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Original Research

Transcranial Photobiomodulation for the Treatment of Major Depressive Disorder. The ELATED-2 Pilot Trial

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Abstract

Objective: Our objective was to test the antidepressant effect of transcranial photobiomodulation (t-PBM) with near-infrared (NIR) light in subjects suffering from major depressive disorder (MDD).
Background: t-PBM with NIR light is a new treatment for MDD. NIR light is absorbed by mitochondria; it boosts cerebral metabolism, promotes neuroplasticity, and modulates endogenous opioids, while decreasing inflammation and oxidative stress.
Materials and methods: We conducted a double-blind, sham-controlled study on the safety and efficacy (change in Hamilton Depression Rating Scale [HAM-D_{17}] total score at end-point) of adjunct t-PBM NIR [823 nm; continuous wave (CW); $28.7 \times 2\,cm^2$; $36.2\,mW/cm^2$; up to $65.2\,J/cm^2$; 20–30 min/session], delivered to dorsolateral prefrontal cortex, bilaterally and simultaneously, twice a week, for 8 weeks, in subjects with MDD. Baseline observation carried forward (BOCF), last observation carried forward (LOCF), and completers analyses were performed.
Results: The effect size for the antidepressant effect of t-PBM, based on change in HAM-D_{17} total score at end-point, was 0.90, 0.75, and 1.5 (Cohen's *d*), respectively for BOCF ($n = 21$), LOCF ($n = 19$), and completers ($n = 13$). Further, t-PBM was fairly well tolerated, with no serious adverse events.
Conclusions: t-PBM with NIR light demonstrated antidepressant properties with a medium to large effect size in patients with MDD. Replication is warranted, especially in consideration of the small sample size.

Keywords: depression, low-level laser therapy, randomized controlled trial

Introduction

Twenty-one million Americans (about 10%) suffered from a depressive episode over the past year.[1] Major depressive disorder (MDD) is the third leading cause of global disability[2]; the global cost of mental illness is expected to more than double by 2030, with depressive disorders at the forefront.[3] Sadly, 43% of primary care patients who experience a 6-month anxiety or depressive disorder diagnosis do not receive treatment, with most preferring self-management.[4] Although registered medications are proven cost-effective antidepressants,[5] many people in mild to moderate psychological distress prefer self-help over professional help or prescription medications.[6] Limiting factors—which might contribute to undertreatment—with current first-line intervention for MDD are as follows: (1) the burdensome side effects associated with pharmacological treatments[7,8] and (2) the need for frequent sessions and specialized professionals when opting for

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evidence-based psychotherapies.[9] Device-based interventions for MDD, such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, and vagus nerve stimulation, are approved as third- or fourth-line treatments for resistant depression.[10] Device-based antidepressant treatment, which is safe, inexpensive, and easy to administer at home, could represent a valuable first-line option for depressed patients who prefer complementary and alternative medicine.

Transcranial photobiomodulation (t-PBM) with near-infrared radiation (NIR) has emerged as a potential antidepressant treatment in both animal models[11–15] and human studies.[16–19] t-PBM consists of delivering NIR—or red light—to the scalp of the patient, which penetrates the skull and modulates function of the adjacent cortical areas of the brain. PBM with red light and/or NIR appears to increase brain metabolism (by activating the cytochrome C oxidase in the mitochondria), to increase neuroplasticity, and to modulate endogenous opioids, while decreasing inflammation and oxidative stress.[20–26] t-PBM penetrates deeply into the cerebral cortex,[27–29] modulates cortical excitability,[30,31] and improves cerebral perfusion[32–34] and oxygenation.[35] Studies have suggested that it can significantly improve cognition in healthy subjects,[36–38] and in subjects with traumatic brain injury (TBI).[39–41] The safety of t-PBM has been studied in a sample of acute 1410 stroke patients, with no significant differences in rates of adverse events between t-PBM and sham exposure.[42–44] Uncontrolled studies suggest an antidepressant effect of t-PBM in subjects suffering from MDD.[16–19]

Aims of the study

We report here on the first, randomized, double-blind, sham-controlled, pilot trial of the antidepressant effect of t-PBM in MDD patients.

Materials and Methods

This single-site study—Evaluation of LEDs Therapeutic Effect in Depression (ELATED-2)—was approved by the Massachusetts General Hospital (MGH) institutional review board (IRB). Recruitment began in February 2014, and the study was completed in August 2015. The main sources of recruitment were weekly Craigslist advertisements and people calling in to the general research line of the MGH Depression Clinical and Research Program.

Inclusion and exclusion criteria

Adult subjects (18–65 years of age) meeting the (Structured Clinical Interview for the DSM-IV—*Diagnostic Statistical Manual*, Fourth Edition) criteria for MDD, with at least a moderate degree of depression severity [Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) total score ranging 14–24], were included in the study after providing written informed consent. The MGH IRB required a maximum permitted $HAM\text{-}D_{17}$ score of 24 to prevent inclusion of patients at greater risk of suicide. During this episode, subjects could have failed no more than one FDA-approved antidepressant medication (for at least 6 weeks) and no more than one course of structured psychotherapy for depression (for at least 8 weeks). Other exclusionary conditions included active substance use disorders (prior 6 months), lifetime psychotic episodes, bipolar disorder, active suicidal ideation, and homicidal ideation, in addition to unstable medical illness and recent stroke (prior 3 months). Women of child-bearing potential were required to use a birth control method if sexually active; pregnancy and lactation were exclusionary. To allow maximum light penetration and minimize potential risks of local tissue damage from the use of NIR, the following conditions were also exclusionary: (1) having a forehead skin condition likely to impede light penetration, such as tattoo or birth mark; (2) taking a light-activated medication (prior 14 days); and (3) having a head implant; the latter criterion to prevent possible dislodgement associated with vasodilation, as in the case of endovascular stents.

Study design and treatment

Eligible subjects were randomized to an 8-week study with twice weekly double-blind t-PBM NIR versus sham treatment. At each treatment session, NIR or sham was administered to the forehead bilaterally, simultaneously [Omnilux New U, light emitting diode, manufactured by Photomedex, Inc., Montgomeryville, PA—see Supplement on Technology section in Supplementary Data (see Supplementary Data at www.liebertpub.com/pho) and Figs. 1 and 2 for placements and dosimetry]. The choice of an LED device, as opposed to a

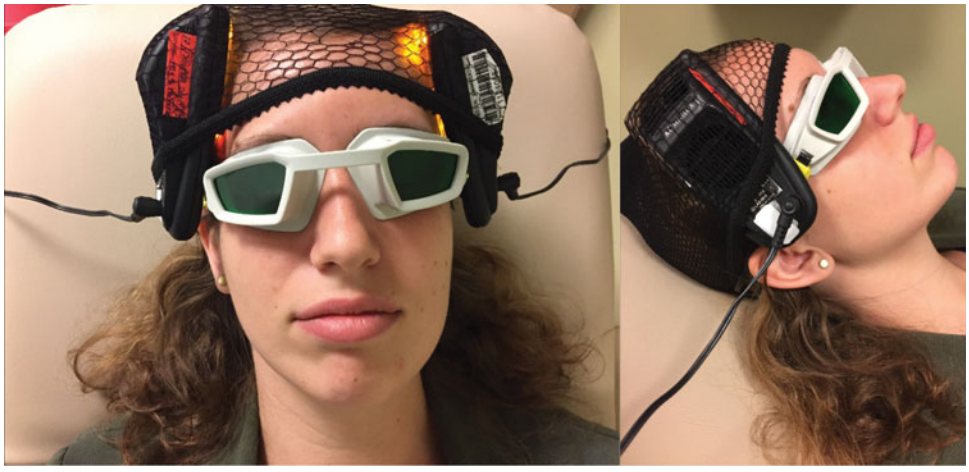

FIG. 1. The pictures show the handheld portions of the Omnilux New U devices, which are pressed against the forehead of the subject, bilaterally and simultaneously on the F3 and F4 sites (reference to EEG placement sites).

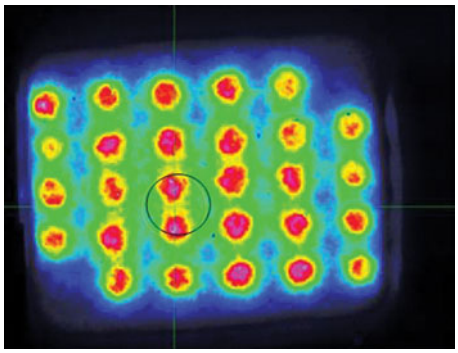

FIG. 2. The picture shows the intensity gradient for the NIR produced by the 28 LEDs of the Omnilux New U device (with a color scale depicting the highest intensity in red). A spot of maximum average intensity across 1 cm^2 aperture is indicated by the black circle. Active device #1124053. NIR, near infrared.

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laser device, was supported by a prior study on t-PBM for MDD.[16] The device used for this study emitted NIR at a wavelength of 823 nm, corresponding to the peak absorption spectrum for our biological target: cytochrome C oxidase.[45] In cadaver heads, the same device delivered 2% of the light at a penetration depth of 1 cm from the skin surface on frontal areas.[27] A 2% penetration rate allows an NIR energy density equivalent to the fluence inducing neurological benefit in animal models [fluence: 0.85–1.27 J/cm^2, not accounting for blood-related attenuation of light on the prefrontal cortex (i.e., optical energy per unit area, expressed in J/cm^2)].[22] As we were targeting the dorsolateral prefrontal cortex (dlPFC), we simultaneously directed the NIR to the F3 (left) and F4 (right) sites on the forehead—derived from the electroencephalography (EEG) placement map.[16] Since previous studies suggested that 1 and 6 sessions of t-PBM were insufficient to determine a sustained antidepressant response,[16,18] we extended the course of t-PBM to 8 weeks with a total of 16 sessions (out of 18 planned visits to the clinic); twice a week sessions had been acceptable and well tolerated in our proof-of-concept study.[18] The study clinician had the option to adjust the duration of light exposure after completion of week 3 and 5 (after 6 and 10 sessions, respectively) from 20 min ($\sim$40 J/cm^2) to 25 ($\sim$50 J/cm^2) and 30 min ($\sim$60 J/cm^2), respectively. Instructions were to increase exposure per protocol, as tolerated, to maximize the antidepressant effect. Each device had a treatment window of 28.7 cm^2, so the maximum cumulative dose over the entire treatment course was 43.7 kJ. The exposure time was designed to allow a fluence of 60 J/cm^2, despite relatively low power density (irradiance) of 33.2 mW/cm^2—based on settings reported by the manufacturer. Similar and greater NIR fluences have been associated with antidepressant response and improved cognition in prior reports.[16,18,36] All, but three 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 end-point).

Randomization and blinding

Two t-PBM device types were available for each modality (NIR and sham). The apparent behavior of the devices was identical for both modalities: noise upon working, feeling of warmth, and visual signs were indistinguishable. However, only NIR mode t-PBM device produced the therapeutic NIR energy. NIR light is invisible and undetectable to patients and physicians. The study research assistant used permuted block randomization with varying block sizes to randomize subjects in 1:1 manner to each pair of instruments as ''A'' and ''B.'' Only the research assistant was able to identify each pair of instruments as ''A'' and ''B.'' The investigators and the subjects remained blind to the subject assignment, since the label on each device was covered before treatment administration. Photomedex, Inc. provided the blinding codes of NIR and sham for each labeled pair of devices, which were kept in a sealed envelope at the study site.

Clinical outcome measures

The primary outcome measure was the total score of the HAM-D_{17} for depressive symptoms,[46] in accordance to our initial report before study enrollment (Clinicaltrials.gov). The HAM-D_{17} scale—with 17 items—aims to quantify the degree of depression in patients who already have a diagnosis of MDD. Questions focus on neurovegetative and other depressive symptoms experienced over the past 7 days. Answers to questions are rated on a scale of 0–4 or 0–2, with higher scores indicating more severe pathology. Scores on the HAM-D_{17} typically fall into the following ranges: (1) not depressed = 0–7; (2) mildly depressed = 8–13; (3) moderately depressed = 14–18; (4) severely depressed = 19–22; and (5) very severely depressed = 23 and over. The Clinical Global Impression–Improvement (CGI-I) subscale was adopted as a secondary measure for the overall clinical benefit.[47] The total score of the Quick Inventory of Depressive Symptomatology (QIDS) was used as a self-rated outcome measure of depression.[48] Tolerability was assessed with an Adverse Event Form, which allowed the recording of an adverse event's description, start and end dates, intensity and seriousness, relation to the treatment, as well as any action taken and final outcome. A specific semi-structured scale, the Transcranial Light Therapy Self-Report Questionnaire (T-SR-Q) was completed by participants at week 4 and 8. The scale explored any discomfort related to the treatment sessions, to detect potential reasons of unblinding. Blinding questionnaires also tracked the subject and clinician beliefs of assignment to active treatment at week 4 and at week 8.

Study sample and data cleaning

Twenty-one subjects were randomized, received at least one t-PBM session, and were included in the analyses (Table 1A, B). For self-rated scales (secondary measures), the sample is limited to 20 subjects, since 1 subject (#4) randomized to NIR consistently skipped several answers across scales and for the duration of the study. This subject carried a diagnosis of attention-deficit disorder and reported significant difficulties concentrating while off stimulants. The completers—who were followed for the entire 8-week study period and who received a clinical assessment immediately after—were 13 subjects. As briefly mentioned, three subjects (#6, #10, #19) were censored as part of the a-priori data cleaning process due to their starting a new

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Table 1. Diagnosis, Treatment, Depression Outcome and Adverse Events in Subjects Treated with Transcranial Photobiomodulation NIR Mode (A) and Sham Mode (B)

Subjects on t-PBM NIR mode	*Age*	*Gender*	*Current diagnosis*	*Concomitant antidepressant treatment (duration)*	*Treatment sites on forehead*	*Number of t-PBM sessions (NIR)*	*Maximum duration of t-PBM session (min)*	*Baseline HAM-D_{17}*	*Last visit HAM-D_{17} (weeks of t-PBM)*	*Adverse events (day of onset)*
A. NIR mode t-PBM group										
#1	49	F	MDD, PD; SAD; PTSD	Sertraline 200 mg/day (≥6 weeks)	F3, F4 proximity	16	30	19	10 (8 weeks)	None
#2	58	F	MDD	Psychotherapy (>12 weeks)	F3, F4 proximity	14	30	19	18 (7 weeks)	Day 47: gastrointestinal sickness
#3	64	M	MDD, PTSD	None	F3, F4	14	30	21	3 (8 weeks)	Day 0: restless sleep Day 2: headaches Day 7: taste illusion Day 10: abdominal bloating Day 50: gout
#4	24	F	MDD, PTSD, OCD	None	Fp1, Fp2	10	30	28	16 (8 weeks)	Day 50: self-harm
#5	27	M	MDD, Anxiety NOS	None	F3, F4	4	20	16	6 (2 weeks)	Day 2: insomnia
#6	39	M	MDD	None	F3, F4	10	25	18	18 (5 weeks)	None
#7	41	M	MDD	Psychotherapy (>2 years)	F3, F4	15	30	21	3 (8 weeks)	Day 0: insomnia Day 14: irritable mood
#8	44	F	MDD	Venlafaxine 75 mg/day (6 weeks)	F3, F4 proximity	16	30	21	0 (8 weeks)	Day 0: visual illusions (vivid colors)
#9	50	F	MDD	None	F3, F4 proximity	15	25	21	5 (8 weeks)	Day 0: visual illusion (vivid colors) Day 35: irritable mood Day 47: decreased memory; word finding difficulties Day 56: irritable mood
#10	50	F	MDD, GAD, PTSD	Nortriptyline[a] 50 mg/day (>2 years) Citalopram 40 mg/day (24 weeks)	F3, F4	1	20	22	19 (3 weeks)	None

(*continued*)

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Table 1. (Continued)

Subjects on t-PBM sham mode	*Age*	*Gender*	*Current diagnosis*	*Concomitant antidepressant treatment (duration)*	*Treatment sites on forehead*	*Number of t-PBM sessions (sham)*	*Maximum t-PBM session duration (min)*	*Baseline HAM-D_{17}*	*Last visit HAM-D_{17} (weeks of t-PBM)*	*Adverse events (day of onset)*
B. Sham mode t-PBM group										
#11	52	M	MDD, PTSD, GAD	Psychotherapy (≥8 weeks)	F3, F4 proximity	14	30	19	19 (8 weeks)	None
#12	50	F	MDD, Anxiety NOS	None	Fp1, Fp2	16	30	19	22 (8 weeks)	None
#13	64	F	MDD	None	F3, F4	14	30	26	17 (8 weeks	None
#14	48	M	MDD, GAD, SAD	None	F3, F4	6	20	20	19 (3 weeks)	None
#15	29	M	MDD, GAD, SAD	None	F3, F4	15	30	22	10 (8 weeks)	Day 15: left torso pain Day 28: insomnia
#16	64	F	MDD, GAD	Venlafaxine 75 mg/day Psychotherapy (both 2 years)	Fp1, Fp2	16	30	19	5 (8 weeks)	None
#17	24	F	MDD	None	F3, F4	16	30	17	20 (8 weeks)	None
#18	60	M	MDD	Fluoxetine 20 mg/day (1 year)	F3, F4 proximity	16	30	16	2 (8 weeks)	Day 14: headaches Day 13: belching
#19	53	F	MDD	None	F3, F4	8	25	14	10 (4 weeks)	None
#20	62	F	MDD	None	F3, F4 proximity	2	20	22	— (1 week)	—
#21	52	F	MDD, PTSD	Wellbutrin 300 mg/day Quetiapine 75 mg/day (both ≥6 weeks) Psychotherapy (≥8 weeks)	F3, F4	2	20	21	— (1 week)	—

Grayed rows: for study subjects who did not complete the 8-week study or missed the assessment right after.
Day 0: less than 24 h from first t-PBM session.
"—" missing assessment due to early dropout.
[a]Subject #10 was already on nortriptyline maintenance when she experienced her index episode and failed to respond to citalopram during her index episode.
F3, F4, EEG mapping sites corresponding to the dorsolateral prefrontal cortex; Fp1, Fp2, EEG mapping sites corresponding to the frontal poles.
EEG, electroencephalography; GAD, generalized anxiety disorder; HAM-D_{17}, Hamilton Depression Rating Scale; MDD, major depressive disorder; NIR, near infrared radiation; OCD, obsessive compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; t-PBM, transcranial photobiomodulation.

psychoactive treatment during the course of the study. One more subject (#2), who completed the 8 weeks of t-PBM sessions, performed follow-up assessment outside the permitted timeframe and the end-point was set a priori as the penultimate assessment. Four more subjects were lost to follow-up: two of them after 2 and 3 weeks of t-PBM sessions (#5, #14), while the remaining two subjects (#20, #21) failed to return to the clinic for their 1-week visit and therefore had no post-treatment assessments (see Fig. 3 for the subjects' flow chart).

Analyses

We tested our study hypothesis that t-PBM NIR mode will decrease HAM-D_{17} scores in study subjects significantly more than the sham. The dependent variable was our primary outcome of depression severity (as measured by the HAM-D_{17} total score); the independent variable was our comparison, the NIR and sham groups. We used three approaches: (1) intent-to-treat approach with baseline observation carried forward (BOCF; $n=21$),[49] (2) intent-to-treat approach with last observation carried forward (LOCF; $n=19$),[50] and (3) completers sample ($n=13$). The LOCF approach allows the inclusion in analyses of subjects who received treatments and had at least one assessment after baseline; their last available assessment is considered the end-point and used for the analyses. The BOCF approach differs from the LOCF as it also allows the inclusion in the analyses of subjects who received treatments, but did not complete any assessments afterwards; for these isolated cases, the baseline assessment is also the end-point (all other subjects' data are computed as in the LOCF). The completers' approach restricts the analyses to subjects who finished the 8-week trial and therefore, for all completers, the assessment after completion is used as end-point for the analyses. A Mann–Whitney *U* test was chosen—after noting skewed distribution of outcome data—comparing the change in the total severity score from baseline to end-point. To calculate the effect size of t-PBM, we adopted the Cohen's *d* formula for the change of HAM-D_{17} total score from baseline to end-point. We examined *post hoc* the self-rated QIDS total score for depression (BOCF, LOCF, and completers approach). We also compared the overall rates of antidepressant response and remission at end-point for the two groups. Rates of antidepressant response and remission were calculated according to the HAM-D_{17} total score (≥50% decrease and score ≤7, respectively) and the CGI-I scale (response equal to score 1 or 2). All response and remission rates were compared by Pearson's chi-square test. For any type of adverse event, we reported its frequency and described its characteristics, relation to the treatment, any action taken, and final outcome. Baseline characteristics for the two groups were compared by Mann–Whitney *U* test and Pearson's chi-square test, respectively, for continuous and nominal variables. To assess blinding, Pearson's chi-square test was used to determine if the distribution of subjects across treatment groups differed from the relative guess of clinicians and subjects; a percentage was reported to indicate the proportion of subjects whose assignment was correctly guessed. For all analyses, significance was set at $p \le 0.05$.

Results

Baseline characteristics

There were no significant differences among the two groups at baseline in terms of demographic and clinical characteristics as well as concurrent antidepressant treatment (Table 2), except for a history of more MDD episodes

Table 2. Baseline Demographic and Clinical Characteristics of Subjects Receiving Transcranial Photobiomodulation in NIR and Sham Mode

	NIR (n = *10*)	*Sham* (n = *11*)	p
Demographic characteristics			
Age, years, mean (SD)	45.0 (12.8)	50.7 (13.3)	ns
Gender, female, *n* (%)	6 (60)	6 (56)	ns
Race, *n* (%)			ns
White	9 (90)	10 (91)	
Black or African American	0	1 (9)	
Asian	1 (10)	0	
Ethnicity, *n* (%)			
Non-Hispanic	10 (100)	11 (100)	
Clinical characteristics, mean (SD)			
HAM-D_{17} total score	20.6 (3.2)	20.2 (4.3)	ns
CGI-severity	4.4 (0.5)	4.4 (0.5)	ns
Months of current MDD episode	14.5 (15.4)	19.9 (22.0)	ns
Age of MDD onset	15.5 (6.7)	31.6 (19.6)	ns
Number of MDD episodes	4.3 (1.7)	2.6 (1.8)	0.047
Number of hospitalizations	1.0 (1.3)	1.3 (2.4)	ns
Current antidepressant treatment, *n* (%)			
None	5 (50)	7 (64)	
Psychotherapy alone	2 (20)	1 (9)	
Antidepressant medication(s)—no psychotherapy	3 (30)	1 (9)	
Antidepressant medication(s) and psychotherapy	0	2 (18)	

ns, nonsignificant ($p > 0.05$).
CGI, Clinical Global Impression; NIR, near infrared radiation; SD, standard deviation.

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in the t-PBM NIR group (mean 4.3 ± 1.7 vs. 2.6 ± 1.8; $z = 1.988$, $p = 0.047$).

Prior and baseline antidepressant treatment

Roughly half of the sample in the NIR mode (40%; $n = 4$) and in the sham mode (64%; $n = 7$) groups had not received an antidepressant medication or psychotherapy during this MDD episode. Three subjects per group had tried psychotherapy during this episode. Three NIR and two sham subjects had tried one antidepressant medication during this episode. Two and one subjects in the NIR and sham group, respectively, had undergone two medication trials. During the study, all subjects continued their baseline antidepressant treatment, if any (Table 1A, B), except subject #8 who discontinued her psychotherapy at baseline. During the study, the maximum exposure time (min) per session of t-PBM was nearly identical in the two groups (mean 26.5 ± 4.12 vs. 26.8 ± 4.62; $z = -0.316$, $p = 0.752$).

Antidepressant effect according to clinician-rated measurement

The mean change in HAM-D_{17} total score in subjects receiving t-PBM in NIR mode was significantly greater than in subjects receiving sham mode with the BOCF approach [NIR ($n = 10$) -10.8 ± 7.55 vs. sham ($n = 11$) -4.4 ± 6.65; $z = 1.982$, $p = 0.047$] and with the completers approach [NIR ($n = 6$) -15.7 ± 4.41 vs. sham ($n = 7$) -6.1 ± 7.86; $z = 2.158$, $p = 0.031$]. However, the threshold for significance was not reached with the LOCF approach [NIR ($n = 10$) -10.8 ± 7.55 vs. sham ($n = 9$) -5.33 ± 7.04; $z = 1.556$, $p = 0.119$]. Figure 4 illustrates the mean HAM-D_{17} total scores over the course of the study for the two t-PBM groups (BOCF and completers). The effect size for the antidepressant effect of t-PBM, based on change in HAM-D_{17} total score at end-point, was 0.90, 0.75, and 1.5 (Cohen's *d*), respectively, for BOCF, LOCF, and completers.

Antidepressant effect according to self-rated measurement

In the *post hoc* analyses, the antidepressant effect of t-PBM NIR mode, measured by self-rated QIDS total scores, approached significance only in completers (BOCF: $n = 20$, -5.3 ± 5.81 vs. -3.0 ± 3.00; $z = 0.877$, $p = 0.380$; LOCF: $n = 18$, -5.3 ± 5.81 vs. -3.7 ± 2.91; $z = 0.576$, $p = 0.565$; and completers: $n = 12$, -9.8 ± 4.09 vs. -4.3 ± 3.04; $z = 1.874$, $p = 0.061$).

Antidepressant response and remission rates

At end-point, response and remission per the HAM-D_{17} occurred in 5 out of 10 (50%) subjects in the NIR mode. In the sham mode, response and remission occurred in 3 and 2 subjects out of 11, respectively (27% and 18%) (response: $n = 21$; $\chi^2 = 1.15$; df = 1; $p = 0.284$ and remission: $n = 21$; $\chi^2 = 2.39$; df = 1; $p = 0.122$). Response in the NIR mode was attained after 2 weeks of t-PBM ($n = 3$) and after 3 and 4 weeks ($n = 1$ for each time point); in the sham mode, it occurred after 3, 4, and 5 weeks of t-PBM ($n = 1$ for each time point). At end-point, 60% of NIR versus 18% of sham subjects were at least ''much improved'' according to the CGI ($n = 21$; $\chi^2 = 3.88$; df = 1; $p = 0.049$).

Blinding of subjects and clinicians

None of the subjects reported excessive skin warming (T-SR-Q), which supported our blinding. All correlations between treatment assignment and its guess from the subjects were nonsignificant, with a 60% rate of correct guesses at week 4 ($n = 15$; $\chi^2 = 1.03$; df = 1; $p = 0.310$) and 54% at week 8 ($n = 11$; $\chi^2 = 0.24$; df = 1; $p = 0.621$). However, clinicians' guesses were significantly different among the two groups at both week 4 ($n = 14$; $\chi^2 = 4.66$; df = 1; $p = 0.031$) and week 8 ($n = 10$; $\chi^2 = 4.28$; df = 1; $p = 0.038$), with a 79% and 80% rate of correct guesses, respectively.

Adverse events

The t-PBM sessions were well tolerated. None of the adverse events was serious and all, but one had resolved at study end. Only one subject (#9) in the NIR mode group required dose adjustment due to irritable mood, which first became apparent at day 35 (after eight t-PBM sessions and after reaching 25 min of irradiation/session). While some irritable mood persisted with the lower t-PBM dose (20 min), the subject was able to complete the study. After study completion, this subject was contacted by phone by study staff (P.C.), reported complete resolution of irritability. In terms of the relationship of adverse events to the study intervention (t-PBM), only two subjects receiving the sham mode developed an adverse event at least ''possibly related'' to the intervention according to the investigators: (#15) experienced insomnia at day 28 and (#18) headaches at day 14. Instead, in the NIR mode, five subjects developed one or more adverse events at least ''possibly related'' to the intervention: three subjects (#3, #5, #7) experienced insomnia (at day-0, 2, 14); three subjects (#8, #9, #3) experienced illusions such as ''seeing vivid colors'' or ''tasting from an ashtray'' (at day-0, 0, 7); two subjects (#7, #9) experienced irritable mood (at day-14, 35) and subject #3 experienced headaches at day 2 and abdominal bloating at day 10. Overall, the NIR mode group experienced more adverse events and more early-onset events (first 7 days). Noticeably, in the same group, the onset of several adverse events occurred within 24 h from the first t-PBM session (day-0) and with some adverse events—such as headaches and vivid illusions—occurring within 1 h from the t-PBM session. Illusionary phenomena were sporadic and typically present only after the first sessions and were short lasting (30 min). All, at least ''possibly related,'' adverse events were either mild or moderate, except in two cases (#3 with severe restless sleep, headaches, and taste illusions and #8 with severe visual illusions). One subject (#4), who only partially responded to t-PBM NIR mode superficially cut her wrists and took five pills of acetominophen with the intent to self-harm (day-50). The subject denied suicidal intent and this event—considered ''unrelated'' by the study investigator—was neither life-threatening nor required medical attention; the subject reported being upset after an argument with her boyfriend and wanting his attention.

Discussion

Our study demonstrated preliminary evidence of an at least medium effect size for the antidepressant efficacy of t-PBM NIR (Cohen's $d \geq 0.75$ for all analyses). t-PBM was

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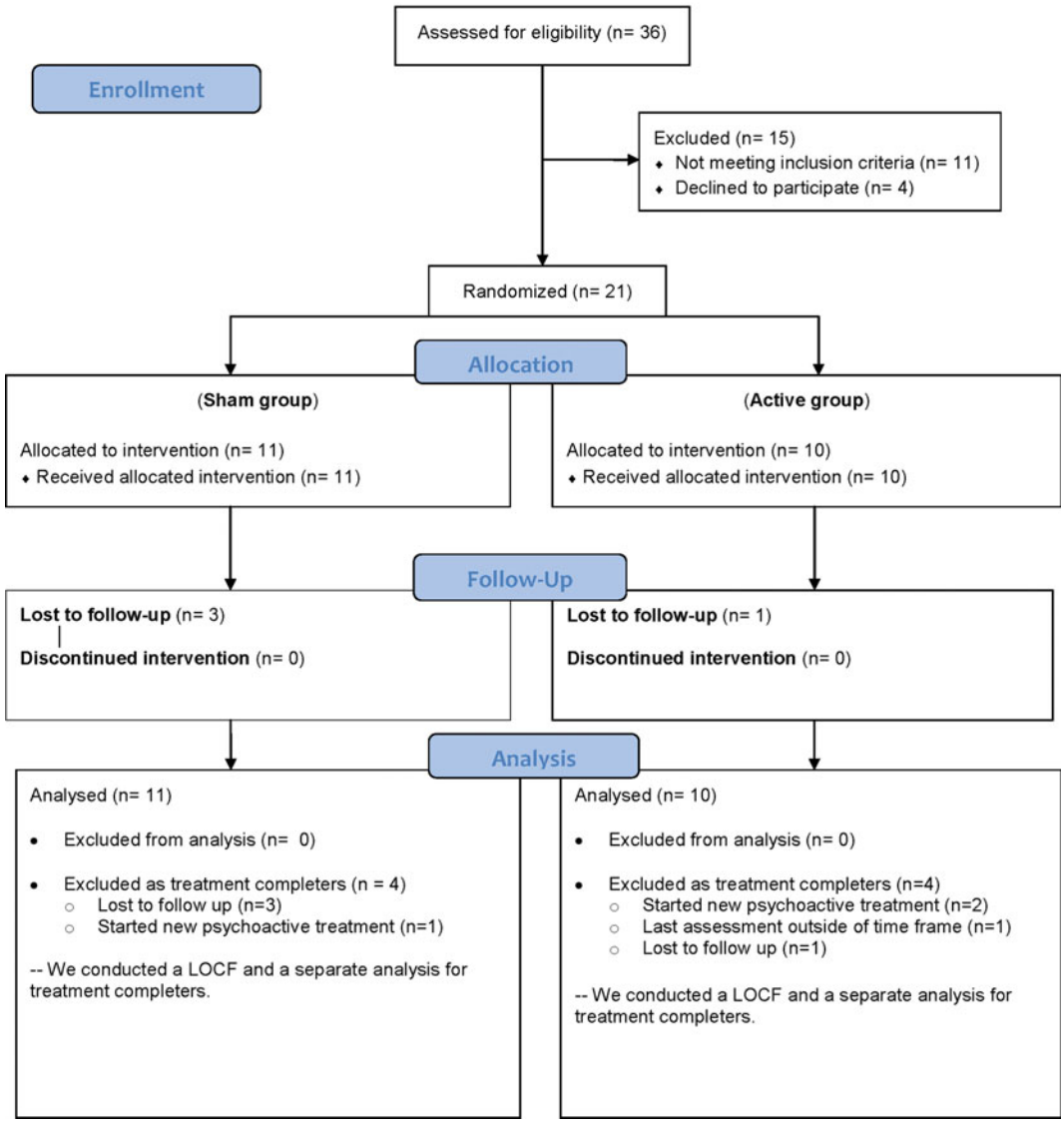

FIG. 3. CONSORT clinical trial flow diagram.

fairly well tolerated with none of the adverse events causing study discontinuation and only one case requiring dose adjustment. Attrition rates were the average for clinical trials. The one episode of self-harm during the study was considered unrelated to t-PBM by the study investigator and was neither life-threatening nor required medical attention. While it is unclear if t-PBM might worsen suicidal ideation in some cases, a recent report suggests the opposite.[51]

Our results are consistent with open-label reports that also demonstrated an antidepressant effect for t-PBM in MDD patients[16–19] and with a sham-controlled study on enhancement of attention bias modification for depression with t-PBM.[52] The neuromodulatory effect of t-PBM has also been documented in double-blind, randomized, sham-controlled studies in healthy subjects, demonstrating cognitive enhancement of t-PBM.[36–38] Our detection of a medium to large effect size of t-PBM (0.75–1.5) in MDD is also noteworthy, however, common for small studies. Interestingly, early-onset adverse events occurred exclusively in the NIR mode group (5/9 subjects) and included unusual and unanticipated perceptual disturbances, such as visual and taste illusions (3/9 subjects). It is possible that raters were biased toward positive outcomes by the report of early adverse events in the t-PBM NIR-group, as raters' correct prediction of t-PBM assignment

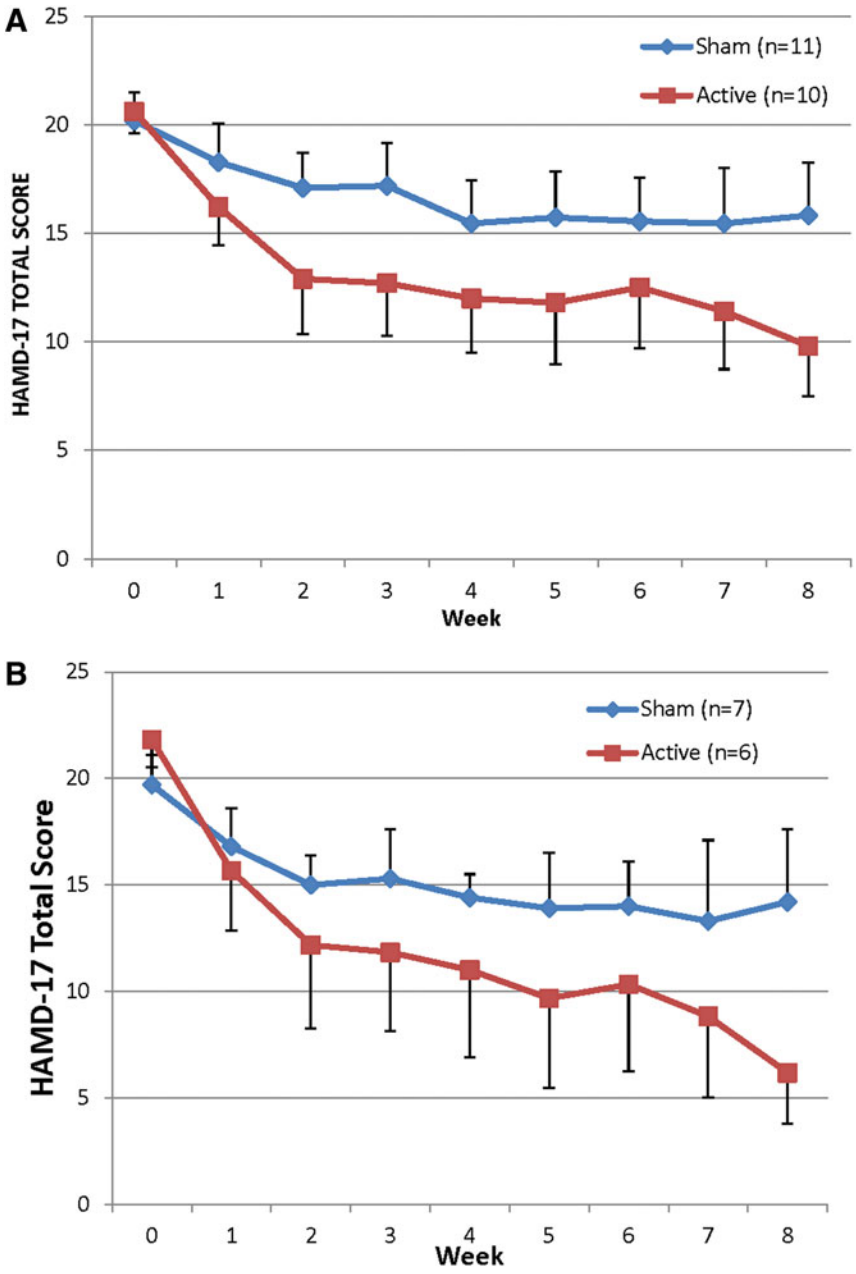

FIG. 4. Graph of mean HAM-D_{17} total score in subjects treated with NIR light (red line) and in subjects treated with sham (blue line); **(A)** all study subjects included ($n=21$); **(B)** only completers included ($n=13$). **(A)** All subjects (intent to treat—end-point carried forward; mean ± SE). **(B)** Completers only (imputed values for three missing data points from interim visits; mean ± SE). Error bars on one side of each line. HAM-D_{17}, Hamilton Depression Rating Scale; SE, standard error.

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was 80%. The *post hoc* analyses of the self-report measure of the antidepressant effect—while not reaching statistical significance in a smaller sample size—showed similar trends in terms of effect size and *p*-value in completers ($p=0.06$), despite the prediction of t-PBM assignment by subjects did not exceed chance (50%).

From a cellular and molecular perspective, the beneficial effect of t-PBM (NIR) on brain metabolism is the primary putative mechanism for its antidepressant effect. In experimental and animal models, PBM (NIR and red light) is absorbed by cytochrome C oxidase and, by stimulating the mitochondrial respiratory chain, leads to increased ATP production.[23–25] In a study on healthy subjects, t-PBM (NIR) improved cerebral oxygenation, supposedly through an increase in cerebral blood flow coupled with increased oxygen demands.[35] Similarly, a study in MDD subjects found that t-PBM led to a nearly significant increase in regional cerebral blood flow.[16] Both studies relied on functional NIR spectroscopy to assess oxygenation and blood flow. In a case report of chronic TBI, the improvement in brain perfusion subsequent to t-PBM was imaged with single-photon emission computerized tomography (SPECT).[32] Multiple studies have reported regional and global brain hypometabolism in MDD[53–57]; moreover, metabolic abnormalities seem to improve after antidepressant treatment or after recovery.[58–60]

From a neurophysiological perspective, decreased activity in the prefrontal areas has been implicated in the dysfunction of emotion regulation in depressed patients.[61] The emotion regulation circuitry is dependent on top-down regulation, mediated by the prefrontal cortex, in particular by the dlPFC.[61] In our study, t-PBM (NIR mode) was

simultaneously directed to the F3 F4 EEG reference points of the scalp or in close proximity—in all, but one subject—suggesting that modulation of the dlPFC and the emotion-regulation circuitry might be the mechanism for the antidepressant effect.

Our study has six main limitations: (1) the small sample size precludes generalizability and warrants replication in larger cohorts of MDD patients; the low placebo effect might partly explain the medium to large effect size and the significant findings, despite the small sample; (2) the emergence of early-onset adverse events might have affected the quality of blinding for the clinicians, however, not for study subjects; (3) the two-arm design, with only one NIR regimen, precludes any inference on the ideal parameters of stimulation with regard to clinical efficacy and tolerability; (4) the use of BOCF and of LOCF does not model for potential improvement or worsening of depression after dropout; yet it provides information on overall outcome—accounting for known early dropout in sham-treated subjects[62]—while the completers analysis is exempt from modeling biases; (5) the lack of long-term follow-up precludes the evaluation of sustainability of the therapeutic effect and long-term tolerability; and (6) the study was not designed to investigate mechanisms; specific studies are needed to correlate clinical effects with the effect of NIR on brain circuitry and metabolism.

Conclusions and Summary

t-PBM with NIR could be a novel intervention for patients suffering from MDD, who have demonstrated intolerance or refractoriness to antidepressants or prefer nonpharmacological approaches. t-PBM is mechanistically different from other existing device-based treatments for MDD, which typically employ electromagnetic modulation of cortical neurons. Numerous NIR LED devices are FDA approved for sale over the counter; they are considered safe for personal use and—provided FDA approval for this specific indication—may represent an inexpensive option for the home treatment of MDD, under appropriate medical supervision. If t-PBM were to be confirmed as an effective and safe treatment for MDD, it would be well suited for adoption among the expanding range of therapeutic options for MDD.

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