33.2 mW /cm^2, up to 65.2 J/cm^2, 16 S., dorsolateral prefrontal cortex, total: 1043.2 J/cm^2	HAM-D17	Medium to large antidepressant effect size by performing PBMT on MDD
6. Maiello, 2019 GAD [9]	15 P, pilot study	830-nm LED, CM, 30 mW/ cm^2, 36 J/ cm^2, forehead using LED-cluster headband, 56 S., total: 2016 J/cm^2	SIGH-A, CGI-S, PSQI	PBMT can be an alternative treatment for generalized anxiety disorder
7. Kerppers 2020 [38] Dep. /Anx	22 P, controlled	945-nm LED, CM, 110 mW, 9.25 J/ cm^2, 30 S. to frontal bone, total: 277.5 J/cm^2	HADS, faces test, design test, Grippe strength test	PBMT ameliorates brain function and may reduce anxiety and depression clinically
8. Alipour 2020, Depression [39]	6 P, ***RCT***	800–810-nm LEDs, CM, 3.5 W/cm^2, 630–840 J/cm ^{2}, 10 S., forehead F3 and F4 sites of EEG, total: 6300–8400 J/cm^2	BDI, qEEG	PBMT can be useful in treatment of depression and cognitive function
9. O' Donnell [40] 2021, bipolar disorder	5P, sham-controlled crossover	1064-nm laser, CM, 0.25 W/cm^2, 75 J/ cm^2/site, forehead, 5 S. total dose: 750 J/cm^2	Cognitive flexibility, verbal fluency, working memory sustained attention, impulsivity with tasks	PBMT is effective in improving the accelerated cognitive decline in bipolar disorder in elderly

P (participants), min (minutes), depression/ anxiety, (Dep. /Anx.), major depressive disorder (MDD), Generalized anxiety disorder (GAD), Standard Clinical Diagnostic Interview (SCID), Hamilton depression rating scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Center for Epidemiologic Studies – Depression Scale

Table 3 Useful parameters of PBMT

	Human studies	Animal studies
Depression &/or anxiety	8 articles, 800 to 830 nm, 250 mW/cm^2, 60 J/cm^2	7 articles, 810 nm, 3 to 35 mW/cm^2, 2 to 33 J/cm^2
Bipolar disorder	1 article, 1064 nm, 250 mW/cm^2, 75 J/cm^2	

Level of evidence of PBMT effectiveness

The level of evidence for a therapeutic intervention is determined by a hierarchical classification system used to select the best therapeutic method. In evidence-based medicine (EBM), RCT is the best type of study to recommend a treatment, and a systematic review of RCTs with homogeneous outcomes can provide the strongest evidence of recommendation [26]. High-quality RCTs are classified as level 1B and low-quality RCTs are classified as level II B type of evidence. Based on grade practice recommendations, level IB evidence or consistent findings from multiple studies of levels II, III, or IV are classified as grade 1 (strong recommendation). Level II, III, or IV evidence with consistent findings is classified as grade 2 (recommendation). Inconsistent findings of levels II, III, or IV, and level V evidence are classified as grades 3 and 4 which are optional and require further investigations [26, 41, 42]. In the current study, individual case-controls are classified as level IIIB [38, 40] while case series are classified as level IV of evidence [9, 33, 34]. Four RCTs have been included in this review which performed on depression [35–37, 39]. Although the results of these studies are homogeneous, the quality of RCTs may vary. Therefore, a risk of bias assessment was performed to determine the quality of RCTs.

Assessing risk of bias of RCTs (Table 4)

In present study, we used the Cochrane risk-of-bias tool for randomized trials (RoB 2), which is structured in domains to cover the types of bias that may affect RCT results [43]. The judgement about the risk of bias can be "low" or "high" risk of bias or can express "unclear" (Table 4). Among 2 included clinical trials, 50% ($n=2$) and 50% ($n=2$) listed as good and poor-quality studies respectively. None of them was fair qualified. The high-quality RCTs have been performed in depression. The highest bias was detected in "allocation concealment" domain. "Other bias" was included wrong statistical analysis or wrong methodology (Fig. 2). All of the papers had low risk bias in the "selective reporting" domain. The most common problem was due to unclear information.

Discussion

Mood disorders are common and can severely affect a person's quality of life. Pathological changes in mood disorders include neuroinflammation, changes in neurotransmitter metabolism, impaired neural plasticity, and mitochondrial dysfunction [21, 44]. PBMT has been increasingly used to treat mood disorders and studies have confirmed its ability to reduce neuroinflammation, neurotransmitter imbalances, and mitochondrial dysfunction, but the question is: what is the level of evidence for its effectiveness? Can it be strongly recommended for the treatment of mood disorders? As mentioned earlier, the best type of study to determine the level of evidence is RCT but RCTs are not of the same quality and their quality should be determined by assessment the risk of bias. In this study, in assessing the risk of bias, 50% of RCTs were identified as of poor quality. However, in Disner et al. [36], uncertainty occurred in the field of allocation concealment, meaning that the results of this paper can be as qualified as a cohort study that is considered a high-level study. Therefore, it can be claimed that 75% of the RCTs had reliable results.

The effects of PBMT in the treatment of depression include increased brain metabolism, modulated

Table 4 Risk of bias of the included studies according to Cochrane risk-of-bias tool for randomized trials (RoB 2)

	Domain 1 Random sequence generation	Domain 2 Allocation concealment	Domain 3 Selective reporting	Domain4 Other bias	Domain 5 Blinding of participants and personnel	Domain 6 Blinding of outcome assessment	Domain 7 Incomplete outcome data	Total
1. Cassano 2015	L	L	L	L	L	L	U	G
2. Disner 2016	U	H	L	L	L	U	L	P
3. Cassano 2018	L	L	L	L	L	L	L	G
4. Alipour 2020	U	U	L	H	H	H	L	P

U: Unclear Risk of Bias, L: Low Risk of Bias, H: High Risk of Bias, P: Poor Quality, G: Good Quality

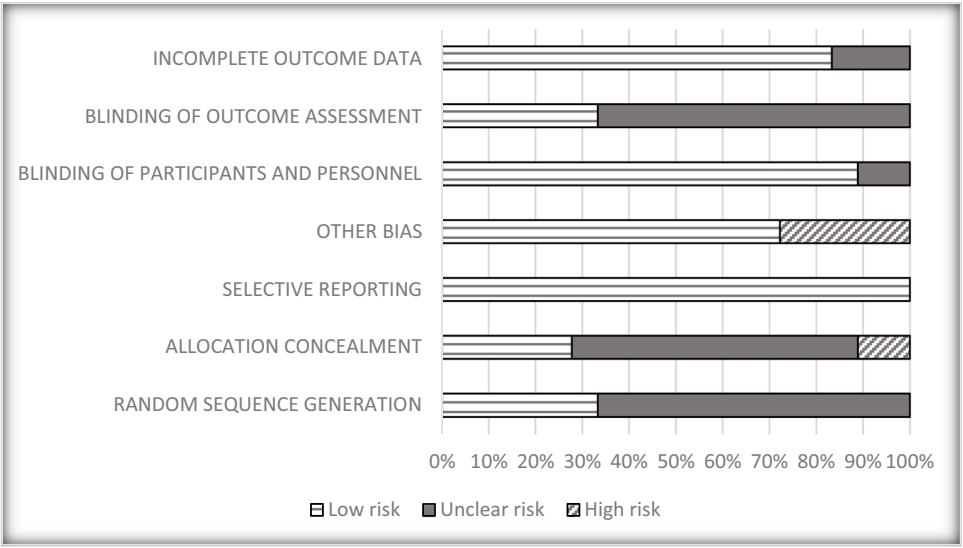

Fig. 2 The distribution of different Risks of bias in accordance with Cochrane risk-of-bias tool for randomized trials (RoB 2)

neurotransmitter metabolism, reduced neuroinflammation, and oxidative stress [19]. There were 14 studies including 4 RCTs, all of which confirmed the effectiveness of PBMT. In one animal and two human studies, subjects with depression also manifest an anxiety disorder and PBMT was reported to be effective in improving both disorders. The 2 high-quality RCTs have been performed in patients with at least a moderate grade of major depressive disorder (MDD) using Hamilton Depression Rating Scale (total score between 14 and 24) [35, 37]. The maximum permitted score of 24 was for prevention of inclusion of patients at higher risk of suicide. Both of the RCTs reported the medium to large effect size of PBMT in MDD. A strong recommendation is given when there is level I of evidence or consistent evidence from levels II, III, and IV studies. Animal studies are not classified in evidence-based medicine. In the current study, there are 2 high-quality RCTs (level IB), 2 low-quality RCTs (level IIB), a case control (level IIIB), and 2 pilot studies (level IV). Overall, according to the Grade Practice Recommendations, PBMT can be classified as strongly recommended for moderate grade of depression [26]. Of course, it should be noted that depression is a multifactorial complex disorder which is often associated with underlying diseases and the specialist should decide whether to use PBMT alone or in combination with medications and psychotherapy. In both good quality RCTs, taking one FDA-approved antidepressant and a psychotherapy course was allowed for the patients. Combination therapy may or may not be more effective than PBMT alone. Comparing the effectiveness of combination therapy including medication, psychotherapy, and PBMT with PBMT alone is recommended in future studies.

The exact mechanism of the anti-anxiety effect of PBMT is still being investigated, but an increase in serotonin level, a decrease in NO in the prefrontal cortex and hippocampus, and a decrease in serum cortisol levels have been shown to occur in patients after tPBM [9, 30]. There have been 4 studies in the treatment of anxiety, including a controlled animal study, a controlled study (level IIIB), and 2 pilot studies (level IV). Of the 3 human studies, 2 have been performed in the treatment of anxiety associated with depression [34, 38]. A pilot study have been performed in the treatment of generalized anxiety disorder (GAD) with at least moderate severity of disease in Clinical Global Impression Severity Scale [9]. All of these studies have confirmed the effectiveness of PBMT and according to the "Grade Practice Recommendations," the consistent findings of the studies of levels II, III, or IV can be classified as recommended [26]. Therefore, PBMT can be classified as recommended for the treatment of anxiety.

Only one controlled study has been performed in the treatment of bipolar disorder, and further studies are needed to classify PBMT as recommended for this disorder.

Conclusion

In recent years, PBMT has been growingly used in the treatment of mood disorders and good results have been reported. From this review, wavelengths between 800 and 830 nm, power density of 250 mW/cm^2, and energy densities between 60 and 120 J/cm^2 were the most widely used parameters of PBMT in the treatment of mood disorders. Based on grade practice recommendations, PBMT can be strongly recommended for treatment of moderate levels of MDD and recommended for anxiety disorder. Further studies are needed to recommend PBMT for the treatment of bipolar disorder.

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Author contribution S. M., S. C., and K. M.: contributed in idea, conception, study design, acquisition collecting data, analysis or interpretation of data, and drafting the primary and finalized article. K. M.: writing, editing and reviewing the manuscript, the study was a part of KM PhD. Project, M. F. and R. F.: contributed in conception and study design from the aspect of clinical representations and interpretation of the results.

Declarations

Ethics approval and consent to participate All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. "This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors."

Conflict of interest The authors declare no competing interests.

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