Journal of Alzheimer's Disease 83 (2021) 1453–1469
DOI 10.3233/JAD-210586
IOS Press

Dosimetry and Clinical Efficacy of Transcranial Photobiomodulation for Major Depression Disorder: Could they Guide Dosimetry for Alzheimer's Disease?

Marco Antonio Caldieraro[a,b,*], Tatiana Laufer-Silva[a,b] and Paolo Cassano[c,d]
[a]*Centro de Pesquisa Experimental (CPE) e Centro de Pesquisa Clínica (CPC), Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre – RS, Brasil*
[b]*Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Departamento de Psiquiatria e Medicina Legal, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Porto Alegre – RS, Brasil*
[c]*Harvard Medical School, Boston, MA, USA*
[d]*MGH Division of Neuropsychiatry, Massachusetts General Hospital, Boston, MA, USA*

Accepted 1 August 2021
Pre-press 1 September 2021

Abstract.
Background: Major depressive disorder (MDD) is prevalent and has significant impact on individuals and society. Cognitive symptoms are frequent in MDD and insufficiently treated by antidepressant medications. Transcranial photobiomodulation (t-PBM) is a novel device therapy which shows promise as an antidepressant and pro-cognitive treatment. To date, despite the encouraging results, the optimal stimulation parameters of t-PBM to treat MDD are not established, and clinical studies are very heterogeneous in terms of these parameters. While the literature provides guidance on the appropriate fluence to achieve therapeutic results, little is known on the other parameters.
Objective: To evaluate the relationship between different parameters and the antidepressant effect of t-PBM.
Methods: We reviewed clinical studies on MDD and on depressive symptoms comorbid with other diseases. We calculated the standardized effect size of the change in symptoms severity before and after t-PBM and we performed a descriptive analysis of the reviewed papers.
Results: The greatest effect sizes for the antidepressant effect were found in studies using pulse-wave t-PBM with high peak irradiance (but low average irradiance) over large skin surface. One well-designed and sufficiently powered, double-blind, sham-controlled trial indicated that t-PBM with low irradiance over a small skin surface is ineffective to treat depression.
Conclusion: The use of t-PBM for Alzheimer's disease and for dementia is still at its inception; these dosimetry lessons from the use of t-PBM for depression might serve as guidance.

Keywords: Alzheimer's disease, cognition disorders, depression, low-level light therapy, photobiomodulation

INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders worldwide. The lifetime prevalence of MDD in the United States is 16.6%, and the 12-month prevalence is about 6.6% [1, 2]. Depression significantly impacts individuals

*Correspondence to: Marco Antonio Caldieraro, Serviço de Psiquiatria, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350 4° andar, Porto Alegre – RS, 90035-903, Brazil. Tel.: +55 (51) 33598294; Fax: +55 (51) 33598294; E-mail: mcaldieraro@hcpa.edu.br.

ISSN 1387-2877/$35.00 © 2021 – IOS Press. All rights reserved.

and society: it decreases productivity at work, impairs daily activities and psychosocial functioning, and increases medical costs [3–5], representing the second leading cause of years lived with disability in the world [6].

The need for new antidepressant treatments

Psychotherapy and medication are well-established treatments for MDD [7]. However, these treatments have shortcomings. Evidence-based psychotherapies require frequent sessions and specialized professionals, consequently access is limited [8]. Remission from depressive symptoms is not achieved in 33% of patients, even after four consecutive attempts with initial medication monotherapy followed by optimized treatment strategies [9]. Also, antidepressant medications are frequently associated with burdensome side effects, which can compromise treatment adherence [10, 11]. In fact, nonadherence is strongly linked to concern about side effects [12]; relapses are common even when adherence is maintained [13].

Device-based treatments are alternatives for MDD patients who do not respond to, do not tolerate, or do not accept antidepressant medications or psychotherapy. Electroconvulsive therapy (ECT), transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS) are FDA-approved for treatment resistant depression. Despite their efficacy, these strategies are complex and require multiple visits to the clinical facility (ECT and rTMS) or anesthesia (ECT) [14]. VNS requires a surgery to implant the device. Therefore, there is a clear need for safe and non-invasive devices, either portable or wearable, but definitely easy to use and suitable for home-delivered treatments.

Photobiomodulation for depressive symptoms

Photobiomodulation (PBM) previously known as "low-level light therapy" or "low-level laser therapy" is an emerging device-based treatment for central nervous system pathologies [15]. PBM uses red or near-infrared (NIR) light to modulate cellular metabolism, cellular signaling, inflammatory processes, and growth factors production [16]. Light in these wavelengths penetrates through human tissues and has a wide range of molecular, cellular, tissular, and vascular effects locally and systemically [17]. PBM is already used for the treatment of a variety of conditions such as muscle pain [18], wounds [19], neuropathic pain [20], headache [21], periorbital wrinkles [22], and alopecia [23].

Although the antidepressant efficacy of PBM is not yet stablished, initial studies are promising and reported significant antidepressant effect [24–26]. Few studies suggested that systemic PBM (s-PBM), when the light is delivered to parts of the body other than the head, might be beneficial for MDD [27–29]. However, most studies in the field focused on transcranial PBM (t-PBM) [24, 30]. Transcranial PBM is a non-invasive treatment which uses low-power lasers or light-emitting diodes (LEDs) to deliver light to the scalp aiming to modulate neuronal activities and to improve depressive symptoms [15].

Photobiomodulation for cognitive symptoms

Diminished ability to think or concentrate is one of the defining symptoms of MDD, listed among the criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). Cognitive deficits during a depressive episode can present as a subjective complaint and can be observed by others [31]. The severity of these deficits can be demonstrated by neuropsychological tests [32] and it is correlated with biomarkers of neuroendocrinal disfunction [33]. Cognitive impairment is also associated with worse functioning and worse quality of life [34, 35]. However, there is little evidence of cognitive improvement promoted by antidepressant medications; some of them can even be detrimental to cognitive function [11]. Interestingly, t-PBM is also under investigation as a pro-cognitive intervention [15], with promising results for traumatic brain injury (TBI) [36] and other neurodegenerative disorders [37]. So, t-PBM has the potential to treat both the mood and cognitive symptoms of MDD.

Mechanisms of action of photobiomodulation

The exact mechanisms underlying the antidepressant effect of PBM are still not entirely clear. The absorption of light energy by the cytochrome C oxidase (CCO) and the resultant improvement in the metabolic capacity of neurons (due to more oxygen consumption and ATP production) seems relevant [15, 38]. NIR appears to initiate a cascade of subcellular events which can yield changes in the injured neuron or other cells [39, 40]. In addition

to the increase in ATP, changes in mitochondrial permeability that alter the intermembrane potentials within the mitochondria result in the production of reactive oxygen species (ROS). ROS are potent second messenger molecules which are involved in cell signaling, enzymatic activation, nucleic acid synthesis, protein synthesis, and activation of transcription factors [41]. Also, increased production of ROS leads to the activation of nuclear factor kappa β (NF-κβ) and cellular antioxidant mechanisms resulting in a reduction in oxidative stress. Other documented effects of t-PBM are the reduction of neuroinflammation and the increased production of neurotrophins such as the brain-derived neurotrophic factor (BDNF). NIR radiation also contributes to the displacement of nitric oxide (NO) from the CCO molecule. NO is a vasodilator and thus increases local blood flow [42, 43]. MDD is a complex disorder with multiple pathophysiological mechanisms. All the above-described actions of t-PBM were reported as relevant to MDD, since they potentially could address and reverse the following pathophysiological processes of MDD: decreased energy metabolism and blood flow in the pre-frontal cortex, decreased BDNF, increased neuroinflammation, and increased oxidative stress [25].

The biphasic dose response of photobiomodulation: Irradiance and surface

To achieve therapeutic results, it is important that the appropriate dose of light reaches the target tissue. Too low doses have no effect and too high doses may have inhibitory effects; this property is known as the biphasic dose response to PBM [38]. To irradiate the human prefrontal cortex, light needs to penetrate about 1 to 1.5 cm of skin, skull, cerebrospinal fluid, and meninges. The actual dose that will reach the cortex depends on the total energy delivered to the scalp and on what proportion of this energy penetrates up to the brain. In biological tissues, the scattering and absorption of light by biomolecules cause the decrease in energy which effectively reaches the cerebral cortex. In other words, irradiance and fluence decrease as the light reaches deeper tissues [44]; the stimulation parameters selected for treatment will determine these parameters at the target tissue [45]. This becomes especially important in clinical studies, since human skulls are thicker when compared to other species used for pre-clinical studies (mouse, rat, and rabbit) [46]. In a review of penetration studies, Salehpour and colleagues observed an average transcranial penetration of red and NIR light (630–810 nm) that ranged from 0.2 to 10% in humans (scalp and skull) [44].

The optimal transcranial stimulation parameters for the treatment of MDD are still to be established. Clinical studies on t-PBM for MDD are highly heterogeneous in terms of parameters, transcranial sites, and treatment regimens; therefore, limiting any inferences on dose-response. The most important parameters considered in these studies are wavelength, fluence, irradiance, and window (total energy per session and exposure time can be derived through simple calculations).

The wavelength is the most referenced parameter, and it influences penetration and absorption of light energy by the CCO (however defining, similar wavelengths of light have very similar penetration and absorption patterns). Energy absorption peaks for the CCO occur in both the red and NIR wavelengths [47]. Among this bandwidth, better penetration occurs within the NIR spectrum [48–50]. Yuan and colleagues using computerized modeling, observed that 810 nm wavelength provides the highest energy deposition (compared to 670 nm, 850 nm, 980 nm, and 1064 nm) [51], replicating a previous finding from the same group [50]. A study in unfixed cadaver brains demonstrated that an 808 nm 5 W laser, 7.07/cm^2, applied to the scalp, delivered -0.001 mW/cm^2 [52]. This wavelength range coincides with one peak of absorption for the CCO [39].

Fluence (or energy density) is defined as the total energy delivered per unit area during a given period (e.g., the duration of one treatment session) and is usually expressed in joules per square centimeter (J/cm^2). Irradiance (or power density) is defined as the power of the light source per unit area, usually expressed in milli-watts per square centimeter (mW/cm^2) [25].

To assess the biphasic dose response of PBM on brain disorders Huang and colleagues [38] conducted a study in a mouse model of traumatic brain injury. They delivered the same wavelength (810 nm), constant irradiance 25 mW/cm^2 and different fluences of 0.03, 0.3, 3, 10, and 30 J/cm^2 and subsequently measured the intracellular levels of ROS, mitochondrial membrane potential (MMP), and adenosine triphosphate ATP. Low-level light was found to induce a significant increase in ATP and MMP at intermediate fluences with a peak at 3 J/cm^2 and a decrease of the same at higher fluences. ROS followed the

same pattern of ATP and MMP in the lower fluences, reaching a peak at 3 J/cm^2. However, after a decrease at 10 J/cm^2, an even greater peak of ROS was observed at 30 J/cm^2. These interesting results prompted the field to consider the fluence of 3 J/cm^2 at the target tissue as the optimal fluence for treatment.

Studies in cell cultures, *in vitro*, and animal models indicate that insufficient irradiance or too short exposure time will have no effect on the pathology, and that too high irradiance and/or prolonged exposure time can have inhibitory effects. Therefore, there might be an ideal balance between irradiance and time to produce maximum beneficial effect [38, 53]. Since fluency is the product of irradiance and time, it is tempting to speculate that any combination of irradiance and time will result in similar effects if the fluency is similar, i.e., regardless of how radiant exposure is achieved. However, the individual parameters (irradiance and time) are critical and should always be measured and reported accurately. Thus, any useful concept of exposure reciprocity needs to include a highlight that treatment modalities may only be effective within a window of specific irradiation parameters [53]. But it is also possible that different irradiances, high as opposed to low irradiance, might have different effects, even if the fluence is maintained the same. An additional layer of complexity is that pre-human studies on biphasic dose response can hardly inform human dosimetry in healthy subjects and even less so in the clinical setting. Three studies assessing the effects of t-PBM on cortical excitability in healthy subjects addressed this issue of translating biphasic dose response to humans. Two of them used continuous wave (CW). The most recent of these two studies using CW (810–820 nm) [54] reported increased cortical excitability when using a fluence (74 J/cm^2) comparable to the skin fluence of 60 J/cm^2—the latter is commonly used in MDD clinical trials—and when using an irradiance (310 mW/cm^2) comparable to the high-end values of 250 mW/cm^2 used in some MDD clinical trials. The other study using CW, which applied a much higher fluence (300 J/cm^2) and a higher irradiance (500 mW/cm^2), reported instead decreased cortical excitability [55]. The third and last study [56] shed light at a longer wavelength (905 nm) and pulsed light with a very high frequency (5,000 Hz), this resulted in extremely high peak irradiance (100 W/cm^2) despite a low mean irradiance (50 mW/cm^2), the resulting fluence was the highest (1024 J/cm^2) of the three studies; the authors reported decreased cortical excitability (parameters per personal communication of Dr. Ljubica Konstantinovic).

Stimulation window is another relevant parameter. First, if all the other parameters are kept the same, increasing the window will result in increased total energy. Using a simulation model, Yue and Humayun suggested that multiple sources produce remarkably improved photon flow to a given brain area. They indicated that by applying a uniformly distributed array of multiple emitters to the scalp, it is possible to increase the density of brain photons while keeping each emitter operating under safe thermal and electrical limits [45]. While the authors claim that deep penetration of light can occur by using multiple, uniformly distributed emitters, the energy deposition beyond superficial cortical layer remains very small in their simulations and unlikely to be of clinical significance [57–59]. Nevertheless, a potentially meaningful increase in energy deposition per cm^2 might occur when superficial brain areas are targeted.

Further developments of t-PBM for the treatment of MDD require better understanding of best stimulation parameters. Although current evidence provides some guidance on optimal fluence, there is little information on how other parameters can influence treatment outcomes. The understanding of how different stimulation parameters modulate brain activity to treat MDD will likely inform predictions on dosimetry for other disorders of the central nervous system (CNS), such as Alzheimer's disease. With this goal in mind, we performed a review of clinical studies on t-PBM for MDD and we suggested their categorization based on treatment parameters and on improvement of depressive symptoms. Given the impact of irradiance on cortical excitability—as shown in our description of biphasic dose response in healthy subjects—we centered our categorization of the clinical trials on high versus low irradiance and expanded to other parameters.

METHODS

We searched clinical studies on PubMed and ClinicalTrials.gov using the following keywords: ("photobiomodulation" OR "near-infrared radiation" OR "NIR" OR "low-level light therapy" OR "low-level laser therapy" OR "LLLT" OR "near-infrared light therapy" OR "NILT") AND ("depression" OR "depressive disorder"). The search was performed in September and October 2020. A search on the refer-

ences of the studies identified in the PubMed search was also performed. Studies on t-PBM for MDD and those on t-PBM for other diagnosis with comorbid depressive symptoms were included. Only clinical studies on the transcranial modality were included. Pre-clinical studies or clinical studies on systemic PBM were excluded. Single case reports were also excluded.

Given the heterogeneity of the selected studies, a statistical comparison of the results was not possible, so we performed a descriptive analysis of the reviewed papers, after standardizing the outcome measures for depression. Since the selected studies used different scales to assess depressive symptoms, we calculated the standardized effect size (SES) of the change in symptoms severity before and after t-PBM, to obtain a more uniform and comparable measure. The Hamilton Depression Rating Scale (HAM-D) was used in most studies. Whenever studies adopted more than one scale to assess depression severity, we prioritized the results from the HAM-D, since the latter was the most used scale. Most studies used an open protocol, therefore lack of randomization was not considered exclusionary. Open trials were considered positive, or likely to reflect an antidepressant effect for t-PBM, if there was an improvement in depressive symptoms, while comparing pre- and post-treatment, equivalent or greater to 1.0 SES. This stringent threshold for open trials was adopted to prevent us from overestimating the antidepressant efficacy of t-PBM; since the placebo effect was not controlled for and since the latter is expected to be high in open studies. Randomized clinical trials (RCTs) were considered positive if the active treatment resulted in a greater reduction of depressive symptoms compared to sham treatment; this was operationalized as an effect size equal or greater than 0.5 SES; therefore, choosing another conservative threshold of at least a moderate antidepressant effect in a double-blind trial. To evaluate the results of the RCTs in comparison with the open trials, we also selected just the participants in the active arm of the RCTs and estimated their SES (for the improvement of depressive symptoms) from pre- to post-treatment. An equally stringent threshold of SES (relatively to the open trials) equal to or greater than 1.0 was chosen for the latter comparison to identify a likely positive effect on depressive symptoms. While the placebo effect might be lower in an RCT (relatively to an open trial), we kept a high bar (SES $\geq$ 1.0) for the active arm to determine the likelihood of an antidepressant effect, due to the frequent in-office visits for t-PBM.

RESULTS

Eight clinical studies were included in the review and are described in detail below. They consisted in three small RCTs and three open label studies and two retrospective case series (see Table 1). All studies used light in the NIR spectrum. There was a clear split on the irradiances used in the studies. Six studies used CW. Of those, three studies used high irradiance (250 mW/cm^2 to 700 mW/cm^2), and three studies used low irradiances (22.2 mW/cm^2 to 54.8 mW/cm^2). Overall, studies with high irradiance tended to use smaller stimulation windows and those with lower irradiance used larger windows (Fig. 1). However, two studies used pulsed wave (PW) with high peak irradiance, and low average irradiance, over a large surface and one study (CW) used low irradiance over a small surface. So, we divided the studies in four clusters, considering the irradiance and the stimulation window: a) low irradiance over small surface; b) high irradiance over small surface; c) low irradiance over large surface; and d) high peak irradiance with low average irradiance over large surface.

Low irradiance over small surface

ELATED-3 [60] was a well-designed RCT, featuring a relatively novel design based on double-randomization: the sequential parallel comparison design (SPCD) [61]. Accordingly, outpatients with MDD were randomized to NIR or sham (1 : 2) for 6 weeks: at the end of this first phase, subjects who did not respond to sham were re-randomized to NIR or sham (1 : 1) for additional 6 weeks (second phase). The study device was the TPBM-1000 (LED $\sim$2 W), manufactured by Litecure LLC, which shed light bilaterally on the forehead at four spots (Fp1, Fp2, F3, and F4), for 20 min twice a week. Parameters included the following: wavelength 830 nm, CW, irradiance of 54.8 mW/cm^2 and a fluence of 65.8 J/cm^2, on a 35.8 cm^2 window, reaching a total energy of 2.35 kJ per session and 28.3 kJ for the entire course of 6 weeks. Initially, 49 subjects were randomized to receive NIR treatment ($n = 18$) or participate in the sham group ($n = 31$). After 6 weeks, the non-responders in the sham group ($n = 17$) were re-randomized to receive active treatment ($n = 10$) or remain in the sham group ($n = 7$) for 6 more weeks. In the end SPCD design phase 1 ($n = 49$) and phase 2 ($n = 17$) samples are first analyzed separately, and ultimately pooled effects sizes and significance can be estimated ($n = 66$). As previously mentioned, for the

Table 1
Photobiomodulation parameters in clinical studies for the treatment of depression

Study	Design	Diagnosis (n – active treatment)	Number of Treatments (duration)	Wavelength	Irradiance	Fluence	Total Window	Energy per session/total energy in the study	Instrument	Results	Score at baseline	Score after treatment*	Standardized Effect Size**
Low irradiance over small surface													
Iosifescu et al. (2020) [60]	RCT Double-blind, sequenced, parallel design (SPCD)	MDD ($n = 49$)	Twice a week	830 nm	54.8 mW/cm^2	65.8 J/cm^2	35.8 cm^2	2.4 kJ/28.3 kJ	HAM-D17	Improvement on HAM-D scores for t-PBM not superior to sham	Phase 1	LOCF	Active t-PBM arm pre verse post treatment: 0.68
		Phase 1 (NIR $n = 18$) (sham $n = 31$)	20 min x 4 sites (6 weeks)	CW							NIR 19.7 ± 2.8	–3.4 ± 5.0	Active t-PBM versus sham: 0.17 (NS)
		Phase 2 (NIR $n = 10$) (sham $n = 7$)	Total follow-up: 6 weeks each phase								Sham 20.1 ± 5.0	–4.3 ± 5.0	Active t-PBM arm pre versus post treatment: 0.40
											Phase 2	LOCF	Active t-PBM versus sham: 0.38 (NS)
											NIR 16.1 ± 5.2 Sham 19.3 ± 7.1	–2.6 ± 6.5 –5.1 ± 7.0	
High irradiance over small surface													
Schiffer et al. (2009) [63]	Open Pilot	Resistant MDD ($n = 10$)	One session 4 min	810 nm CW	250 mW/cm^2	60 J/cm^2	2 cm^2	0.12 kJ/0.12 kJ	HAM-D21	Decrease in HAM-D scores. Rates of response: 40% at week 2 and 20% at week 4.	23.9 ± 8.8	All subjects	
												–13.2 ± 7.9 (week 2)	1.67
			Total follow-up: 4 weeks									–6.5 ± 7.3 (week 4)	0.89
Cassano et al. (2015) [61]	Open Pilot	MDD ($n = 4$)	Twice a week	808 ± 10 nm	700 mW/cm^2	84 J/cm^2	28.4 cm^2	2.4 kJ/14.4 kJ	HAM-D17	Rates of remission: 50% at weeks 6-7 (HAM-D17 ≤ 7)	19.8 ± 4.4	LOCF ($n = 4$)	
			2 min x 4 sites (3 weeks)	CW								13 ± 5.4	1.39
			Total follow-up: 8 weeks										

Disner et al. (2016) [64]	RCT	Symptoms of depression ($n = 51$)	Two sessions	1,064 nm	250 W/cm^2	60 J/cm^2	27.2 cm^2	1.6 kJ/3.3 kJ	CES-D [a]	Right PBM enhanced the effect of ABM on depression (CES-D) in ABM-responders.		Completers ($n = 46$)	Right active t-PBM arm, pre versus post treatment: 0.85
	Parallel design	(NIR on left $n = 18$)	4 min x 2 sites (48 h)	CW						No significant differences in decrease of CES-D across PBM groups when ABM-responsiveness was not factored.	Right 30.6 ± 9.8	22.5 ± 9.5	Left active t-PBM arm, pre versus post treatment: 0.50 (NS)
		(NIR on right $n = 18$)	Total follow-up: 2 weeks								Left 27.1 ± 8.0	22.6 ± 9.7	Right Active t-PBM arm versus sham: 0.09 (NS)
		(sham $n = 15$)									Sham 32.0 ± 11.9	21.7 ± 8.1	
Low irradiance over large surface													
Naeser et al. (2014) [79]	Open Pilot	Chronic TBI ($n = 11$)	3/ week	870 and 633 nm	22.2 mW/cm^2	13 J/cm^2	247 cm^2	3.2 kJ/57.8 kJ	BDI	Trend towards significance (BDI) after 6 weeks	17.4 ± 9.9	All subjects	
		depressed ($n = 8$)	10 min x 11 sites (6 weeks)	CW								13.3 ± 6.1	0.52
Cassano et al. (2018) [62]	RCT double-blind, parallel design	MDD (NIR $n = 10$) (sham $n = 11$)	Twice a week	823 nm	36.2 mW/cm^2	40, 50, 60 J/cm^2	57.4 cm^2	3.4 kJ (max)/ 45.6 kJ (8 weeks)	HAM-D17	Decrease in HAM-D scores significantly greater in the PBM group (BOCF but not LOCF).	HAM-D	LOCF ($n = 19$)	
			20–30 min (8 weeks)	CW					CGI	Response rate (CGI) higher in the PBM group at endpoint: 50% versus 27% in controls.	NIR 20.6 ± 3.2*	–10.8 ± 7.6	Active t-PBM arm pre versus post treatment: 1.43
									QIDS	No significant differences at QIDS	Sham 20.2 ± 4.3	–5.3 ± 7.0	Active t-PBM versus sham: 0.75 (NS)

(*Continued*)

Table 1
(*Continued*)

Study	Design	Diagnosis (*n* – active treatment)	Number of Treatments (duration)	Wavelength	Irradiance	Fluence	Total Window	Energy per session/total energy in the study	Instrument	Results	Score at baseline	Score after treatment*	Standardized Effect Size**
High peak irradiance with low average irradiance over large surface													
Morries et al. (2015) [68]	Retrospective case series	Chronic TBI depressed (*n* = 10)	2-3/week (6 weeks)	810 and 980 nm	Average: 20.6–51.5 mW/cm^{2a}	55 to 81 J/cm^2	212–474 cm^2	4.8–9 kJ/	QIDS-SR	BDI and QIDS-SR scores decreased from moderately depressed range to non-depressed range		All subjects	
			8–12 mins per session 10 sessions (*n* = 6) 20 sessions (*n* = 4)	PW (10 Hz)	Peak: 200–300 mW/cm^{2a}			48–180 kJ	BDI		QIDS-SR, 12.9 ± 4.6 BDI, 25.3 ± 12.1	(*n* = 10) 2.2 ± 2.3 (*n* = 7) 12 ± 6.5	3.10 1.43
Henderson and Morries (2017) [69]	Retrospective case series	Chronic TBI depressed (*n* = 39)	8–34 treatments (8 + weeks)	810 and 980 nm	Average: 30–45 mW/cm^{2b}	55 to 81 J/cm^2	222–327 cm^2	~10 kJ [b]	HAM-D	Decrease in HAM-D and QIDS scores		All subjects	
			30 min per session 12 or fewer sessions (*n* = 12) 13 or more sessions (*n* = 27)	PW (10 Hz)	Peak: 200–300 mW/cm^{2b}				QIDS-SR		HAM-D, 21.5 ± 5.2 QIDS-SR 14.1 ± 3.3	6.0 ± 5.1 3.4 ± 3.3	2.99 3.24

*Results presented with a minus sign (–) indicate mean decrease in the depression rating scale score. Results without a minus size indicate mean post-treatment score in the depression rating scale. **For the RCTs the Standardized Effect Sizes (SESs) of the difference between pre and post treatment depression scores on the active treatment group only are presented in addition to the SESs of the difference between improvement in active versus sham treatment to allow for a comparison of these studies with open studies. [a]CES-D Scores for each group were kindly provided by Dr. Seth Disner. [b]Average and peak irradiance not reported in the original study and estimated based on the other parameters. MDD, major depressive disorder; CW; continuous wave; HAM-D, Hamilton depression rating scale; RCT, randomized clinical trial; LOCF, Last observation carried forward; BOCF, Baseline observation carried forward; NIR, near-infrared radiation; CES-D, Center for Epidemiologic Studies–Depression Scale; PBM, photobiomodulation; ABM, attention bias modification; TBI, traumatic brain injury; BDI, Beck Depression Inventory; CGI, Clinical Global Improvement; QIDS, Quick Inventory of Depressive Symptomatology; PW, pulsed wave; QIDS-SR, Quick Inventory of Depressive Symptomatology self-report; NS, Non-significant.

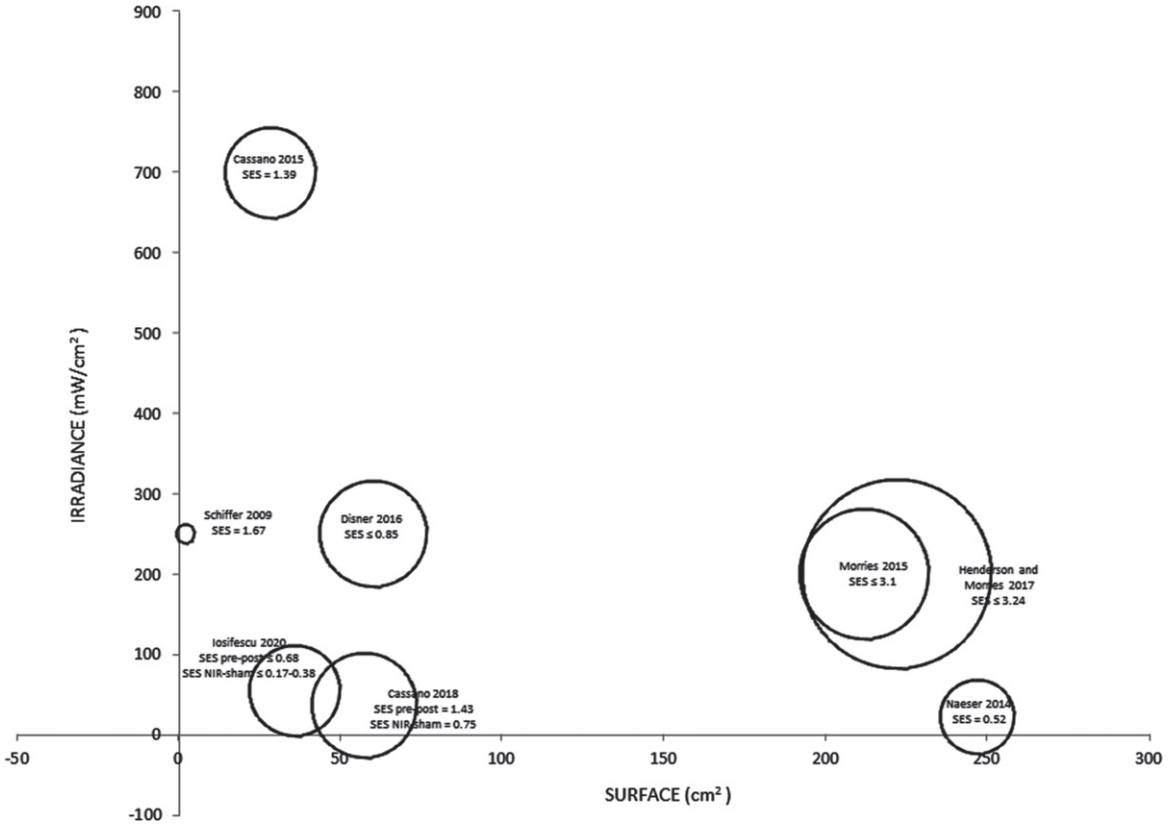

Fig. 1. Distribution of the clinical studies on t-PBM for depression considering irradiance (mW/cm^2- vertical axis), stimulation surface (cm^2 - horizontal axis), and total energy per session (kJ –diameter of the circles). Higher standardized effect size (SES) observed on studies using PW with high peak energy over large stimulation surfaces. Non-significant antidepressant effect observed on studies using low irradiance over small surface.

purpose of extracting a measure of effect size which could be compared across all studies (including open studies), we also selected just the participants in the active arm. When comparing the pre- and post-treatment scores in participants who received the active treatment, there was a reduction in depression scores at the HAM-D17 of 3.44 ± 5.03 (SES = 0.68) in phase 1 and 2.6 ± 6.52 (SES = 0.40) in phase 2. However, differently from the ELATED-2 trial [62] (described below), there was no superiority of the active treatment over sham ($p_{phase1} = 0.378$; $SES_{phase1} = 0.17$ and $p_{phase2} = 0.302$; $SES_{phase2} = 0.38$). The placebo effect observed in the sham group was low indicating this was a negative study and not a failed trial. The lower total energy delivered per session and the smaller stimulation surface used in this study (compared to ELATED-2) could explain the negative results. Also, the stimulation sites F3 and F4 were obstructed by hair, which likely induced light scattering and reduced light penetration to the brain at these sites.

High irradiance over small surface

In the first preliminary open trial that assessed the benefits of t-PBM in MDD, Schiffer et al. [63] delivered a single transcranial NIR application to the left (L) or right (R) forehead (areas F3 and F4, respectively) in 10 patients, with treatment-resistant depression (nine with a comorbid anxiety disorder). They considered the emotional hemispheric valence (which represents the trend of a cerebral hemisphere, left or right, having, as a characteristic, a more positive psychological disposition than the other) for the choice of which hemisphere would receive the active t-PBM treatment. Using an LED instrument (Marubeni America Corp.), and the following parameters: wavelength: 810 nm, CW, irradiance: 250 mW/cm^2, fluence: 60 J/cm^2 on a 2 cm^2 total window and over 4 min per site. The HAM-D21 baseline mean score (23.9 ± 8.8) decreased by 13.20 ± 7.9 points at 2 weeks post treatment. Four weeks post treatment, the scores were higher than after 2 weeks,

but still lower than baseline by 6.50 ± 7.3 points. The pre- versus post treatment SES was 1.67 ($p = 0.001$) after two weeks post treatment and 0.89 ($p = 0.003$) at the end of the 4-week follow-up. The hemisphere where t-PBM was applied was not mentioned as having interfered with the decrease in HAM-D scores.

An open pilot study (ELATED-1) evaluated 4 patients with moderate to severe MDD (nontreatment resistant) who were treated with 3 weeks of twice a week sessions of t-PBM [61]. At each treatment session, NIR was administered to the forehead bilaterally at four sites (2 min per site, 7.1 cm^2 window each, total window 28.4c m^2), using a class 4 laser, Neurothera (PhotoThera, Inc.). Parameters included: NIR wavelength of 808 nm, irradiance 700 mW/cm^2 and fluence 84 J/cm^2, for a total energy of 2.4 kJ per session. In this small sample, baseline mean HAM-D17 scores decreased from 19.75 ± 4.35 (SD) to 13 ± 5.35 (SD) within 8 weeks ($t = 7.905$; $df = 3$; $p = 0.004$), with LOCF analysis. Standardized effect size of improvement was 1.39 for the LOCF.

A randomized, sham-controlled RCT was the first to test the hypothesis that t-PBM could augment Attention Bias Modification (ABM), as an antidepressant intervention for adults with elevated symptoms of depression [64]. ABM has been shown to decrease symptoms of anxiety; however, the results are less consistent in depression [65]. Fifty-one subjects were randomized to receive two sessions of t-PBM either on their right forehead, left forehead, or sham; all subjects also received a pair of sessions of ABM, before and after each delivery of t-PBM. The interval between the two t-PBM sessions was 48 h. The Center for Epidemiologic Studies–Depression Scale (CES-D) was administered at baseline and repeated at week 1 and at the end of the 2-week follow-up. The ACG-5000 high-density laser was used (Cell Gen Therapeutics, Dallas, TX, USA) at two sites (13.6 cm^2 window each; total surface of 27.2 cm^2) for 4 min per site, with the following parameters: wavelength of 1064 nm, irradiance of 250 mW/cm^2, and fluence of 60 J/cm^2, with a total energy of 1.63 kJ per session and 3.6 kJ the entire course. In participants who responded to the ABM, the improvement was enhanced by the right t-PBM, while no significant add-on effects were observed for the left and sham t-PBM. We calculated the SES (Cohen's d) specifically for the antidepressant effect of t-PBM, regardless of the response to ABM, based on data kindly provided by Dr. Seth Disner. At week-2, right t-PBM decreased CES-D scores from 30.61 ± 9.76 to 22.47 ± 9.46 ($p < 0.01$; SES = 0.85) and left t-PBM from 27.06 ± 8.04 to 22.63 ± 9.72 ($p = 0.82$; SES = 0.5). Right t-PBM was less effective than sham (also delivered on the right) on depressive symptoms (SES = 0.09).

Considering a SES > 1.0 as indicative of an antidepressant effect within active treatment, two open trials using *high irradiance over small surfaces* were positive, both using a diagnosis of MDD as the main criterion to include participants. The third study in this section, a RCT of t-PBM to enhance ABM, did not demonstrate an overall antidepressant effect of t-PBM, based on both the SES within active arm and the SES towards sham (SES < 0.5 threshold). This latter study included participants with depressive symptoms, instead of participants who received a formal diagnosis of MDD. Although NIR delivered to the right forehead was associated with an enhancement of ABM, the overall antidepressant effect size for t-PBM was small.

Low irradiance over large surface

An open-protocol study examined 11 chronic [66] TBI subjects (5 of the 10 participants were found to have moderate or severe depression scores on the Beck Depression Inventory). The participants received 18 sessions of t-PBM (3 times/week for 6 weeks). During each session the treatment was applied for 10 min to each of 11 scalp placements. LEDs were placed on the midline from front-to-back hairline; and bilaterally on frontal, parietal, and temporal areas (window 247 cm^2). The LED Console Units (MedX Health, Model 1100, Toronto) used de following parameter: wavelength of 870 and 633 nm, irradiance of 22.2 mW/cm^2 and fluence of 13 J/cm^2. Baseline mean BDI scores decreased from 17.4 ± 9.9 (SD) to 13.27 ± 6.11 (SD). The decrease on BDI scores ($p = 0.045$; SES = 0.52) was subthreshold based on the desired antidepressant effect size within active treatment.

The ELATED-2 Pilot study [62] was a double-blind, sham-controlled study on the safety and efficacy of t-PBM and aimed to test the therapeutic benefit of t-PBM as a standalone or combination treatment in MDD. Twenty-one patients with moderate to severe depression (HAM-D17) were randomized to receive t-PBM NIR treatment ($n = 10$) or sham ($n = 11$) with the Omnilux New U light emitting diode (Photomedex, Inc., Montgomeryville, PA) twice a week for 8 weeks. During each session, NIR (823 nm) was delivered to the forehead bilaterally, aiming to irradiate the dorsolateral pre-frontal cortex. While

sessions started off at 20 min, the study clinician had the option to adjust the duration of light exposure to 25 and 30 min. These adjustments increased the fluence from 40 J/cm^2 to 50 J/cm^2 and 60 J/cm^2, respectively. Other treatment parameters were power 1 W, CW, irradiance 33.2 mW/cm^2, window 57.4 cm^2 with a total energy of 3.4 kJ per session and 45.6 kJ for the entire course. The active arm was significantly better than sham in lowering depressive symptoms according to the HAM-D17 scores (SES = 0.90; $p = 0{,}047$), when a baseline observation carried forward (BOCF) analysis was performed, however, not in the LOCF (SES = 0.75; p = ns). Remission rate (HAM-D17 ≤ 7) was 50% in the active treatment group and 27% in the sham group. The mean baseline HAM-D17 score for the 10 participants randomized to the active treatment group was 20.6 ± 3.2 and decreased to 10.8 ± 7.55 (SES = 1.43). There were more side-effects reported in the active treatment group, but no serious adverse events were observed in the study [67].

In this section examining *low irradiance over large surface*, the only open study was negative for threshold antidepressant effects, while the RCT was positive. Of note, the irradiance and fluence used in the open study were remarkably lower than in all other studies included in this review. Also, this open study was designed to assess the effects of t-PBM on TBI; therefore, mood changes were assessed as a secondary outcome and were averaged among participants with severe to minimal depressive symptoms. Instead, the positive RCT included participants based on their diagnosis of MDD and applied a much higher fluence.

High peak irradiance with low average irradiance over large surface

Two studies from the same group evaluated PW using high power devices with high peak irradiance but low average irradiance over a large surface. They used different devices, so the stimulation parameters are presented as a range. A sweeping technique was used, which is common for high power devices. Treatments used high irradiance and brief pulses with no light delivered during the interval between pulses. Consequently, the average energy delivered per second at each cm^2 is similar to what reported for the low irradiance studies using CW; however, the energy during each pulse of light (when the lasers are in fact emitting) is similar to what reported for the high irradiance studies using CW.

The first of these two studies [68] was a retrospective case series using high-power NIR lasers (Class IV): the LT1000 (LiteCure, Newark, DE, USA) or the Diowave 810 (Diowave, Riviera Beach, FL, USA). The authors evaluated 10 patients with chronic TBI, of whom 6 were also diagnosed with MDD; all patients presented depressive symptoms, and 6 expressed suicidal ideation. In terms of parameters, the wavelength was 810/980 nm or 810 nm, the fluence ranged from 55 to 81 J/cm^2, and the light was pulsed at 10 Hz. Irradiance was not described in the original paper. Based on the other parameters reported by the authors, we estimated an average irradiance range of 21–52 mW/cm^2, with a peak irradiance range of 200–300 mW/cm^2. The treatment was delivered two to three times per week. Patients received either ten ($n = 6$) or twenty ($n = 4$) sessions of t-PBM; each session lasted 8–12 min and involved either two or three sites over bilateral frontal and temporal regions (97 to 162 cm^2 per site and 212–474 cm^2 as the total window). Total energy was between 4.8 to 9 kJ per session and 58 to 180 kJ for the entire course. The treatment resulted in a significant reduction in the QIDS-SR and BDI scores. At baseline the mean QIDS-SR score was 12.9 ± 4.6 and it decreased to 2.2 ± 2.3 after the entire course of t-PBM ($p < 0.00001$; SES = 3.10). The mean BDI score decreased from 25.3 ± 12.1 at the baseline to 12 ± 6.5 at endpoint ($p < 0.01$; SES = 1.43). Noticeably, after the course of t-PBM sessions, none of study subjects endorsed suicidal ideation.

The second study, also a retrospective case series, included 39 sequential patients with chronic TBI and co-morbid depression, who were treated with t-PBM in the authors' clinic [69]. NIR was delivered to the forehead and temporal regions bilaterally, for 9–12 min on each area (total window 222–327 cm^2) and for 30 min total per session. The study included three different Class IV lasers [LT1000 (LiteCure, Newark, DE, USA), Diowave 810 (Diowave, Riviera Beach, FL, USA), or Aspen Laser (Denver, CO, USA)]. The power ranged from 8 to 15 W and the fluence ranged from 55 to 81 J/cm^2. Irradiance was not described in the original paper. Based on the other parameters reported by the authors, we estimated an average irradiance range of 30–45 mW/cm^2, with a peak irradiance range of 200–300 mW/cm^2. The total number of t-PBM sessions was variable depending upon individual patient improvement and ranged from 8 to 34 sessions (12 participants underwent 12 or fewer treatments; 27 participants had 13 or

more treatments). The mean HAM-D score decreased from 21.48 ± 5.24 at the baseline to 6.0 ± 5.12 at endpoint ($p < 0.001$; SES = 2.99). The QIDS-SR was self-rated before and after the course of treatment. At baseline the mean QIDS-SR score was 14.1 ± 3.3 and it decreased to 3.41 ± 3.3 after the entire course of t-PBM ($p < 0.001$; SES = 3.24). Of note, patients who received ≥ 13 sessions of t-PBM improved the most. Interestingly, some patients continued to show a response even after 55 months of follow-up.

These two studies on t-PBM with *high peak irradiance (but low average irradiance) over large surface* were positive for the antidepressant effect, as they both met the SES threshold criterion we used for open studies (SES > 1.0). Both studies included participants with chronic TBI who had comorbid depressive symptoms. They were also the only studies included in this review to adopt PW.

DISCUSSION

When reviewing the antidepressant effect of t-PBM, its large variability is unquestionable. Also, the studies are few and limited by their methodology. Drawing definite conclusions on effective parameters for t-PBM is risky and unwarranted. Nevertheless, we need guidance over potentially effective parameters to adopt in future larger and well-designed t-PBM studies, for depression and for other neuropsychiatric disorders. The effects of t-PBM likely depend on the combination of multiple parameters used for stimulation. In the field, there has been an overreliance on fluence as the key parameter to define t-PBM. Perhaps, the most critical finding of our review is that even enough fluence leads to ineffective treatment for depression, if t-PBM is administered on a too small surface, with too low irradiance and possibly too brief exposure. Therefore, our review suggests the existence of a t-PBM *dead zone* without therapeutic effects for depression, and possibly for other neuropsychiatric disorders. Our review also attempts to delineate the boundaries of this *dead zone* based on multiple t-PBM parameters, relatively to other—effective—combinations of parameters.

The clinical efficacy map for the antidepressant effect of t-PBM

As a rule, studies that adopted t-PBM either with high irradiance over small surface or with low irradiance over large surface led to noticeable antidepressant effects. This distribution suggests that there might be at least two very different modalities of t-PBM, although the relative efficacy and the exact mechanisms are still unknown. Intuitively, the field of t-PBM has adopted small surface when using high irradiance to maintain good tolerability and has compensated for low irradiance with large surface to enhance therapeutic effects; the validity of this approach seems to be corroborated by our review using standardized effect sizes for the antidepressant effect.

While our review offers only limited insights over very high or very low irradiance, one study used very low irradiance (and low fluence) over a large surface. The effects on depression were minimal, suggesting that spreading NIR energy over a large surface might not entirely compensate for the decrease in light intensity after the latter is very low. This combination of parameters could also be considered a *dead zone*, however given the very limited data and the lack of comparative design we refrain from drawing conclusions.

With the same caution we exerted above, when discussing a potential additional *dead zone*, we also postulate the existence of an *optimal zone* with the most therapeutic t-PBM settings, based on antidepressant effects. Within the studies characterized by low average irradiance over large surface, the use of PW light with high peak irradiance appeared extremely beneficial, with effect sizes at least twice as large as in the other studies. The retrospective design of the PW studies, their focus on chronic TBI, rather than MDD, and the lack of replication by independent groups render the existence of an *optimal zone* of t-PBM parameters still speculative, although probable.

The contribution of isolated t-PBM parameters to the antidepressant effect

Because any t-PBM treatment is defined by many stimulation parameters and because the reviewed studies often differ in multiple t-PBM parameters, any inferences on isolated parameters are also quite speculative. As indicated by previous studies [38], the role of *fluence* as a critical parameter to the therapeutic effect was strengthened by our review. In fact, the study reporting the lowest antidepressant effect size was also the one using the lowest fluence ($13\ J/cm^2$) [66]. Of note, participants in this study had depression co-morbid with TBI, so the latter might also

have influenced the clinical outcome. All other studies used higher (40 to 84 J/cm^2) fluences and the ones who reached high fluences also achieved the largest antidepressant effect sizes [68, 69]. However, fluence on its own does not sufficiently explain the mixed results observed in our review of the literature. Especially, the RCTs provided mixed results on the superiority of the active treatment compared to sham despite the adoption of supposedly enough fluence ($\geq$60 J/cm^2). Surely, these negative RCTs had some methodological limitations. For instance, the negative RCT reported by Disner et al. [64] included participants with depressive symptoms, instead of a DSM diagnosis of MDD. Also, the same trial was designed to assess the enhancement of ABM by t-PBM, rather than t-PBM as a monotherapy; therefore, it is difficult to interpret the direct antidepressant effect of t-PBM in this study. Also puzzling, the ELATED-3 study [60], designed to confirm the antidepressant effect observed in ELATED-2, was negative, despite both studies recruited very similar samples of participants with MDD [62]. The ELATED-2 study had reported a positive result for the same antidepressant outcomes. One simple explanation for these mixed and negative results would be that the improvements observed in the open trials were just due to placebo effect. An alternative and more complex explanation is that fluence does not sufficiently define a t-PBM treatment; but rather the interaction between all parameters of stimulation used in t-PBM does. Fluence is not an independent variable that is uniquely defined. Someone could deliver 1 J/cm2 in an infinite number of ways, for instance 100 W/cm^2 in 0.01 s or at the extreme 0.01 W/cm^2 in 100 s. Therefore, we cannot solely rely on delivered fluence to determine and compare distinct t-PBM sessions, for their propensity to induce clinical and biological effects. Fluence is a good proxy, but still insufficient to fully characterize a t-PBM session.

As fluence is the product of *irradiance* and *time of exposure*, to maintain a similar fluence the increase in one of these two parameters must be coupled with a decrease in the other. Although antidepressant effects were reported by studies using high irradiance and short stimulation time, better results were reported by studies using longer sessions and lower irradiances. This finding could suggest that a given amount of energy is more effective when distributed over a longer time, compared to its delivery at higher irradiance in a shorter time. However, the two most effective studies using PW [68, 69] included more variables in this complex equation, such as peak irradiance, pulse frequency and duty cycle. These studies reported large antidepressant effects while using low average irradiance, but effectively high irradiance during each pulse, when the light is on. Whether, in the PW studies, the high peak irradiance was the most relevant parameter in explaining the high yield or whether the longer treatment session, resulting from the intervals between pulses, was more relevant is unknown. New studies, comparing different combinations of these parameters are necessary to allow further conclusions.

The *stimulation window* is another relevant parameter. As fluence represents the energy delivery per unit area in a given session, any increase in the stimulation window results in greater *total energy* delivered per session, assuming fluence is kept the same. Also, greater stimulation widows presumably result in larger cortical areas being exposed to the light. In the studies we reviewed, those reporting optimal antidepressant effects used the largest stimulation windows. A first interpretation of this finding is that the greater is the total energy per session and the larger is the cortical area stimulated, the bigger is the antidepressant effect from direct neuromodulation by photons. Another potential explanation for lies on the systemic and indirect effects of PBM. While the transcranial approach aims at stimulating brain tissue subjacent to the stimulation spot, the systemic approach contemplates that the effect of the photons on superficial and peripheral tissues such as the skin of the forehead and its blood components, including free circulating mitochondria, might eventually impact brain function [70]. The scalp is highly irrigated, so a significant volume of blood is irradiated when the light is delivered to a large surface of the head. Also, the bone marrow of the skull has a substantial number of stem cells [71] that can be stimulated by the light energy [15], it has been postulated that stem cells could travel to the brain.

The studies that used lower irradiances over higher surfaces also tended to use more treatment sessions. Both the total *number of sessions* and the higher *frequency of sessions per week* could have an impact on the overall antidepressant effect of t-PBM. Schiffer et al. [63] treated participants with a single session and reported an antidepressant effect after 2 weeks, which however tapered after 4 weeks lapsed from the only t-PBM session, suggesting that repeated sessions could be necessary for a sustained effect.

Finally, the *position of the light probe* on the scalp might be an important factor in determining the antidepressant effect of t-PBM. The studies where

the F3 and F4 sites on the forehead were the focus t-PBM, and the studies which included F3 and F4 with presumably high energy, were also the ones to report large effect sizes [62, 63, 68, 69]. Another parameter, considering the position of the light probe, is laterality. While other non-invasive brain stimulation techniques such as rTMS [72] and TDCS [73] aim to stimulate only one hemisphere or use different stimulus for each hemisphere, this parameter is usually neglected on t-PBM studies. Only two studies included for this review used unilateral t-PBM while the others treated both brain hemispheres with the same stimulus.

Considering all these parameters, we might attempt to explain the most reliable finding of our review: the fact that low irradiance and small surface represented a therapeutic dead zone as shown by the negative results of the ELATED-3 trial [60]. Although the fluence delivered by the device was comparable to positive studies, since the study used a small stimulation window, the total energy delivered per session (2.35 kJ) and the total energy delivered over the course of the study (28.2 kJ – NIR-NIR arm; or 14.1 kJ – sham-NIR arm) were much lower than in the positive ELATED-2 study (3.44 kJ per session and 45.6 kJ total). Additionally, the actual sites on the forehead for the light probes were limited to the frontal poles (Fp1 and Fp2), as other stimulation sites were obstructed by hair (F3 and F4).

Limitations of our review

This review presents several limitations related to the characteristics of the sampled studies. The studies were mostly open trials or small RCTs, so oftentimes efficacy could not be confirmed with an adequate comparison design. Other significant limitation was the methodological differences between the reviewed studies. The t-PBM parameters used in the selected trials were very heterogeneous, preventing us from individuating the most critical parameters responsible for the variability in the antidepressant effect size. The inclusion criteria for study participants were also quite different across studies. Some studies included only participants with a primary diagnosis of MDD, while others assessed change in depressive symptoms occurring in patients treated with t-PBM for a neurological disease. The limited number of studies, which were using mostly very similar wavelengths of NIR, prevented us from adequately assessing the impact of the latter as an additional t-PBM parameter.

Implications for Alzheimer's disease

Despite these limitations, our results point to some important conclusions which should be considered when planning future trials on t-PBM for MDD and for other CNS diseases, such as Alzheimer's disease. In sum, when a sufficient fluence was used, a significant antidepressant effect was reported by studies using high irradiances over small surfaces. Even higher antidepressant effects were reported by studies using PW with high peak irradiances, and low average irradiances, over very large surfaces. On the other hand, disappointing results were reported by one study (the ELATED-3 study) using low irradiance over a small surface.

Whenever planning a study or clinical treatment with t-PBM the following guidelines on parameters' selection should be considered. Enough fluence must be delivered and our results indicate that better antidepressant effects might be obtained if this fluence is distributed during a longer stimulation time by using PW, with high peak irradiances and with pauses between pulses of stimulation. The delivery of greater amounts of energy, by widening the stimulation window and by increasing the number of sessions, also seems beneficial. The negative results of the ELATED-3 study indicate no efficacy for treatments using low irradiances over small surfaces, even when enough fluence is delivered. Given the limitations of the examined literature, these conclusions should be considered as tentative guidelines to be tested in and possibly confirmed by future studies, rather than established protocols on treatment parameters.

Recently, there has been growing interest in the application of t-PBM to the treatment and prevention of neurodegenerative disorders, such as Alzheimer's disease [74]. Naturally, given the recent interest in the field, there are less published studies on t-PBM for the treatment of Alzheimer's disease or dementia. Noticeably, these studies have mostly focused on the use of high-irradiance t-PBM over small surface [75, 76], with one exception where t-PBM was shed over very large surfaces and presumably with low irradiance [77]. To the best of our knowledge, the optimal zone of t-PBM parameters for depression has not yet been tested for the treatment of Alzheimer's disease. It is however encouraging that the same dose produced remarkable pro-cognitive effects in chronic TBI.

While we already discussed the limitations of our review, additional limitations apply when mak-

ing inferences over diseases other than MDD. For instance, when treating Alzheimer's disease, multiple sources of light and even panirradiation of the whole scalp, with a helmet of LEDs, might be a preferable strategy. Also, if using single or few light sources to treat Alzheimer's disease, the position of the light source(s) could be moved from the forehead to lateral sites, better suited for direct targeting of the parietal cortex. When using pulse t-PBM, it has been speculated that frequencies around 40–100 Hz could induce entrainment of the cortex and pacing of brain activity within gamma oscillations. If this were proven, these frequencies of pulsing could be very beneficial to treat Alzheimer's disease or even just to alleviate and slow cognitive decline [78].

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-0586r1).

REFERENCES

[1] Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Arch Gen Psychiatry* **62**, 593-602.

[2] Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Üstün TB, Wang PS (2009) The global burden of mental disorders: An update from the WHO World Mental Health (WMH) Surveys. *Epidemiol Psichiatr Soc* **18**, 23-33.

[3] Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC (2015) The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry* **76**, 155-162.

[4] Lépine JP, Briley M (2011) The increasing burden of depression. *Neuropsychiatr Dis Treat* **7**, 3-7.

[5] König H, Riedel-Heller S, Luppa M, Heinrich S, Angermeyer M (2007) Cost-of-illness studies of depression: A systematic review. *J Affect Disord* **98**, 29-43.

[6] Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, Vos T, Whiteford HA (2013) Burden of depressive disorders by country, sex, age, and year: Findings from the Global Burden of Disease Study 2010. *PLoS Med* **10**, e1001547.

[7] Olfson M, Blanco C, Marcus SC (2016) Treatment of adult depression in the United States. *JAMA Intern Med* **176**, 1482-1491.

[8] Parikh SV, Quilty LC, Ravitz P, Rosenbluth M, Pavlova B, Grigoriadis S, Velyvis V, Kennedy SH, Lam RW, MacQueen GM, Milev RV, Ravindran AV, Uher R, CANMAT Depression Work Group (2016) Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 2. Psychological treatments. *Can J Psychiatry* **61**, 524-539.

[9] Sinyor M, Schaffer A, Levitt A (2010) The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial: A review. *Can J Psychiatry* **55**, 126-135.

[10] Cassano P, Fava M (2004) Tolerability issues during long-term treatment with antidepressants. *Ann Clin Psychiatry* **16**, 15-25.

[11] Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, Hasnain M, Jollant F, Levitt AJ, MacQueen GM, McInerney SJ, McIntosh D, Milev RV, Müller DJ, Parikh SV, Pearson NL, Ravindran AV, Uher R (2016) Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *Can J Psychiatry* **61**, 540-560.

[12] Hunot VM, Horne R, Leese MN, Churchill RC (2007) A cohort study of adherence to antidepressants in primary care: The influence of antidepressant concerns and treatment preferences. *Prim Care Companion J Clin Psychiatry* **9**, 91-99.

[13] Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, Nierenberg AA (2009) STAR*D: Revising conventional wisdom. *CNS Drugs* **23**, 627-647.

[14] Rosa MA, Lisanby SH (2012) Somatic treatments for mood disorders. *Neuropsychopharmacology* **37**, 102-116.

[15] Hamblin MR (2016) Shining light on the head: Photobiomodulation for brain disorders. *BBA Clin* **6**, 113-124.

[16] Heiskanen V, Hamblin MR (2018) Photobiomodulation: Lasers: vs. light emitting diodes? *Photochem Photobiol Sci* **17**, 1003-1017.

[17] Chung H, Dai T, Sharma SK, Huang Y-Y, Carroll JD, Hamblin MR (2012) The nuts and bolts of low-level laser (light) therapy. *Ann Biomed Eng* **40**, 516-533.

[18] Ferraresi C, Hamblin MR, Parizotto NA (2012) Low-level laser (light) therapy (LLLT) on muscle tissue: Performance, fatigue and repair benefited by the power of light. *Photonics Lasers Med* **1**, 267-286.

[19] Chaves ME de A, Araújo AR de, Piancastelli ACC, Pinotti M (2014) Effects of low-power light therapy on wound healing: LASER x LED. *An Bras Dermatol* **89**, 616-623.

[20] Harkless L, DeLellis S, Carnegie DH, Burke TJ (2006) Improved foot sensitivity and pain reduction in patients with peripheral neuropathy after treatment with monochromatic infrared photo energy–MIRE. *J Diabetes Complications* **20**, 81-87.

[21] Allais G, Lorenzo C De, Quirico PE, Lupi G, Airola G, Benedetto C (2003) Non-pharmacological approaches to chronic headaches: Transcutaneous electrical nerve stimulation, lasertherapy and acupuncture in transformed migraine treatment. *Neurol Sci* **24**, S138-142.

[22] Hersant B, SidAhmed-Mezi M, Bosc R, Meningaud JP (2015) Current indications of low-level laser therapy in plastic surgery: A review. *Photomed Laser Surg* **33**, 283-297.

[23] Zarei M, Wikramanayake TC, Falto-Aizpurua L, Schachner LA, Jimenez JJ (2016) Low level laser therapy and hair regrowth: An evidence-based review. *Lasers Med Sci* **31**, 363-371.

[24] Askalsky P, Iosifescu DV (2019) Transcranial photobiomodulation for the management of depression: Current perspectives. *Neuropsychiatr Dis Treat* **15**, 3255-3272.

[25] Cassano P, Petrie SR, Hamblin MR, Henderson TA, Iosifescu DV (2016) Review of transcranial photobiomodulation for major depressive disorder: Targeting brain metabolism, inflammation, oxidative stress, and neurogenesis. *Neurophotonics* **3**, 031404.

[26] Caldieraro MA, Cassano P (2019) Transcranial and systemic photobiomodulation for major depressive disorder: A systematic review of efficacy, tolerability and biological mechanisms. *J Affect Disord* **243**, 262-273.

[27] Quah-Smith JI, Tang WM, Russell J (2005) Laser acupuncture for mild to moderate depression in a primary care setting–a randomised controlled trial. *Acupunct Med* **23**, 103-111.

[28] Quah-Smith I, Smith C, Crawford JD, Russell J (2013) Laser acupuncture for depression: A randomised double blind controlled trial using low intensity laser intervention. *J Affect Disord* **148**, 179-187.

[29] Gabel CP, Petrie SR, Mischoulon D, Hamblin MR, Yeung A, Sangermano L, Cassano P (2018) A case control series for the effect of photobiomodulation in patients with low back pain and concurrent depression. *Laser Ther* **27**, 167-173.

[30] Salehpour F, Rasta SH (2017) The potential of transcranial photobiomodulation therapy for treatment of major depressive disorder. *Rev Neurosci* **28**, 441-453.

[31] Papakostas GI (2014) Cognitive symptoms in patients with major depressive disorder and their implications for clinical practice. *J Clin Psychiatry* **75**, 8-14.

[32] McIntyre RS, Soczynska JZ, Woldeyohannes HO, Alsuwaidan MT, Cha DS, Carvalho AF, Jerrell JM, Dale RM, Gallaugher LA, Muzina DJ, Kennedy SH (2015) The impact of cognitive impairment on perceived workforce performance: Results from the International Mood Disorders Collaborative Project. *Compr Psychiatry* **56**, 279-282.

[33] Corrêa MS, Balardin JB, Caldieraro MAK, Fleck MP, Argimon I, Luz C, Bromberg E (2012) Contextual recognition memory deficits in major depression are suppressed by cognitive support at encoding. *Biol Psychol* **89**, 293-299.

[34] MacQueen GM, Memedovich KA (2017) Cognitive dysfunction in major depression and bipolar disorder: Assessment and treatment options. *Psychiatry Clin Neurosci* **71**, 18-27.

[35] Evans VC, Iverson GL, Yatham LN, Lam RW (2014) The relationship between neurocognitive and psychosocial functioning in major depressive disorder. *J Clin Psychiatry* **75**, 1359-1370.

[36] Naeser MA, Martin PI, Ho MD, Krengel MH, Bogdanova Y, Knight JA, Yee MK, Zafonte R, Frazier J, Hamblin MR, Koo BB (2016) Transcranial, red/near-infrared light-emitting diode therapy to improve cognition in chronic traumatic brain injury. *Photomed Laser Surg* **34**, 610-626.

[37] Naeser MA, Hamblin MR (2011) Potential for transcranial laser or LED therapy to treat stroke, traumatic brain injury, and neurodegenerative disease. *Photomed Laser Surg* **29**, 443-446.

[38] Huang Y-Y, Sharma SK, Carroll J, Hamblin MR (2011) Biphasic dose response in low level light therapy - an update. *Dose Response* **9**, 602-618.

[39] Karu TI, Kolyakov SF (2005) Exact action spectra for cellular responses relevant to phototherapy. *Photomed Laser Surg* **23**, 355-361.

[40] Rojas JC, Gonzalez-Lima F (2011) Low-level light therapy of the eye and brain. *Eye Brain* **14**, 49-67.

[41] Karu TI (2008) Mitochondrial signaling in mammalian cells activated by red and near-IR radiation. *Photochem Photobiol* **84**, 1091-1099.

[42] Machado MO, Veronese N, Sanches M, Stubbs B, Koyanagi A, Thompson T, Tzoulaki I, Solmi M, Vancampfort D, Schuch FB, Maes M, Fava GA, Ioannidis JPA, Carvalho AF (2018) The association of depression and all-cause and cause-specific mortality: An umbrella review of systematic reviews and meta-analyses. *BMC Med* **16**, 112.

[43] Zhao Y, Vanhoutte PM, Leung SWS (2015) Vascular nitric oxide: Beyond eNOS. *J Pharmacol Sci* **129**, 83-94.

[44] Salehpour F, Cassano P, Rouhi N, Hamblin MR, De Taboada L, Farajdokht F, Mahmoudi J (2019) Penetration profiles of visible and near-infrared lasers and light-emitting diode light through the head tissues in animal and human species: A review of literature. *Photobiomodul Photomed Laser Surg* **37**, 581-595.

[45] Yue L, Humayun MS (2015) Monte Carlo analysis of the enhanced transcranial penetration using distributed near-infrared emitter array. *J Biomed Opt* **20**, 088001.

[46] Lapchak PA, Boitano PD, Butte PV, Fisher DJ, Hölscher T, Ley EJ, Nuño M, Voie AH, Rajput PS (2015) Transcranial near-infrared laser transmission (NILT) profiles (800nm): Systematic comparison in four common research species. *PLoS One* **10**, e0127580.

[47] Karu T, Kolyakov SF (2005) Exact action spectra for cellular responses relevant to phototherapy. *Photomed Laser Surg* **23**, 355-361.

[48] Jagdeo JR, Adams LE, Brody NI, Siegel DM (2012) Transcranial red and near infrared light transmission in a cadaveric model. *PLoS One* **7**, e47460.

[49] Litscher D, Litscher G (2013) Laser therapy and stroke: Quantification of methodological requirements in consideration of yellow laser. *Int J Photoenergy* **2013**, 575798.

[50] Cassano P, Tran AP, Katnani H, Bleier BS, Hamblin MR, Yuan Y, Fang Q (2019) Selective photobiomodulation for emotion regulation: Model-based dosimetry study. *Neurophotonics* **6**, 1.

[51] Yuan Y, Cassano P, Pias M, Fang Q (2020) Transcranial photobiomodulation with near-infrared light from childhood to elderliness: Simulation of dosimetry. *Neurophotonics* **7**, 1.

[52] Tedford CE, DeLapp S, Jacques S, Anders J (2015) Quantitative analysis of transcranial and intraparenchymal light penetration in human cadaver brain tissue. *Lasers Surg Med* **47**, 312-322.

[53] Huang YY, Chen ACH, Carroll JD, Hamblin MR (2009) Biphasic dose response in low level lightherapy. *Dose Response* **7**, 358-383.

[54] Song P, Han T, Lin H, Li S, Huang Q, Dai X, Wang R, Wang Y (2020) Transcranial near-infrared stimulation may increase cortical excitability recorded in humans. *Brain Res Bull* **155**, 155-158.

[55] Chaieb L, Antal A, Masurat F, Paulus W (2015) Neuroplastic effects of transcranial near-infrared stimulation (tNIRS) on the motor cortex. *Front Behav Neurosci* **9**, 147.

[56] Konstantinović LM, Jelić MB, Jeremić A, Stevanović VB, Milanović SD, Filipović SR (2013) Transcranial application of near-infrared low-level laser can modulate cortical excitability. *Lasers Surg Med* **45**, 648-653.

[57] Lampl Y, Zivin JA, Fisher M, Lew R, Welin L, Dahlof B, Borenstein P, Andersson B, Perez J, Caparo C, Ilic S, Oron U (2007) Infrared laser therapy for ischemic stroke: A new treatment strategy: Results of the NeuroThera Effectiveness and Safety Trial-1 (NEST-1). *Stroke* **38**, 1843-1849.

[58] Huisa BN, Stemer AB, Walker MG, Rapp K, Meyer BC, Zivin JA, Investigators N-1 and-2 (2013) Transcranial laser therapy for acute ischemic stroke: A pooled analysis of NEST-1 and NEST-2. *Int J Stroke* **8**, 315-320.

[59] Zivin JA, Sehra R, Shoshoo A, Albers GW, Bornstein NM, Dahlof B, Kasner SE, Howard G, Shuaib A, Streeter J, Richieri SP, Hacke W, Investigators N-3 (2014) NeuroThera® Efficacy and Safety Trial-3 (NEST-3): A double-blind, randomized, sham-controlled, parallel group, multicenter, pivotal study to assess the safety and efficacy of transcranial laser therapy with the NeuroThera® Laser

System for the treatment of acute ischemic stroke within 24h of stroke onset. *Int J Stroke* **9**, 950-955.

[60] Iosifescu D, Norton R, Tural U, Collins K, Taboada L De, Foster S, Cusin C, Rette D, Arnold M, Schoenfeld D, Mischoulon D, Cassano P (2020) Very low-level transcranial photobiomodulation in major depression: The Elated-3 study. In *2020 Virtual Meeting of the Society Biological Psychiatry (Virtual Poster Session).*

[61] Cassano P, Cusin C, Mischoulon D, Hamblin MR, Taboada L De, Pisoni A, Chang T, Yeung A, Ionescu DF, Petrie SR, Nierenberg AA, Fava M, Iosifescu D V (2015) Near-infrared transcranial radiation for major depressive disorder: Proof of concept study. *Psychiatry J* **2015**, 352979.

[62] Cassano P, Petrie SR, Mischoulon D, Cusin C, Katnani H, Yeung A, De Taboada L, Archibald A, Bui E, Baer L, Chang T, Chen J, Pedrelli P, Fisher L, Farabaugh A, Hamblin MR, Alpert JE, Fava M, Iosifescu DV (2018) Transcranial photobiomodulation for the treatment of major depressive disorder. The ELATED-2 Pilot Trial. *Photomed Laser Surg* **36**, 634-646.

[63] Schiffer F, Johnston AL, Ravichandran C, Polcari A, Teicher MH, Webb RH, Hamblin MR (2009) Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: A pilot study of 10 patients with major depression and anxiety. *Behav Brain Funct* **5**, 46.

[64] Disner SG, Beevers CG, Gonzalez-lima F (2016) Transcranial laser stimulation as neuroenhancement for attention bias modification in adults with elevated depression symptoms. *Brain Stimul* **9**, 780-787.

[65] Mogoaşe C, David D, Koster EHW (2014) Clinical efficacy of attentional bias modification procedures: An updated meta-analysis. *J Clin Psychol* **70**, 1133-1157.

[66] Naeser MA, Zafonte R, Krengel MH, Martin PI, Frazier J, Hamblin MR, Knight JA, Meehan WP, Baker EH (2014) Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: Open-protocol study. *J Neurotrauma* **31**, 1008-1017.

[67] Cassano P, Caldieraro MA, Norton R, Mischoulon D, Trinh N-H, Nyer M, Dording C, Hamblin MR, Campbell B, Iosifescu DV (2019) Reported side effects, weight and blood pressure, after repeated sessions of transcranial photobiomodulation. *Photobiomodul Photomed Laser Surg* **37**, 651-656.

[68] Morries LD, Cassano P, Henderson TA (2015) Treatments for traumatic brain injury with emphasis on transcranial near-infrared laser phototherapy. *Neuropsychiatr Dis Treat* **11**, 2159-2175.

[69] Henderson TA, Morries LD (2017) Multi-watt near-infrared phototherapy for the treatment of comorbid depression: An open-label single-arm study. *Front Psychiatry* **8**, 187.

[70] Sommer AP, Trelles MA (2014) Light pumping energy into blood mitochondria: A new trend against depression? *Photomed Laser Surg* **32**, 59-60.

[71] Iwashita T, Tada T, Zhan H, Tanaka Y, Hongo K (2003) Harvesting blood stem cells from cranial bone at craniotomy - A preliminary study. *J Neurooncol* **64**, 265-270.

[72] Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS (2016) The Clinical TMS Society consensus review and treatment recommendations for TMS therapy for major depressive disorder. *Brain Stimul* **9**, 336-346.

[73] Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, Veronezi BP, Nogueira BS, Aparicio LVM, Razza LB, Chamorro R, Tort LC, Fraguas R, Lotufo PA, Gattaz WF, Fregni F, Benseñor IM (2017) Trial of electrical direct-current therapy versus escitalopram for depression. *N Engl J Med* **376**, 2523-2533.

[74] Salehpour F, Khademi M, Hamblin MR (2021) Photobiomodulation therapy for dementia: A systematic review of pre-clinical and clinical studies. *J Alzheimers Dis* **83**, 1431-1452.

[75] Saltmarche AE, Naeser MA, Ho KF, Hamblin MR, Lim L (2017) Significant improvement in cognition in mild to moderately severe dementia cases treated with transcranial plus intranasal photobiomodulation: Case series report. *Photomed Laser Surg* **35**, 432-441.

[76] Chao LL (2019) Effects of home photobiomodulation treatments on cognitive and behavioral function, cerebral perfusion, and resting-state functional connectivity in patients with dementia: A pilot trial. *Photobiomodul Photomed Laser Surg* **37**, 133-141.

[77] Berman MH, Halper JP, Nichols TW, Jarrett H, Lundy A, Huang JH (2017) Photobiomodulation with near infrared light helmet in a pilot, placebo controlled clinical trial in dementia patients testing memory and cognition. *J Neurol Neurosci* **8**, 176.

[78] Iaccarino HF, Singer AC, Martorell AJ, Rudenko A, Gao F, Gillingham TZ, Mathys H, Seo J, Kritskiy O, Abdurrob F, Adaikkan C, Canter RG, Rueda R, Brown EN, Boyden ES, Tsai L-H (2016) Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature* **540**, 230-235.

[79] Naeser MA, Zafonte R, Krengel MH, Martin PI, Frazier J, Hamblin MR, Knight JA, Meehan WP, Baker EH (2014) Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain Injury: Open-protocol study. *J Neurotrauma* **31**, 1008-1017.