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Case Series

Maintenance Transcranial Photobiomodulation Following an Acute rTMS Course for Recurrent Major Depressive Disorder and Generalized Anxiety Disorder: A Case Series

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Abstract

This study underscores feasibility of transcranial photobiomodulation (tPBM) as a maintenance strategy for patients with treatment-resistant Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) following an acute course of repetitive Transcranial Magnetic Stimulation (rTMS). Weekly psychometric assessments showed maintenance of symptom improvements, quantified via PHQ-9 (Patient Health Questionnaire-9) and GAD-7 (Generalized Anxiety Disorder 7-item scale). The observed symptom stability may be related to the effects of tPBM in promoting neuronal mitochondrial function and adenosine triphosphate (ATP) synthesis, cerebral blood flow, and adaptive neuroplasticity. However, the study is limited by absence of a control group, which underscores the need for further, large-scale, randomized and blinded trials to determine whether tPBM offers additive benefit beyond the natural durability of rTMS.

Keywords: Transcranial Photobiomodulation (tPBM); Repetitive Transcranial Magnetic Stimulation (rTMS); Dorsolateral Prefrontal Cortex (DLPFC); Neuromodulation; MDD (Major Depressive Disorder); Patient Health Questionnaire-9 (PHQ-9); Generalized Anxiety Disorder-7 item scale (GAD-7)

Introduction

This study focuses on transcranial photobiomodulation (tPBM) as a modality to achieve and maintain remission in Major Depressive Disorder (MDD) in patients following an acute course of 36 repetitive transcranial magnetic stimulation (rTMS) sessions. tPBM is a novel form of neuromodulation involving non-retinal exposure to near-infrared light (NIR) administered via a headset device with light-emitting diodes (LEDs) [1]. NIR passes through a series of layers, including the scalp, periosteum, skull bone, meninges, dura, and onto the cortical surface of the brain [2]. These photons induce cytochrome c oxidase activity in neuronal and endothelial mitochondria, resulting in increased ATP synthesis via enhanced activity of the electron transport chain. Ultimately, the increased ATP promotes cerebral blood flow via nitric oxide synthesis, as well as adaptive neuroplasticity and neuroprotection [3-6].

Case History

Case 1

Patient is a 66-year old Caucasian male diagnosed with MDD and GAD in 2006. The patient reported occupational and health-related stress due to recurrent basal cell carcinomas, degenerative disc disease, and psoriatic arthritis. He had been a target of identity theft in 2006, which resulted in financial stress. He reported recurrent major depressive episodes lasting 2 to 3 weeks. He also described chronic depressive symptoms lasting approximately 2 years each from 2009 - 2011 and 2013 - 2015, consistent with a diagnosis of persistent depressive disorder with intermittent major depressive episodes (double depression). rTMS was therefore recommended in late 2024 to alleviate his symptoms due to lack of response from antidepressant trials, including therapeutic doses of escitalopram and bupropion for at least 6 to 8 weeks each.

Case 2

Patient is a 60-year old Asian male with a history of early-onset depressive symptoms, with his first depressive episode reported at age 11. He reported worsening of depression and anxiety in 2001, associated with incarceration and probation following an arrest. Another depressive episode occurred in 2019 following the passing of the patient's partner. This led to a suicide attempt via medication overdose in 2022. For the next 6 months, he underwent intensive psychiatric treatment, including inpatient and step-down care. Due to inadequate response to multiple antidepressant trials, including escitalopram, fluoxetine, venlafaxine, and bupropion for at least 6 to 8 weeks each, he was referred for rTMS in late 2024.

Case 3

Patient is a 55-year old Caucasian female who reported her first depressive episode in 1995 during pregnancy, consistent with a diagnosis of MDD with peripartum onset. The patient reported periods of avolition, anhedonia, and passive suicidal ideation without plan or intent. She was recommended rTMS in late 2024 due to inadequate response to multiple antidepressant trials, including paroxetine, venlafaxine, and bupropion for at least 6 to 8 weeks each.

Materials and Methods

Subjects

Participants were selected based on a clinical diagnosis of MDD refractory to at least 2 antidepressants of different classes. The subjects had no contraindications to TMS, such as ferromagnetic implants within 12 inches of the head, cardiac pacemaker, implantable cardioverter defibrillator, and history of epilepsy or brain lesions [7]. The subjects were recommended 36 rTMS sessions based on clinical data demonstrating sustained remission of depressive symptoms in patients who completed this number of treatments [8]. They received 36 rTMS sessions, followed by 30 tPBM sessions via Titan-IR Pro® over 8 weeks. They did not take any antidepressant or anxiolytic medications for the duration of the study.

Repetitive transcranial magnetic stimulation (rTMS) treatment

rTMS was administered by certified neurotechnologists using the Stimware® software installed in the Apollo TMS Therapy System. Using the 10-20 system, the F3 location (Left Dorsolateral Prefrontal Cortex) corresponding to Brodmann areas 8 and 9 was approximated on the scalp [9]. The motor threshold (MT) was determined at a location in the primary motor cortex which elicited contralateral thumb twitch at the lowest intensity. Treatment parameters for left DLPFC stimulation included a frequency of 10 Hz, 3000 pulses, 40 pulses per train, 75 trains per session, and an intertrain interval of 11 seconds. The left DLPFC was approximated 5.5 cm anterior to the motor cortex, and each treatment was targeted at this location for 18 minutes and 34 seconds [10]. Treatment intensity was capped at 100% of the MT, which the subjects tolerated without scalp discomfort, headache, or seizure.

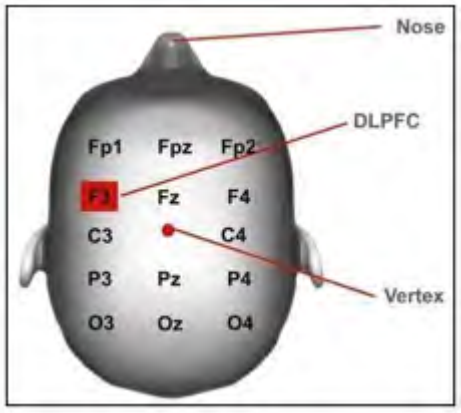

Figure 1: 10-20 system locations.

Photobiomodulation therapy

Patients were started on 30 tPBM sessions spread out over the course of 2 months following the end of their rTMS course. Each session consisted of a 20-minute gamma protocol. Gamma wave activity is associated with heightened perception, cognitive processing, problem-solving, attentional selection, working memory, and emotional regulation [11,12]. Treatment was done in a quiet, dimly lit room, with patients positioned comfortably, either seated or lying down. Red light and NIR were administered via a dual-wavelength therapeutic window: an ATP window between 600 - 900 nm, and an ion channel window between 900 - 1000 nm. These wavelengths fall within the optical window of 600 - 1100 nm, which is known for its ability to penetrate tissue and reach deep photoacceptors involved in mitochondrial function and ion channel modulation [19]. Treatment was administered via 52 LED clusters on the Titan-IR Pro® headset (Medify), distributed along the Fp1, Fp2, F7, and F8 locations. NIR was administered via pulsed mode at 40 Hz with an average irradiance of 23 mW/cm^2. The total treatment window area is 64.5 cm^2. The resulting fluence per session was 27.5 J/cm^2. 1.77 kJ was administered per treatment, with a total of 53.2 kJ over the course of treatment.

Psychometric questionnaire administration

Symptoms were monitored using standardized psychometric questionnaires. The Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) were administered weekly throughout the treatment course. These surveys were also administered at 3 time points on a 3-month naturalistic follow-up period following conclusion of the tPBM course. Treatment response is defined as ≥ 50% improvement in survey scores, while remission is defined as ≥ 80% improvement [13]. The 3-month post-tPBM follow-up corresponds to approximately 6 months following completion of the acute rTMS course, accounting for the 8-week tPBM maintenance phase.

Results

Case 1	Pre-rTMS: 10 / 31 / 24	Midpoint: 12 / 23 / 24	Post-rTMS: 2 / 5 / 25	Pre-tPBM: 2 / 12 / 25	2 / 19	2 / 27	3 / 4
PHQ-9	22	7	5	6	1	1	0
GAD-7	13	4	6	6	4	3	2

Case 1	3 / 12	3 / 20	3 / 26	4 / 2	4 / 7	1 month post-tPBM: 5 / 6 / 25	2 months post-tPBM: 6 / 7 / 25	3 months post-tPBM: 7 / 7 / 25
PHQ-9	0	1	2	1	1	2	3	2
GAD-7	3	2	1	2	1	2	1	1

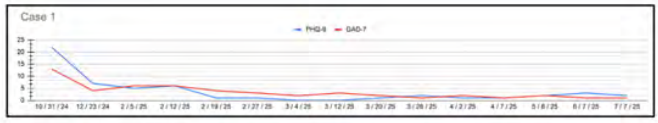

Figure 2: PHQ-9 and GAD-7 scores for case 1.

Case 2	Pre-rTMS: 11 / 5 / 24	Midpoint: 12 / 10 / 24	Post-rTMS: 1 / 8 / 25	Pre-tPBM: 3 / 5 / 25	3 / 12	3 / 19	3 / 26
PHQ-9	24	15	4	5	3	3	3
GAD-7	13	8	3	2	4	2	1

Case 2	4 / 2	4 / 9	4 / 16	4 / 23	4 / 29	1 month post-tPBM: 5 / 28 / 25	2 months post-tPBM: 6 / 25 / 25	3 months post-tPBM: 7 / 22 / 25
PHQ-9	3	2	4	3	2	1	3	3
GAD-7	2	1	3	2	2	1	2	4

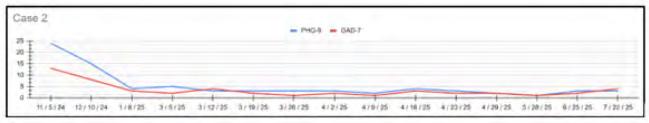

Figure 3: PHQ-9 and GAD-7 scores for case 2.

Case 3	Pre-rTMS: 11 / 26 / 24	Midpoint: 12 / 24 / 24	Post-rTMS: 1 / 23 / 25	Pre-tPBM: 2 / 26 / 25	3 / 5	3 / 12	3 / 19
PHQ-9	20	7	7	7	8	4	3
GAD-7	9	7	7	7	7	4	1

Case 3	3 / 26	4 / 2	4 / 9	4 / 16	4 / 25	1 month post-tPBM: 5 / 28 / 25	2 months post-tPBM: 6 / 25 / 25	3 months post-tPBM: 7 / 23 / 25
PHQ-9	1	5	6	5	4	5	5	5
GAD-7	5	7	5	7	4	4	5	7

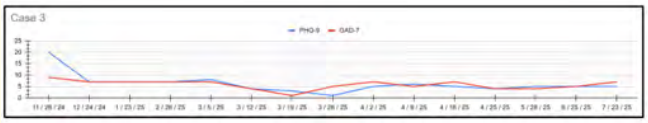

Figure 4: PHQ-9 and GAD-7 scores for case 3.

To characterize within-patient symptom change over time, we calculated the standardized mean change (Cohen's d) separately for each participant, comparing pre-tPBM values with scores obtained during the 3-month post-tPBM follow-up. These effect sizes are presented descriptively and are intended to illustrate the magnitude of change in symptom frequency per patient. For PHQ-9, standardized within-patient changes were: Case 1 (d = -0.94), Case 2 (d = -1.09), and Case 3 (d = -0.84). For GAD-7, values were: Case 1 (d = -1.52), Case 2 (d = -0.87), and Case 3 (d = -0.93). The individual trajectories indicate sustained symptom improvement following initiation of maintenance tPBM after completion of the acute rTMS course.

Additionally, because patient scores were heavily weighted by the rTMS phase (specifically pre-rTMS), we analyzed patient scores from pre-tPBM through 3 months post-tPBM utilizing Kendall's tau and Spearman's rho. Patient 1 showed a significant decrease in GAD-7 scores (Kendall's $\tau B = -0.76$, Spearman's $\rho = -0.85$, $p < .001$, $N = 12$). No other patient scores yielded statistically significant results. However, Patient 2 showed a negative trend in PHQ-9 scores, and Patient 3 showed a negative trend in both PHQ-9 and GAD-7 scores.

Discussion

Studies have established robust durability of symptom improvements from an acute course of 36 rTMS sessions [8]. A meta-analysis by Senova., *et al*. pooled 18 studies published between 2002 and 2018 on the durability of rTMS response rates 3 and 6 months post-treatment. Among responders, 66.5% of 732 patients sustained response at month 3 (95% CI = 57.1 - 74.8%), while 52.9% of 695 patients sustained response at month 6 (95% CI = 40.3 - 65%) [14]. In addition, Cohen., *et al*. conducted a retrospective cohort study on 204 rTMS patients with MDD remission, defined as a Hamilton Rating Scale for Depression (HAMD) score of 7 or less. Event-free remission with the end point defined as relapse (HAMD score > 8) was 60% at 3 months and 22.6% at 6 months following completion of rTMS sessions. The researchers highlighted the role of maintenance treatment in potentially increasing the durability of MDD remission [15].

Research also exists indicating feasibility of wearable, self-administered tPBM in MDD patients. A randomized controlled trial conducted by Guu., *et al*. (2025) revealed significant improvements in depressive symptoms in 48 patients, quantified via HAMD and Beck Depression Inventory (BDI). While the study showed no between-group differences in both surveys, significant reductions in Pittsburgh Sleep Quality Index (PSQI) scores were found in the experimental group compared to the sham group, indicating a potential hypnotic effect of tPBM [16].

By the end of the study, Patients 1 and 2 reported sustained MDD remission, evidenced by psychometric scores indicating improved mood, sleep, energy, concentration, and interest. They also evidenced continued remission of GAD symptoms such as irritability, restlessness, racing thoughts, and worry [17]. Patient 3 continued to report periods of anhedonia, concentration deficits, and guilt, but with decreased intensity and frequency compared to before starting her treatment course. Nonetheless, all 3 patients were able to sustain response, defined as a ≥ 50% reduction in psychometric scores, over the entire tPBM course and follow-up period. The durability window extended approximately 6 months following completion of the acute rTMS phase. This period coincides with the interval in which relapse rates typically rise sharply. Cohen., *et al*. determined event-free remission post-rTMS to be 60% at 3 months to 22.6% at 6 months [15]. In contrast, all 3 patients in the study maintained clinical response throughout the post-rTMS observation period, raising the possibility that adjunct tPBM may contribute to durability post-rTMS. The promising results of this case series may be attributed to DLPFC simulation and recruitment of multiple cortical neural networks, and increased neuronal ATP synthesis via stimulation of the respiratory chain [3-5,18].

Limitations

The use of tPBM for MDD and GAD following an acute rTMS course was limited to a single case series, and is intended to be hypothesis-generating due to small sample size and absence of a sham group. Its feasibility must be further studied using large-scale, randomized and blinded trials in order to validate findings. Another limitation is potential response bias due to the use of self-reported psychometric questionnaires. Also, given the established durability of rTMS response [14], it is not possible to disentangle the independent effect of tPBM as a potential maintenance treatment using this study design. This underscores the need for extended follow-up periods to explore long-term durability compared to rTMS alone.

Conclusion

We report maintenance of MDD symptom improvements in patients after 36 rTMS sessions, followed by 30 tPBM sessions over 8 weeks, and a 3-month follow-up period. Our findings show promising results for tPBM as a safe and potentially beneficial maintenance strategy after an acute rTMS course. These findings should be interpreted as preliminary feasibility data rather than evidence of efficacy, and to inform future randomized maintenance-phase neuromodulation trials.

Author Contributions

KS conceptualized the study. The original draft of this manuscript was written by MO, VR, KM, SM, and KS. Review and additional editing of the manuscript were conducted by CV, RD, NR, KB, and RB.

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Conflict of Interest

We report no potential conflicts of interest regarding the publication of this paper. This manuscript has been read and approved by all authors.

Declaration of Patient Consent

The authors confirm that written informed consent had been obtained from the participants for publication of this paper. Participation in the study adhered strictly to patient privacy and HIPAA guidelines. The participants understood the potential risks and benefits of the interventions.

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