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Very Low-Level Transcranial Photobiomodulation for Major Depressive Disorder:

The ELATED-3 Multicenter, Randomized, Sham-Controlled Trial

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ABSTRACT

Background: Transcranial photobiomodulation (t-PBM) with near-infrared (NIR) light might represent a treatment for major depressive disorder (MDD). However, the dosimetry of administered t-PBM varies widely. We tested the efficacy of t-PBM with low irradiance, low energy per session, and low number of sessions in individuals with MDD.

Methods: A 2-site, double-blind, sham-controlled study was conducted of adjunct t-PBM NIR (830 nm; continuous wave; 35.8 cm^2 treatment area; 54.8 mW/cm^2 irradiance; 65.8 J/cm^2 fluence, 20 min/session; ~2 W total power; 2.3 kJ total energy per session), delivered to the prefrontal cortex, bilaterally, twice a week for 6 weeks, in subjects diagnosed with MDD per the *DSM-IV* criteria. Subjects were recruited between August 2016 and May 2018. A sequential parallel comparison design was used: 18 nonresponders to sham in phase 1 (6 weeks) were re-randomized in phase 2. The primary outcome was reduction in depression severity (Hamilton Depression Rating Scale [HDRS-17] and Quick Inventory of Depressive Symptomatology—Clinician Rating [QIDS-C] scores) from baseline. Statistical analyses used R package SPCDAnalyze2, including all subjects with ≥ 1 post-randomization evaluation.

Results: Of the 54 subjects recruited, we included 49 MDD subjects in the analysis (71% female, mean ± SD age 40.8 ± 16.1 years). There were no significant differences between t-PBM and sham with respect to the change in HDRS-17 ($t = -0.319$, $P = .751$) or QIDS-C ($t = -0.499$, $P = .620$) scores. The sham effect was reasonably low.

Conclusions: Mostly uncontrolled studies suggest the efficacy of t-PBM for MDD; however, its optimal dose is still to be defined. A minimal dose threshold is likely necessary, similarly to other neuromodulation techniques in MDD (electroconvulsive therapy, transcranial magnetic stimulation). We established a threshold of inefficacy of t-PBM for MDD, based on combined low irradiance, low energy per session, and low number of sessions.

Trial Registration: ClinicalTrials.gov identifier: NCT02959307

J Clin Psychiatry 2022;83(5):21m14226

To cite: Iosifescu DV, Norton RJ, Tural U, et al. Very low-level transcranial photobiomodulation for major depressive disorder: the ELATED-3 multicenter, randomized, sham-controlled trial. *J Clin Psychiatry.* 2022;83(5):21m14226.

To share: https://doi.org/10.4088/JCP.21m14226

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Major depressive disorder (MDD) is one of the most debilitating and pervasive psychiatric disorders, affecting over 17 million adults in the US.[1] Globally, MDD is the second largest contributor to years spent living in disability.[2] Despite many existing evidence-based interventions to treat MDD, such as antidepressant medications and psychotherapy, there are barriers to their effective implementation. The efficacy of pharmaceuticals is limited by adherence to treatment and tolerability, while psychosocial interventions are limited by providers' availability and costs.[3]

One option for individuals who do not tolerate, accept, or respond to medications or psychotherapy is device-based treatments. Photobiomodulation (PBM), also called "low-level light therapy" or "low-level laser therapy," is a device-based intervention utilizing light exposure to different areas of the body. Transcranial PBM with near-infrared radiation (NIR), which applies PBM to the brain, was initially tested as a potential acute treatment for ischemic stroke through the NeuroThera Effectiveness and Safety Trials (NEST)[4–6] and in the past decade as a treatment for chronic neuropsychiatric disorders, with promising results.[7]

Transcranial PBM (t-PBM) with NIR, invisible light, penetrates the underlying brain tissue, after being partially dissipated through the scalp and skull,[8] and is mainly absorbed by specific chromophores.[9] When sufficient energy and specific wavelengths are used to ensure its penetration in the brain, t-PBM can modulate subjacent areas of the cerebral cortex.[10,11]

The NIR delivered through t-PBM is absorbed by a mitochondrial enzyme and chromophore, cytochrome *c* oxidase (CCO); supposedly, this is the primary mechanism of action of transcranial NIR. The peak absorption of light energy by CCO occurs

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Clinical Points

- Previous research has suggested that transcranial photobiomodulation (t-PBM) may have antidepressant effects, but the efficacy of t-PBM with low energy output is unclear.
- The present study indicates that t-PBM with low energy output is not associated with a robust antidepressant effect in adults with major depressive disorder.

at 4 different wavelengths; one of these peaks is within the range of 812–846 nm, the same wavelengths that best penetrate human tissues.[12] The energy absorbed by the CCO, acting through the respiratory chain, leads to increased production of adenosine triphosphate (ATP). Previous studies using phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS), which allows in vivo chemical analysis, have demonstrated abnormal bioenergetic metabolism, including decreased ATP, in specific brain areas in subjects with MDD.[13] Also, patients with MDD who respond to antidepressant treatment show an increase in ATP on ^{31}P-MRS.[14] t-PBM, which also can increase brain ATP production, might therefore be a potential treatment for depression.

Preliminary small (n = 10 and n = 4), uncontrolled studies in MDD subjects have suggested that t-PBM is safe, effective, and well tolerated.[15,16] A pilot trial (ELATED-2)[17] further confirmed the benefits of t-PBM as a potential treatment for MDD, well tolerated and with at least moderate effect sizes.[17–19] In the current study, we aimed to test, in a larger sample and with a robust sham-control design, the efficacy and tolerability of repeated sessions of t-PBM over a 12-week period. We specifically tested the antidepressant effect of continuous wave (CW) t-PBM administration, with a particular set of parameters (Table 1) and very low energy output (selected for their excellent prior safety data).

Table 1. Treatment Parameters for t-PBM Delivered as Continuous Wave

Parameter	Value
Wavelength	830 nm
Irradiance	54.8 mW/cm^2
Pulsing rate	NA
Duty cycle	100%
Average power	~2 W
Fluence	65.8 J/cm^2
Duration of t-PBM session	20 min
Treatment window	35.8 cm^2
Cumulative dose	2.3 kJ

Abbreviations: NA = not applicable, t-PBM = transcranial photobiomodulation.

METHODS

This 2-site study, Evaluation of LEDs Therapeutic Effect in Depression (ELATED-3), was a collaboration between researchers at Massachusetts General Hospital (MGH) and the Nathan Kline Institute (NKI). Both institutional review boards (IRB) approved the study. This study was registered with ClinicalTrials.gov (NCT02959307). Recruitment began in August 2016, with study completion occurring in May 2018. The primary sources of recruitment were the respective institutions' research portals, advertisements, and clinical referrals. All participants provided documented informed consent prior to screening procedures.

Inclusion and Exclusion Criteria

Adult subjects (age 18–70 years) who provided written informed consent, met *DSM-IV* criteria for MDD through assessment of the Mini-International Neuropsychiatric Interview,[20] and had at least moderate depression severity, as determined by a Hamilton Depression Rating Scale-17 items (HDRS-17)[21] score ≥ 14 at screening, were included in the study. We excluded subjects with active suicidality (Columbia-Suicide Severity Rating Scale[22] score ≥ 3) and with treatment-resistant depression, defined as ≥ 2 US Food and Drug Administration (FDA)-approved antidepressant medication trials failed during the current depressive episode as assessed by the MGH Antidepressant Treatment Response Questionnaire,[23] or any failed FDA-approved device-based intervention (ie, transcranial magnetic stimulation, electroconvulsive therapy, or vagus nerve stimulation) during the current MDD episode. Other exclusionary conditions included active substance use disorders (prior 3 months), lifetime psychotic episodes, bipolar disorder, poorly controlled medical illnesses, or history of a stroke within the previous 90 days. Women of childbearing potential were required to use an adequate method of birth control; pregnancy and lactation were exclusionary. To allow maximum light penetration and to minimize potential risks of local tissue damage from the use of t-PBM NIR, the following conditions were also exclusionary: (1) having a forehead skin condition near the sites of penetration, such as a tattoo or birthmark; (2) taking a light-activated medication within the prior 14 days; and (3) having any form of implant in the head. Patients were permitted to be on a stable dose of antidepressants or psychotherapy, provided the treatment had been stable prior to enrollment (ie, 6 weeks for antidepressants and 8 weeks for psychotherapy).

Study Design and Treatment

Eligible subjects were randomized to a double-blind, 12-week, twice-weekly treatment with t-PBM NIR vs sham. At each treatment session, t-PBM (or sham) was administered to the left and right forehead bilaterally, simultaneously (LiteCure the Transcranial PhotoBioModulation-1000 [TPBM-1000] device). The choice of an LED device, as opposed to a laser device, was supported by a prior study on t-PBM for MDD.[17] The LED device emitted NIR at a radiation wavelength of 830 nm, corresponding to the peak absorption spectrum for CCO.[24] At the time when we planned ELATED-3, studies using cadaver heads indicated that devices similar to ours could deliver 2% of NIR light deeply, at 1 cm from the skin surface on frontal areas.[25] Based

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on a 2% penetration rate, we estimated that we could reach target regions with NIR energy density equivalent to the fluence previously indicated to induce benefit in neuronal cultures (fluence: 0.3 J/cm^2),[26] blood related attenuation of light on the prefrontal cortex not being accounted for. As we were targeting the dorsolateral prefrontal cortex (dlPFC), we simultaneously directed the NIR to the F3 and F4 sites (defined based on the EEG electrode positioning system) on the forehead; we also directed NIR to Fp1 and Fp2, since prior work showed improvement in positive affect when targeting frontal poles.[27] Since previous studies suggested that 1 and 6 sessions of t-PBM were insufficient to determine a sustained antidepressant response,[15,16] but there was sufficient response after 16 sessions over 8 weeks,[17] we adopted an approach similar to the latter. Because our study design included 2 randomizations of t-PBM vs sham, at baseline and at week 6, study subjects could receive, when allocated to t-PBM, up to 12 sessions of active t-PBM over 6 weeks and up to 24 sessions over 12 weeks. Twice-weekly sessions had been acceptable and well tolerated in our ELATED-1 and ELATED-2 studies.[15,17] The study device (Litecure LLC—TPBM-1000) delivered t-PBM NIR at a wavelength of 830 nm, continuous wave (CW), with an irradiance of 54.8 mW/cm^2, over a treatment window of 35.8 cm^2, for an exposure time of 20 min, resulting in a fluence averaging around 65.8 J/cm^2 and in a total energy per session of 2.3 kJ (see Table 1 for full t-PBM parameters). Additionally, similar and greater NIR fluences on skin have been associated with both antidepressant response and improved cognition.[15,16,27]

Randomization and Blinding

The study utilized a 2-phase sequential parallel comparison design (SPCD) with 6 weeks' treatment duration in each phase. At baseline, in the first phase, eligible subjects were randomized to t-PBM vs sham with a 1:2 ratio. Study subjects randomized to t-PBM in the first phase continued to receive t-PBM NIR for an additional 6 weeks in the second phase. However, they were not included in the statistical analyses of the second phase since they were not re-randomized. Study subjects randomized to sham, in the first phase, were characterized as responders and nonresponders to sham at the end of their phase 1 (ie, first 6 weeks of treatment). Response was defined as ≥ 50% decrease in Quick Inventory of Depressive Symptomatology—Clinician Rating (QIDS-C)[28] total score at week 6 (end of phase 1). Nonresponders to sham in phase 1 were re-randomized (1:1) to t-PBM vs sham in phase 2 (weeks 6 to 12). Both study subjects and investigators were blind to treatment assignment throughout both randomizations. Randomization codes were generated by a statistician not otherwise involved in the study, with separate randomization lists for MGH and NKI, and were programmed in the study devices by LiteCure LLC before the first randomization. To preserve the blinding, the apparent behavior of the t-PBM devices was identical for both modalities (t-PBM and sham) as sound and warmth were matched.

Clinical Outcome Measures

The primary outcome measure was the change in depression severity from randomization to the endpoint of each treatment phase (measured as the change in total score of the HDRS-17, as well as the QIDS-C). The HDRS-17 was administered at screening to determine eligibility, as well as at baseline, midpoint of phase 1 (week 3), at the end of phase 1 and beginning of phase 2 (week 6), at the midpoint of phase 2 (week 9), and at the endpoint of phase 2 (week 12). The QIDS-C was also administered at screening and at every weekly assessment visit following baseline. Tolerability was assessed with an adverse event form, which allowed the recording of adverse events' description, start and end dates, intensity, and relation to the treatment, as well as any action taken and final outcome.

A Priori Sample Size Calculation

We expected 100 subjects to sign informed consent, including screen failures. Assuming that half would have failed the screen, this would have led to randomization of 50 subjects. At each site, (MGH and NKI, separately), we expected approximately an n = 24 with a first randomization 2:1 (sham:NIR), which would have resulted in 16 subjects receiving sham and 8 subjects receiving NIR. We then assumed 70% nonresponse to sham, which would have led to 11 sham "nonresponders," who would have undergone the second randomization (week 6). Assuming a dropout rate of 24% before week 6, we anticipated that 9 subjects from the sham group would have been eligible for the second randomization 1:1 (sham:NIR). This second randomization (week 6) would have resulted in approximately 5 subjects receiving sham and 4 subjects receiving NIR. According to the SPCD, the data from the first randomization (week 0 to 6 of the trial) and the data from the second randomization (week 6 to 12 of the trial) could be pooled, resulting in a total of 16 + 5 = 21 available sham subjects and 8 + 4 = 12 available NIR subjects. With this sample size at each site, MGH and NKI, and after pooling data from both sites, we estimated > 80% power to detect a significant difference ($P \leq .05$) in depression outcome—change in depressive symptoms according to the HDRS-17 total score—based on the relatively large effect size detected in our prior MGH study (ELATED-2).[17]

Statistical Analysis

Descriptive statistics were presented as frequency, mean ± SD, or percent. *T* tests and χ^2 tests, depending on variable features, were used to evaluate sociodemographic variables and side effects. The primary aim of the study was to test the antidepressant effect for t-PBM compared to sham, as measured by the change in HDRS-17 and QIDS-C scores, in a SPCD design. Treatment response was defined as a reduction of ≥ 50% in QIDS-C total scores. The statistical model of SPCD was previously described elsewhere.[29] As previously mentioned, in the SPCD clinical trial design, the subjects who do not respond to sham in the first phase are re-randomized in the second phase in order to increase

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Table 2. Demographic and Clinical Characteristics of the Sample

	t-PBM (n = 18)	Sham (n = 31)	Statistics
Age, mean ± SD, y	37.2 ± 16.5	42.8 ± 15.8	$t_{47} = 1.17$, $P = .25$
Age at MDD onset, mean ± SD, y[a]	17.3 ± 10.0	23.4 ± 16.1	$t_{43} = 1.41$, $P = .17$
Gender, female, n (%)	14 (77.8)	21 (67.7)	$\chi^2_1 = 0.56$, $P = .45$
Race, n (%)			
White	13 (72.2)	27 (87.1)	$\chi^2_3 = 3.21$, $P = .36$
Black	3 (16.7)	2 (6.5)	
Asian	2 (11.1)	1 (3.2)	
Other	0 (0.0)	1 (3.23)	
Ethnicity (not Hispanic or Latino), n (%)	14 (77.8)	25 (80.7)	$\chi^2_3 = 1.78$, $P = .62$
Concomitant treatment (psychotherapy and/or psychotropics, n (%)	13 (72.2)	18 (58.1)	$\chi^2_1 = 0.98$, $P = .32$
Multiple previous depressive episodes, yes, n (%)	10 (71.4)	19 (63.3)	$\chi^2_1 = 0.28$, $P = .60$
Previous hospitalization history, yes, n (%)	7 (43.6)	8 (25.8)	$\chi^2_1 = 1.56$, $P = .21$
Previous history of suicide attempts, yes, n (%)	4 (22.2)	7 (22.6)	$\chi^2_1 = .001$, $P = .98$

[a]Not all participants answered age at onset question at screening. Therefore, the distribution of participants calculated for age at onset was t-PBM (n = 17) and sham (n = 28) for phase 1.
Abbreviations: MDD = major depressive disorder, t-PBM = transcranial photobiomodulation.

Table 3. Change in Depression Severity and Response Rates

	Phase 1						Phase 2[a]						Statistics (t, P value)[b]		
Measure	t-PBM			Sham			t-PBM			Sham			Phase 1	Phase 2	Pooled
HDRS	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD			
Baseline score	18	19.72	2.78	31	20.10	4.94	10	16.10	5.15	7	19.29	7.11			
Score reduction		3.44	5.03		4.29	4.93		2.6	6.52		5.14	7.01	$t = 0.891$, $P = .378$	$t = -1.043$, $P = .302$	$t = -0.319$, $P = .751$
QIDS-C	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD			
Baseline score	18	14.0	2.47	29	14.83	3.13	11	10.73	2.76	7	13.14	5.49			
Score reduction		2.94	3.19		3.59	4.13		0.27	5.33		4.00	5.48	$t = 0.336$, $P = .738$	$t = 0.842$, $P = .404$	$t = -0.499$, $P = .620$
Response[c]	N	%		N	%		N	%		N	%				
Included	18	38		29	62		11	61		7	39				
Response	4	22.2		5	17.2		4	36.4		2	28.6		$t = 0.413$, $P = .679$	$t = 0.348$, $P = .728$	$t = 0.511$, $P = .609$

[a]According to the format of the sequential parallel comparison design model used in this study, only patients who completed phase 1 and did not achieve a treatment response (as indicated by the QIDS-C) are analyzed in phase 2.
[b]Sequential parallel comparison design model statistics for phase 1, phase 2, and pooled.
[c]Treatment response was defined as a reduction of ≥ 50% in QIDS-C score during treatment.
Abbreviations: HDRS = Hamilton Depression Rating Scale; QIDS-C = Quick Inventory of Depressive Symptomatology, Clinician Rating; t-PBM = transcranial photobiomodulation.

signal detection and power. Only sham nonresponders in the first phase are included in the second phase statistical analyses. The data for the two phases are analyzed separately and then pooled. For the safety analyses, we included all participants in phase 2, not just those re-randomized. All statistical analyses were performed using with SPCDAnalyze package version 0.1.0[30] on R software version 3.6.2.[31] The package uses a constrained longitudinal data analysis model. Intent-to-treat and last-observation-carried-forward principles were used. The level of statistical significance was set at $P \leq .05$.

RESULTS

Sample

A total of 54 participants were recruited across both sites, with 5 subjects dropping from treatment before their baseline visit. A total of 49 participants with HDRS-17 assessments were eligible for the statistical analyses. Twelve participants (9 randomized to sham and 3 randomized to t-PBM) dropped out during the first phase. Additionally, 1 participant in the t-PBM arm dropped out in the second phase. A total of 47 participants received the QIDS-C questionnaire. Sociodemographic features of the sample are summarized in Table 2. There were no statistically significant baseline differences between the two study groups. Only 2 subjects changed their concomitant antidepressant medications throughout the study. All but 3 subjects remained on stable antidepressant treatment during the trial; their data were censored after change in concomitant psychoactive therapies (their last available assessment before change in therapies was used as endpoint).

Change in Depression Severity

The number of subjects as well as the overall means, percent changes, and response rates can be seen in Table 3. There was no statistically significant difference between sham and t-PBM treatment assessed by HDRS-17 and QIDS-C in either phase 1 or 2 or when both were pooled. Linear graphs (Figure 1) summarize the mean depression severity changes throughout the study in the sham and t-PBM groups.

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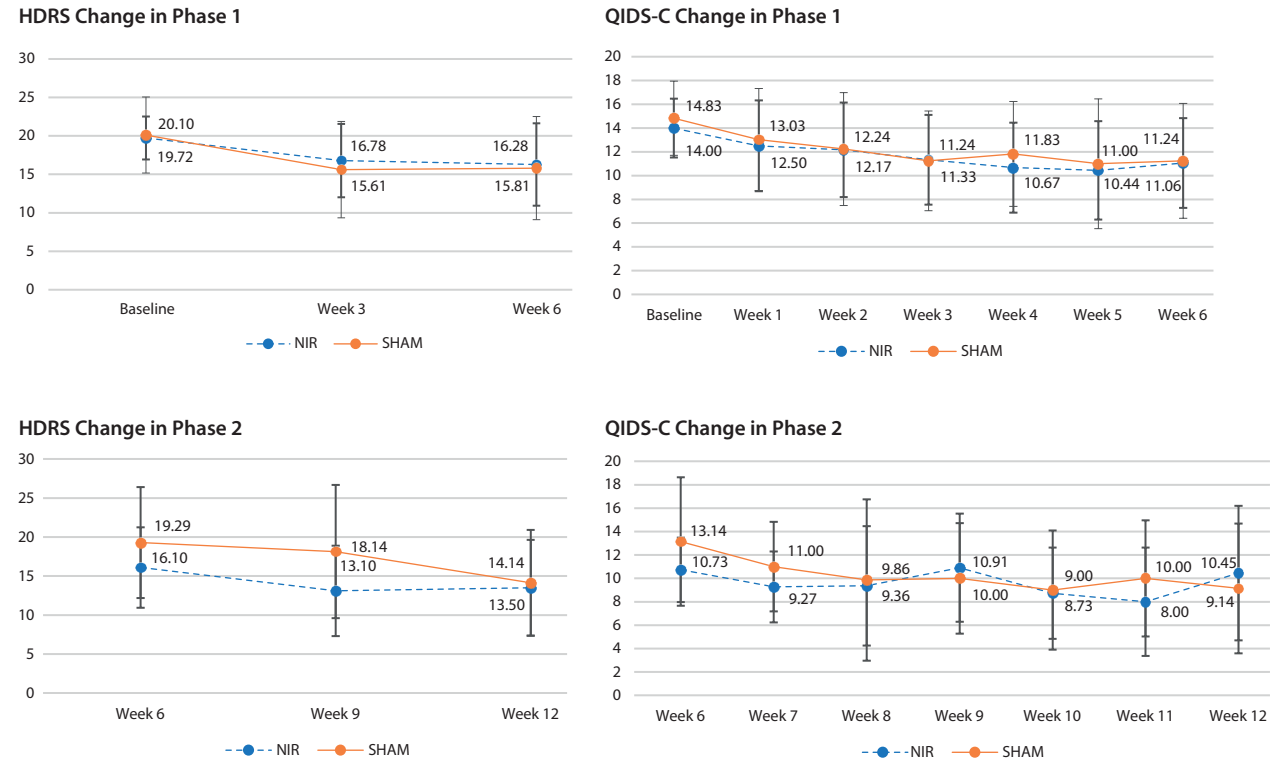
Figure 1. Mean Changes in HDRS-17 and QIDS-C Scores in Phases 1 and 2



Abbreviations: HDRS = Hamilton Depression Rating Scale, NIR = near-infrared radiation, QIDS-C = Quick Inventory of Depressive Symptomatology, Clinician Rating.

Treatment Response

There were 4 responders (22.2%) in the t-PBM arm and 5 (17.2%) in the sham arm in phase 1. There was no significant difference in response rates between the groups ($t = 0.413$, $P = .679$). In phase 2, there were 4 responders (36.4%) in the t-PBM arm and 2 (28.6%) in the sham arm. There was no significant difference between the groups ($t = 0.348$, $P = .728$). The pooled results of phases 1 and 2 showed similar response rates between t-PBM (27.6%) and sham (19.4%) arms.

Adverse Events

Here and in Table 4, we present the rates for any adverse events that occurred in more than 5% of the whole sample during at least 1 study phase. Adverse event frequencies were not significantly different between the t-PBM and sham groups. Thirty-one out of 49 subjects (63.3%) reported an adverse event in phase 1; the rate of participants with at least 1 adverse event in phase 1 was not significantly different between the t-PBM group (n = 21, 67.7%) and sham group (n = 10, 55.6%; $\chi^2_1 = 0.728$, $P = .394$). Twelve out of 18 subjects (66.7%) reported an adverse event in phase 2; the rate of participants with at least 1 adverse event in phase 2 was also not significantly different between the t-PBM group (n = 7, 58.3%) and sham (n = 4, 66.7%; $\chi^2_1 = 0.117$, $P = .732$). None of the frequencies for single adverse events were significantly different between the treatment groups in either phase 1 or 2 (Table 4).

Table 4. Adverse Events[a]

	Phase 1				Phase 2			
	t-PBM (n = 18)		Sham (n = 31)		t-PBM (n = 28)		Sham (n = 10)	
Adverse events	N	%	N	%	N	%	N	%
Headache	6	33.3	5	16.1	3	10.7	2	20.0
Insomnia	2	11.1	3	9.7	3	10.7	1	10.0
Irritability without impulsivity	1	5.6	3	9.7	0	0	1	10.0
Pressure on forehead	2	11.1	2	6.5	2	7.1	0	0
Worsening of preexisting condition	2	11.1	1	3.2	1	3.6	2	20.0
Panic attack	1	5.6	2	6.5	0	0	1	10.0
Upper respiratory infection	0	0	5	16.1	2	7.1	1	10.0
Anxiety	0	0	0	0	0	0	2	20.0

[a] χ^2 test; none of the comparisons are statistically significant.
Abbreviation: t-PBM = transcranial photobiomodulation.

DISCUSSION

In this sample of MDD subjects, t-PBM with CW at relatively low irradiance and low total energy did not have superior antidepressant efficacy compared to sham. t-PBM was well tolerated, with rates of side effects indistinguishable from sham.

In our study, we aimed to achieve sufficient penetration of t-PBM NIR to the brain, based on estimates derived from cadaver and animal studies.[25,32] However, since the conceptualization of our study, the field has increasingly adopted high irradiances—4.5-fold higher than in

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ELATED-3—with consistent neuromodulatory effects.[33] Therefore, despite our preclinical rationale and despite our prior positive clinical trial (ELATED-2), the chosen irradiance might have been suboptimal.[17] A higher irradiance would have also facilitated reaching a higher fluence—greater than or equal to 100 J/cm^2—within a shorter administration time, therefore enhancing feasibility and possibly the odds of antidepressant response. A higher (peak) irradiance could have been reached if we had selected pulse wave (PW) mode of delivery, instead of continuous wave (CW). In a review of the literature published after completion of ELATED-3, we also suggested that PW might be more effective than CW for neuromodulation, therefore adding to to the limitations of the chosen parameters.[34] Furthermore, our device achieved limited delivery of t-PBM NIR energy in multiple other ways. For instance, while the t-PBM sources delivering NIR to Fp1 and Fp2 were unobstructed, the F3 and F4 sites of delivery were often obstructed by hair (which induces, at 830 nm, light scattering and reduces penetration to the brain). In fact, our device did not allow the sources on F3 and F4 to wiggle enough to avoid hair, while still being in proximity of the desired spots. We also know from previous studies that delivering t-PBM NIR to F3 and F4 (or close to) would have been more efficient in comparison to Fp1 and Fp2, when targeting dlPFC.[11] With our lower energy output compared to previous trials, 2.3 kJ per session of total energy instead of 3.4 kJ in the ELATED-2 trial,[17] and the additional reduction due to hair, as low as 1.5 kJ per session, it is likely that the energy delivered to dlPFC by our device was below the necessary threshold to see a clinical effect. Another difference between the two studies was the overall number of t-PBM sessions: in ELATED-2 participants received 16 sessions over 8 weeks, while in ELATED-3 they received 12 sessions over 6 weeks. Therefore, the overall energy delivered in the trial was also limited by the lower number of t-PBM sessions per phase, with up to 28 kJ delivered per phase in ELATED-3, about half of the overall energy delivered in ELATED-2. Presumably, greater efficacy could have been obtained in ELATED-3 if the frequency of sessions was increased, albeit with decreased feasibility and higher cost. In aggregate, the differences in t-PBM parameters and/or number of sessions between the two studies might account for the different results.

Future research in depression should investigate t-PBM at a higher energy output—within the appropriate range of tolerability, as seen in previous studies—with preferential targeting of the F3 and F4 sites, while also avoiding light obstruction by hair. Future research should also consider most effective t-PBM parameters in relation to concomitant antidepressant interventions. The augmentation of psychotherapy and of cognitive training with t-PBM is likely to result in enhanced antidepressant effects; specific, optimal t-PBM parameters should be investigated.[35] Another promising approach is the augmentation of t-PBM with intranasal PBM (i-PBM). While i-PBM does not appear to have direct effects on the brain, it may have systemic anti-inflammatory, antioxidant, and prometabolic effects.[36,37]

While this is a negative study, demonstrating the lack of efficacy of low-energy t-PBM, it is not a failed study, since our SPCD design controlled the placebo effect. The placebo response rate (19%) was similar to both pharmacologic (30%–40%)[38] and device-based trials in MDD.[39] The placebo response rate in our previous ELATED-2 trial (27%), with similar inclusion criteria, was also comparable.[17] In contrast, the overall change in depression severity in the t-PBM arm in ELATED-3, in both the first and the second phases (−3.44 ± 5.03 and −2.6 ± 6.52), was much lower than in the ELATED-2 study (−10.8 ± 7.6). Some drawbacks of the SPCD design should also be mentioned as they might have affected the results of our study. While the overall power of the study was greater thanks to the SPCD design, the power in each phase was less than what expected in a classic parallel design. The inclusion of 2 randomizations, per SPCD design, also forced a shorter length of 6 weeks for each phase in ELATED-3, compared to 8 weeks in ELATED-2. The latter shortfall could have prevented demonstrating the full potential of the antidepressant response to t-PBM.

Our study's limitations include the relatively small sample size and the positioning of the F3 and F4 t-PBM probes over hair, which likely reduced the NIR irradiance on skin and consequently the total energy delivered per session, as discussed previously. Our results reflect the efficacy of the t-PBM parameters ultimately achieved.

In conclusion, t-PBM with low irradiance, low energy per session, and low number of sessions may not be an effective antidepressant strategy. Minimal t-PBM dose thresholds, similarly to those in other antidepressant neuromodulation techniques such as electroconvulsive therapy and transcranial magnetic stimulation, merit further characterization.

Submitted: September 26, 2021; accepted February 24, 2022.

Published online: August 5, 2022.

Relevant financial relationships: In the last 5 years, **Dr Iosifescu** has received consulting honoraria from Alkermes, Allergan, Axsome, Biogen, Centers for Psychiatric Excellence, Global Medical Education, Jazz, Lundbeck, Otsuka, Precision Neuroscience, Sage, and Sunovion and research support (through his academic institution) from Alkermes, AstraZeneca, Brainsway, LiteCure, NeoSync, Otsuka, Roche, and Shire. **Dr Mischoulon** has received research support from Nordic Naturals and heckel medizintechnik GmbH; has received honoraria for speaking from the Massachusetts General Hospital Psychiatry Academy; and works with the MGH Clinical Trials Network and Institute (CTNI), which has received research funding from multiple pharmaceutical companies and National Institutes of Mental Health. **Mr De Taboada** is a stockholder at PThera LLC and the CTO of LiteCure LLC. **Dr Hamblin** is on the following Scientific Advisory Boards: Transdermal Cap Inc, Cleveland, OH; BeWell Global Inc, Wan Chai, Hong Kong; Hologenix Inc. Santa Monica, CA; LumiThera Inc, Poulsbo, WA; Vielight, Toronto, Canada; Bright Photomedicine, Sao Paulo, Brazil; Quantum Dynamics LLC, Cambridge, MA; Global Photon Inc, Bee Cave, TX; Medical Coherence, Boston MA; NeuroThera, Newark DE; JOOVV Inc, Minneapolis-St. Paul MN ; AIRx Medical, Pleasanton CA; FIR Industries, Inc. Ramsey, NJ; UVLRx Therapeutics, Oldsmar, FL; Ultralux UV Inc, Lansing MI; Illumiheal & Petthera, Shoreline, WA; MB Lasertherapy, Houston, TX; ARRC LED, San Clemente, CA; Varuna Biomedical Corp. Incline Village, NV; Niraxx Light Therapeutics, Inc, Boston, MA; has been a consultant for Lexington Int, Boca Raton, FL; USHIO Corp, Japan; Merck KGaA, Darmstadt, Germany; Philips Electronics Nederland B.V.; Johnson & Johnson Inc, Philadelphia, PA;

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Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany; and is a stockholder in Global Photon Inc, Bee Cave, TX; Mitonix, Newark, DE. **Dr Cassano** consulted for Janssen Research and Development and for Niraxx Light Therapeutics Inc; was funded by PhotoThera Inc., LiteCure LLC. and Cerebral Sciences Inc to conduct studies on transcranial photobiomodulation; is a shareholder of Niraxx Light Therapeutics Inc; and has filed several patents related to the use of nearinfrared light in psychiatry. The other authors have nothing to disclose.

Funding/support: This was an investigator-initiated study (to Drs Cassano and Iosifescu) funded by Litecure LLC.

Role of the sponsor: In addition to funding, the sponsor also provided the study devices and related technical support.

Previous presentation: Data were presented in virtual poster format at the Society of Biological Psychiatry Conference, April 20–May 2, 2020; Chicago, Illinois.

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