Tolerability and Safety of Transcranial Photobiomodulation for Mood and Anxiety Disorders

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Abstract: Introduction: Mood and anxiety disorders are a prevalent and significant leading cause of years lived with a disability worldwide. Existing antidepressants drugs are only partially effective, having burdensome side effects. One-third of patients do not achieve remission after several adequate antidepressant trials, and relapses of depression are frequent. Psychotherapies for depression are limited by the lack of trained professionals, and further by out-of-pocket prohibitive costs. Existing FDA-approved, device-based interventions are either invasive or only administered in the office. Transcranial photobiomodulation (t-PBM) with near-infrared (NIR) light may be a promising treatment option for mood and anxiety disorders. Due to its low cost, and ease of self-administration, t-PBM has the potential to become widely accessible. The safety profile of t-PBM is a relevant factor for widespread use and administration. Aim: To further investigate the t-PBM safety profile, this study aims to evaluate the tolerability and safety of t-PBM for the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD). Method: We completed a systematic analysis of the side effects from repeated sessions of t-PBM in three studies: an open-label study for GAD (LIGHTEN GAD) and two randomized control studies for MDD (ELATED-2; ELATED-3). Overall, 80 subjects were studied. Result: Our results show that a low dose of NIR per t-PBM session can be administered with increasing frequency (up to daily sessions) and for several weeks (up to 12 weeks) without a corresponding increase in the occurrence or severity of adverse events. Additionally, there were no significant predictors for the variance in the number of reported adverse events (such as age, sex or diagnosis). Conclusion: The literature indicates that higher dosages of transcranial NIR could lead to greater antidepressant and anxiolytic effects; this study did not find any correlation between the increasing number of t-PBM sessions and the occurrence of adverse events.

Keywords: photobiomodulation; depression; anxiety; neuromodulation
1. Introduction

1.1. Conventional Treatments for Major Depressive Disorder

Major depressive disorder (MDD) is prevalent, affecting the lifetime of 16.2% of the United States population [1], and is among the top leading causes of years lived with a disability (YLDs) worldwide [2]. Existing antidepressants are only partially effective and have burdensome side effects [3,4]. One-third of patients do not achieve remission after several adequate antidepressant trials [5], and relapses of depression are frequent [6]. Antidepressant medications are prescribed globally and have been shown to be effective; however, many patients have complained of a vast array of side effects, often undermining their treatment. We will briefly exemplify the most common side effects associated with the various classes of antidepressants to further the reader’s understanding of treatment limitations. Selective serotonin reuptake inhibitors (SSRIs) are the best tolerated pharmacological agents for the treatment of MDD. However, they still present side effects [7], some of which are common, such as: sexual dysfunction (estimated to be present in about 60% of patients), gastrointestinal dysfunction (e.g., nausea, upset stomach and diarrhea), central nervous system dysfunction (e.g., anxiety, insomnia, sedation, nightmares, and extrapyramidal symptoms), interaction with platelet function (e.g., greater risk of bleeding), hyponatremia, serotonin syndrome—which is rare, however, potentially severe and serious—and discontinuation syndrome, typically after the abrupt cessation of a short half-life medication. Monoamine oxidase inhibitors (MAOIs) are now rarely prescribed due to the potentially life-threatening reaction when food with significant amounts of tyramine is consumed: hypertensive crisis. Interaction with other medications (such as over-the-counter medications) can also be as dangerous. In addition to hypertensive crisis, patients can experience other dysfunctions such as: orthostatic hypotension, weight gain, sedation, sexual dysfunction, hepatotoxicity, and pyridoxine deficiency. Tricyclic antidepressants (TCA) were introduced to replace MAOIs due to their better safety profile; however, they do have the potential to cause arrhythmias and could be lethal in overdose. Some prominent side effects caused by TCA are: anticholinergic side effects (e.g., constipation and dry mouth), sedation and weight gain.

1.2. Conventional Treatments for Generalized Anxiety Disorder

General anxiety disorder (GAD) is characterized by excessive worrying associated with various symptoms such as tremors, palpitations, fatigue, insomnia, trouble concentrating, and restlessness. GAD can be a debilitating condition, and its effects can impair multiple areas of an individual’s life [8]. The disruption to family life, productivity at work, and social life will diminish the quality of life of GAD sufferers. Prevalence estimates vary substantially across nations, with higher lifetime prevalence in high-income countries than in middle-to-low-income countries (5% versus 1.5–3%) [9]. Its high prevalence and socioeconomic impact make GAD a pressing matter to address at all levels of healthcare. Anxiolytic treatments for GAD include benzodiazepines (e.g., diazepam, alprazolam, lorazepam), azapirones (e.g., buspirone), SSRIs (e.g., paroxetine, sertraline), SNRIs, i.e., serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine XR, duloxetine), antihistamines (e.g., hydroxyzine), pregabalin, and atypical antipsychotics (e.g., quetiapine) [10]. While effective in treating GAD, these medications can cause various distressing side effects; therefore, many patients refuse prescription medicines to treat GAD, similarly to patients suffering from MDD. Just to mention some, pregabalin can cause dizziness and somnolence, while sertraline can cause sleep disturbances and vertigo [11]. Benzodiazepines can cause sedation and drowsiness, sexual side effects in some, memory disturbances, impaired psychomotor function, tolerance and dependence issues, and discontinuation syndrome [12]. Hydroxyzine has been shown to cause sedation and weight gain. The atypical antipsychotic quetiapine causes significant weight gain in 15% of users, and also gastrointestinal and sexual side effects. Overall, medication side effects can be distressing and may lead to selecting other non-pharmacological treatments for GAD and for MDD [13].
1.3. Non-Pharmacological Interventions for Mood and Anxiety Disorders

On the other hand, among conventional treatments, psychotherapies for depression and for anxiety are limited by a lack of trained professionals (in evidence-based therapies) and by out-of-pocket prohibitive costs. Existing FDA-approved, device-based (non-pharmacological) interventions are either invasive or only administered in the office, such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS). These procedures usually require multiple visits (ECT and rTMS) and sometimes anesthesia (ECT) or even surgical implantation (VNS). There is a significant unmet need for non-pharmacological treatments (e.g., digital devices) that are effective, safe, and suitable for the in-home treatment of mood and anxiety disorders.

1.4. Transcranial Photobiomodulation

Transcranial photobiomodulation (t-PBM) with near-infrared (NIR) light may be a promising treatment option for various psychiatric and neurological conditions [14–17]. Cadaver studies have shown that NIR can penetrate the skull and soft tissues of the forehead to affect brain cortical areas (10–12). At a cellular level, red and NIR light can stimulate a specific enzyme within the mitochondrial electron transport chain of cytochrome c oxidase (CCO). CCO is the primary photoreceptor responsible for the various effects that t-PBM has on the brain. These effects include ATP production, increased reactive oxygen species, and increased cerebral blood flow (CBF) [18–21].

Many clinical trials have shown that t-PBM can improve depressive symptoms. The first clinical trial of t-PBM used in MDD patients with comorbid anxiety disorders found a decrease in depressive and anxiety symptoms assessed by the HAM-D and the HAM-A scores after a single treatment with NIR, with the most significant decrease seen two weeks post-treatment. No side effects were reported throughout the clinical trial [17]. Our group also showed a reduction in depressive symptoms from baseline after six NIR treatments with no serious side effects and overall good tolerability [16].

Similarly, twice a week NIR t-PBM sessions for eight weeks in patients with major depressive disorder also yielded an antidepressant effect compared to sham. No serious adverse events were reported, but some participants who received the NIR treatment noted headaches, vivid colors, or irritability. Overall, this study showed the tolerability of t-PBM, and none of the reported adverse events caused the study’s discontinuation [22].

Due to its low cost, excellent safety profile, and ease of self-administration, t-PBM has the potential to become widely accessible. However, despite its clear advantages, no consensus exists on the optimal parameters of t-PBM (location of administration, wavelength, intensity, etc.) for central nervous system (CNS) disorders. Similarly, both laser devices and LED devices can be used for t-PBM treatment and have had a similar effect of decreasing depressive symptoms, but these types of devices have not been studied in direct comparison [16,17,23].

1.5. Tolerability and Safety of Transcranial Photobiomodulation

No serious adverse events were found in a literature review of studies on PBM for the treatment of depression [22]. The safety of one session of t-PBM was evaluated in three large RCTs with a pooled sample of 1410 subjects with acute stroke [24–26]. No significant difference in the rate of adverse effects was observed between the groups receiving laser NIR (808 nm; 5 W) or sham. However, clinical studies indicate that repeated sessions are needed for clinically significant improvements to occur, and it is still unclear whether repeated sessions of t-PBM might lead to treatment-emergent side effects. Two open studies using 1 and 6 sessions of t-PBM reported no treatment-emergent side effects [16,17]. A clinical trial with 16 sessions reported an increased number of mild side effects in the active treatment group, the most frequent being insomnia, “seeing vivid colors”, “an ashtray-like taste”, and irritable mood [23]. Secondary analyses of the same RCT have also shown that twice-weekly NIR t-PBM produces mild side effects, including ringing in the ears and headaches. Some small weight gain was also observed in the active treatment group
as opposed to the sham and was attributed to the antidepressant effect of t-PBM [27]. The BMI was lower at baseline in the NIR group (24.15 kg/m²) than in the sham group (29.65 kg/m²), which can explain this difference in weight gain. In the same RCT, a slight but statistically significant increase in diastolic blood pressure was seen in the t-PBM group compared to the sham.

The risk of thermal injury from PBM delivered with the parameters used in the studies we reviewed is considered minimal, and limited to the skin. In ten individuals treated for TBI with 10–15 W lasers—a much higher power than what is commonly used in LED t-PBM—the skin temperature increased to no more than 3 °C with rapid cooling after removing the NIR light. Clinically, patients reported slight skin warming but no discomfort [28]. Inherent to the use of any laser device is the potential risk of retinal lesions. This results from the improper use of the laser and from the shedding of the light beams straight through the lens and from their convergence on the macula; this is mitigated with appropriate safety eyewear and procedures.

Consistent data on its safety profile are required for the widespread use and administration of t-PBM. However, no large clinical trials have been performed with repeated sessions of t-PBM to treat depression and anxiety. Therefore, the power of reported studies to identify more frequent side effects of t-PBM, compared to sham, is limited. To further investigate t-PBM safety, we analyze data on adverse effects from two RCTs on t-PBM for MDD and from one open trial on t-PBM for GAD. All these studies performed identical systematic assessments of adverse effects which were not reported in the primary publications.

2. Materials and Methods

After pooling three databases, we conducted a post hoc analysis on the tolerability and safety of t-PBM when used for mood and anxiety disorders. These three studies were all approved by the Massachusetts General Hospital (MGH) institutional review board (IRB). The studies comprised a single-site open-label t-PBM study investigating the impact of t-PBM on GAD (LIGHTEN GAD) [29], a one-site randomized control study examining t-PBM for MDD (ELATED-2) [23], and lastly, a two-site randomized control study also examining t-PBM for MDD (ELATED-3) [30]. One of the primary authors (PC) was involved in all studies. The ELATED-3 study was a collaboration between researchers at Massachusetts General Hospital (MGH) and at the Nathan Kline Institute (NKI). Both institutional review boards (IRB) approved the ELATED-3 study. In all three studies, informed consent was collected from all participants before the initial screening procedures. The three studies performed a systematic assessment of adverse effects using the Systematic Assessment for Treatment-Emergent Effects—Specific Inquiry (SAFTEE-SI) scale [31] (described below). The data provided by the SAFTEE-SI constitute new data not previously analyzed (except for in the ELATED-2 study); moreover, novel analyses were conducted to explore the dose-dependency of the adverse events.

2.1. Inclusion and Exclusion Criteria

All studies had similar inclusion and exclusion criteria for participation. All subjects were adults aged 18 to 70 years for ELATED-3 and LIGHTEN GAD, while those in ELATED-2 were a maximum of 65 years. For ELATED-2 and -3, the subjects met diagnostic criteria for MDD. The DSM criteria were confirmed through the Structured Clinical Interview for DSM Disorders (SCID) for ELATED-2, and the Mini International Neuropsychiatric Interview (MINI) [32] for ELATED-3. Those in LIGHTEN GAD met diagnostic criteria for GAD with at least moderate severity on the Clinical Global Impression Severity Scale (CGI-S) [33]. Subjects in ELATED-2 and -3 had at least a moderate rating of depression severity (Hamilton Depression Rating Scale, HAM-D17, within 14–24 range final score) [34]. Subjects were excluded from all studies if they had had an active substance use disorder three months before baseline (six months for ELATED-2), lifetime psychotic episodes, bipolar disorder, unstable medical illness, stroke in the previous three months, or any active suicidal or homicidal ideation. Pregnancy and lactation were also exclusionary. Of note,
one subject in the LIGHTEN-GAD study met the criteria for mild alcohol-use disorder but was allowed within the study by the IRB as a protocol exception [30].

The following conditions were also exclusionary to allow optimum light penetration and minimize potential risks of local tissue damage from NIR intervention: (1) having a skin condition or tattoo on the forehead; (2) taking light-activated medication two weeks prior to the visit; (3) having any form of head implant.

2.2. Sample

The sample for this analysis includes 12 subjects of the original LIGHTEN-GAD sample, as three subjects did not have SAFTEE data. The ELATED-2 sample was limited to 18 subjects, as previously determined in the previous secondary analysis of this sample [27]. Lastly, the ELATED-3 sample consisted of 38 subjects of the original 49. Eleven subjects did not have adequate SAFTEE; however, one participant had inadequate data during their active treatment phase, but did have SAFTEE data across their sham treatment phase.

2.3. Procedures

ELATED 2: Subjects were randomized to an eight-week study with twice-weekly double-blind sham or t-PBM therapy, having a total of sixteen sessions. NIR or sham were administered bilaterally to the forehead at each session, targeting the F3 and F4 sites directly affecting the dorsolateral prefrontal cortex (dLPFC). Based on efficacy and tolerability, the study clinician was given the option to adjust the duration of light exposure to between 20 and 30 min. The study devices employed a continuous wave LED source emitting NIR at a wavelength of 823 nm, with a treatment window of 28.7 cm² per each of the two sites, with an irradiance up to 33.2 mW/cm² and fluence up to 60 J/cm². Total energy per session ranged from 2.3 kJ (20 min) to 3.4 kJ (30 min). For a complete description of the dosing procedure, please refer to the original study [23].

ELATED-3: 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, through the LiteCure® Transcranial PhotoBioModulation-1000 (TPBM-1000) device. Utilizing an LED device as opposed to a laser device was supported by the evidence of efficacy in the ELATED-2 trial. The LED device emitted NIR at a radiation wavelength of 830 nm, corresponding to the peak absorption spectrum for cytochrome-C oxidase [35]. The dLPFC was targeted while the investigators simultaneously directed the NIR to the F3 and F4 sites on the forehead. Additionally, as prior work showed benefits when targeting the frontal poles (prefrontal cortex—PFC), the investigators also directed NIR to Fp1 and Fp2 [36]. The study design utilized the sequential parallel comparison design (SPCD) [37], thereby having two randomizations of t-PBM vs. sham, at baseline and at week 6. The study device (Litecure LLC TPBM-1000) delivered CW NIR at a wavelength of 830 nm, with an irradiance of 54.8 mW/cm² and a treatment window of 35.8 cm² for an exposure time of 20 min. This resulted in a fluence averaging around 65.8 J/cm² and a total potential energy per session of 2.3 kJ. For more detailed information on the randomization and blinding procedures of ELATED-2 and -3, please refer to the original studies [23,30].

LIGHTEN-GAD: Eligible subjects participated in an 8-week pilot, open-label treatment trial. Each subject self-administered their at-home t-PBM dosage once a day for eight weeks. The Cerebral Science headband device emitted NIR with an output at 830 ± 15 nm targeting the FP1, FP2, F7, F8, and Fpz (PFC), and thereby covering a total surface of 80 cm² with an average irradiance of 30 mW/cm² (total output power 2.4 W) and an average fluence of 27 or 36 J/cm² over 15 or 20 min, respectively. The total energy delivered was up to 2.9 kJ each session (see Table 1 for full t-PBM NIR parameters) [23,29]. After the baseline visit, subjects received their first t-PBM session in the office with a clinician to properly train participants and assess tolerability. Session length was kept to 15 min intervals during the first week, increasing to 20 min after. Based on subject tolerability, the study clinician had the option to keep the duration of exposure to 15 min or decrease it to 10 min during the
trial. Additionally, participants were given the HAM-D17 at baseline. However, it was not administered at post-treatment (week 8). Therefore, their scores were not included in a subsequent analysis examining the impact of t-PBM on depressive severity.

Table 1. Light output parameters of each study.

|                      | ELATED-2  | ELATED-3  | LIGHTEN-GAD |
|----------------------|-----------|-----------|-------------|
| Wavelength           | 823 nm    | 830 nm    | 830 nm      |
| Irradiance           | 33.2 mW/cm² | 54.8 mW/cm² | 30 mW/cm²  |
| Average power        | ~1.9 W    | ~2 W      | ~2.4 W      |
| Fluence              | 60 J/cm²  | 65.8 J/cm² | 36 J/cm²    |
| Duration of t-PBM session | 20–30 min | 20 min    | 20 min      |
| Treatment window     | 57.4 cm²  | 35.8 cm²  | 80 cm²      |
| Cumulative dose per session | 3.4 kJ   | 2.3 kJ    | 2.9 kJ      |
| Light placement (forehead) | F3, F4 | F3, F4, Fp1, Fp2 | F7, F8, Fp1, Fp2, Fpz |

2.4. Outcome Measures

The main outcome measure for this post hoc analysis of three pooled studies was the emergence of side effects, assessed by the Systematic Assessment for Treatment-Emergent Effects—Specific Inquiry (SAFTEE-SI) scale [31] delivered weekly in all studies. The scale is a checklist of 55 adverse symptoms commonly or possibly experienced during the course of treatment. All items are on a 4-point Likert scale, categorized by severity as: 0—none, 1—mild, 2—moderate, and 3—severe. SAFTEE-SI validity for clinical subjects was shown in the CO-MED study [38]. The frequency of any side effect was based on the number of patients reporting the index side effect at any time during the study.

2.5. Statistical Analyses

All statistical analyses were performed in SPSS (version 28.0). Descriptive statistics were run on available participants to examine demographic characteristics. Because some SAFTEE items could be present at baseline, particularly in a sample of subjects taking psychotropic medication—which can produce side effects—we defined as treatment-emergent any SAFTEE side effect for which severity increased by two or more levels (e.g., from none to moderate or from mild to severe) from baseline, as in a previous study from our group [27]. As studies differed in terms of the t-PBM dose, the frequency of sessions, and the length of trial, only data collected in the first phase of treatment (ranging from six to eight weeks) was utilized. An exception to this rule was made for ELATED-3, for those participants who were first randomized to sham (6 weeks) and then to NIR (6 weeks). For these participants, their sham phase was included in the sham sample, while their NIR phase was in the NIR sample. In order to further balance sham and NIR, the group in ELATED-3 who received sham in both phases had both phases (each of 6 weeks) included in the analyses. The rationale for including both phases of this group is that as no treatment was given in phase one, there would be no potential higher susceptibility to experiencing an adverse event in phase two. Furthermore, analyses were performed within the NIR group itself to examine more nuanced differences between NIR doses.

Chi-square analyses were run between treatment conditions, as was performed in the previous investigation [28]. Additionally, hierarchical regressions were run to examine the impact of the NIR dose on the change in depression score and on the frequency of adverse events when controlling for demographic variables (e.g., age and sex).

Logistic regressions were conducted to determine whether these factors influenced the likelihood of an adverse event occurring.

3. Results

3.1. Sample

As the sample consisted of participants who received either or both sham and NIR, the demographic characteristics of the “sham” and “NIR” comparison groups both included the
subset of participants from ELATED-3 who sequentially received sham and NIR. Therefore, the total collected NIR (n = 48) and sham (n = 32) comparison groups contained the same twelve participants of the thirteen randomized to receive both treatments. One participant was exclusively categorized within the sham group as their NIR phase data were inadequate. It should be noted that, as some participants were randomized to sham treatment twice (two phases of 6 weeks each in ELATED-3; n = 10), they were counted twice for the outcome comparison. Consequently, the total sham group was counted as 32 during demographic analyses and 42 during treatment outcome comparison.

The total NIR and sham groups differed significantly in age ($t(78) = 2.11$, $p = 0.04$), as the sham group was significantly older. Additionally, the sham and NIR groups had a clinically significant difference in baseline depression score ($t(77) = 2.94$, $p = 0.004$), as the sham group was more depressed.

The two groups did not differ significantly in baseline sex, racial, or ethnic differences. It should be noted that the groups were similar in terms of female and male distribution. However, in terms of racial and ethnic identity, the sample was primarily White and non-Hispanic/LatinX participants. (Table 1)

### 3.2. NIR vs. Sham Group Comparison

When comparing the groups in terms of reporting an adverse event, we found in the ELATED-2 subsample that the results replicated a previous paper, where more participants in the NIR group experienced adverse events (6/9) compared to the sham group (2/9). However, the chi-square showed only a trend towards statistical significance ($\chi^2 = 3.60$, $p = 0.06$). In the ELATED-3 subsample, both the NIR group (19/27), and the sham group (26/33) were very comparable in participants who experienced an adverse event, with the chi-square difference test evidencing no significant difference between the two groups ($\chi^2 = 0.56$, $p = 0.45$). When comparing the combined and total samples, both the NIR group (31/48) and the sham group (28/42) had a similar distribution of participants who experienced an adverse event. This was reflected in the chi-square difference test, which evidenced no significant difference between the two groups ($\chi^2 = 0.04$, $p = 0.84$).

The first hierarchical regression run analyzed the influence of biological sex and age in the first step, energy delivered in the second step, change in HAM-D17 score in the third step, and the interaction of change in HAMD17 with energy delivered on the number of adverse events reported (Table 2). The final model was not a significant predictor ($F [5, 70] = 0.15$, $p = 0.96$, $R^2 = 0.01$). No variable significantly predicted the variance in the number of adverse events reported ($p > 0.05$).

### Table 2. Demographic characteristics of the sample.

| Variable | ELATED-2 | | | ELATED-3 | | | LIGHTEN-GAD | | | Total | | | | Statistic |
|----------|---------|---|---|---------|---|---|---------|---|---|---------|---|---|---------|---|
| | tPBM(n = 9) | Sham(n = 9) | tPBM(n = 27) | Sham(n = 23) | tPBM(n = 12) | tPBM(n = 48) | Sham(n = 32) | |
| Age | M(SD) | M(SD) | M(SD) | M(SD) | M(SD) | M(SD) | M(SD) | $t(78) = 2.11$, $p = 0.02$ |
| HAM-D17 | 19.8(1.9) | 19.11(3.5) | 17.2(5.4) | 20.0(6.5) | 10.92(3.0) | 16.1(5.4) | 19.68(5.0) | $\chi^2 = 2.94$, $p = 0.004$ |
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Table 2. Cont.

| Ethnicity                        | ELATED-2 | ELATED-3 | LIGHTEN-GAD * | Total       |
|----------------------------------|----------|----------|----------------|-------------|
| **Race**                         |          |          |                |             |
| White                            | 8(88.9%) | 8(88.9%) | 21(77.8%)      | 20(87.0%)   |
| **Hatian, Black, or African**    |          |          |                |             |
| American                        | 0(0.0%)  | 1(11.1%) | 3(11.1%)       | 2(8.7%)     |
| **Asian**                        |          |          |                |             |
| White and Hatian Black or African American | 0(0.0%) | 0(0.0%) | 1(3.7%)        | 0(0.0%)     |
| **American Indian/Alaskan Native** | 0(0.0%) | 0(0.0%) | 3(11.1%)       | 1(4.3%)     |
| **Ethnicity**                    |          |          |                |             |
| Hispanic or LatinX               | 0(0.0%)  | 0(0.0%)  | 3(11.1%)       | 2(6.3%)     |
| Not Hispanic or LatinX           | 8(88.9%) | 9(100.0%)| 20(74.1%)      | 22(85.7%)   |
| **Jewish**                       | 0(0.0%)  | 0(0.0%)  | 1(3.7%)        | 0(0.0%)     |
| **Not Reported**                 | 1(11.1%) | 0(0.0%)  | 3(11.1%)       | 4(8.3%)     |

* Study did not have sham group. HAM-D = Hamilton Depression Rating Scale.

As the interaction was not significant, the hierarchical regression was re-run without the interaction (Table 3). As with the previous model, this model did not significantly account for the variance of the number of adverse events reported ($F_{[4, 71]} = 0.16, p = 0.96$, $R^2 = 0.01$), where still no variable significantly accounted for variance ($p > 0.05$).

Table 3. Hierarchical regressions predict the number of adverse events reported.

| Predictor                          | $b$      | 95% CI  | $\beta$ | $t$  | $p$  | $R^2$ | $p$  | $F$  | df  | $p$  |
|------------------------------------|----------|---------|---------|------|------|-------|------|------|-----|------|
| Overall Model                      |          |         |         |      |      |       |      |      |     |      |
| Age                                | 0.004    | $[-0.05, 0.05]$ | 0.02 | 0.15 | 0.88 | 0.002 | 0.92 |
| Sex                                | 0.30     | $[-1.32, 1.91]$ | 0.04 | 0.37 | 0.72 | 0.005 | 0.63 |
| Energy Delivered                   | -0.95    | $[-4.85, 2.95]$ | -0.06 | -0.49 | 0.63 | 0.005 | 0.63 |
| Change in HAM-D17                  | -0.31    | $[-0.16, 0.10]$ | -0.06 | -0.47 | 0.64 | 0.01  | 0.64 |
| HAM-D17 x Energy Delivered         | -0.10    | $[-0.65, 0.45]$ | -0.07 | -0.35 | 0.73 | 0.01  | 0.73 |
| Overall Model (NIR Only)           |          |         |         |      |      |       |      |      |     |      |
| Age                                | -0.04    | $[-0.12, 0.04]$ | -0.17 | 0.15 | -0.96 | 0.04  | 0.57 |
| Sex                                | 0.85     | $[-1.89, 3.59]$ | 0.11 | 0.37 | 0.53 | 0.05  | 0.54 |
| Energy Delivered                   | -2.13    | $[-9.08, 4.83]$ | -0.11 | -0.62 | 0.54 | 0.05  | 0.54 |
| Change in HAM-D17                  | 0.002    | $[-0.24, 0.25]$ | 0.003 | 0.02 | 0.99 | 0.05  | 0.99 |
| HAM-D17 x Energy Delivered         | -0.07    | $[-1.22, 1.07]$ | -0.07 | -0.13 | 0.90 | 0.05  | 0.90 |

Logistic regressions were performed to determine the probability of having an adverse event based on the predictor variables. The first model examined the impact of sex and age in the first step, total energy delivered in the second, change in HAM-D17 in the third, and the interaction of energy delivered by the change in HAM-D17 score in the fourth. The null model had a negative two log-likelihood of 94.91 and correctly classified 67% of the adverse event cases ($p = 0.003$). For the first step, age and sex did not significantly predict the probability of having an adverse event, with the negative two likelihoods making no change ($-2 \text{ LL } \chi^2(2) = 94.91, p = 0.50$). Additionally, there was no significant prediction for the second step for total energy delivered ($-2 \text{ LL } \chi^2(1) = 94.85, p = 0.81$), the third step for
change in HAM-D17 ($-2 \text{ LL } \chi^2(2) = 94.29, p = 0.21$), or the fourth step for their interaction ($-2 \text{ LL } \chi^2(2) = 93.03, p = 0.61$).

3.3. Within NIR Group Comparison

Utilizing only the sample that received NIR (ELATED-2, -3, and LIGHTEN GAD), the first hierarchical regression run analyzed the influence of biological sex and age in the first step, energy delivered in the second step, change in HAM-D17 score in the third step, and the interaction of change in HAM-D17 with energy delivered on the number of adverse events reported (Table 3). The final model was not a significant predictor of the number of adverse events reported ($F[5, 29] = 0.29, p = 0.92, R^2 = 0.5$). No variable significantly predicted the variance in the number of adverse events reported ($p > 0.05$).

As the interaction was not significant, the hierarchical regression was re-run without the interaction (Table 3). As with the previous model, this model did not significantly account for the variance of the number of adverse events reported ($F[4, 30] = 0.37, p = 0.83, R^2 = 0.05$), where still no variable significantly accounted for variance ($p > 0.05$).

As with the previous analyses, logistic regressions were utilized to determine the probability of having an adverse event or not based on these predictors. The first model examined the impact of sex and age in the first step, total energy delivered in the second, change in HAM-D17 in the third, and the interaction of energy delivered by the change in HAM-D17 score in the fourth. The null model had a negative two log-likelihood of 43.16 and correctly classified 69% of adverse event cases ($p = 0.03$). For the first step, age and sex did not significantly predict the probability of having an adverse event, with the negative two likelihoods making no change ($-2 \text{ LL } \chi^2(2) = 43.16, p = 0.81$). Again, there was no significant prediction for the second step for total energy delivered ($-2 \text{ LL } \chi^2(1) = 43.15, p = 0.92$), the third step for change in HAM-D17 ($-2 \text{ LL } \chi^2(2) = 43.04, p = 0.75$), or the fourth step for their interaction ($-2 \text{ LL } \chi^2(2) = 42.75, p = 0.49$).

4. Discussion

Although not approved by the FDA, t-PBM with NIR light is a promising treatment option for neuropsychiatric disorders, specifically depression and anxiety. Due to its low cost and ease of self-administration, t-PBM has the potential to become widely accessible. Its safety profile is likely to affect the extent of adoption of t-PBM. To further investigate the tolerability and safety of t-PBM, this study narrowed its focus on the use of t-PBM for the treatment of MDD and GAD.

We completed a systematic analysis for the side effects of repeated sessions of t-PBM in three studies: one open-label study for GAD (LIGHTEN GAD), and two randomized control studies on MDD (ELATED-2 and -3). Overall, 80 subjects were studied. Our results give evidence that t-PBM with the parameters used in these three studies is well tolerated —within the exposed dosimetry—and higher dosages of NIR do not correspond to higher occurrences of adverse events. Additionally, no variable predicted a significant variance in the number of adverse events reported, i.e., for age, sex, or type of disease.

Previously, in a much smaller sample, we reported a systematic assessment of side effects from repeated sessions of LED t-PBM (low dose) for MDD. In our analysis, no serious adverse events occurred, and the profile of side effects was reported as benign [27]. Side effects were transient and only a trend for statistical significance was seen, as the active group experienced side effects three times more than the sham group. Nevertheless, the small sample size limited the interpretation of the results. A small amount of weight gain was seen in the active treatment group, but this was not significant compared to the sham group. Regarding its effects on blood pressure, t-PBM was also benign. However, a statistically significant increase in diastolic blood pressure in the t-PBM group was observed compared to sham: a clinically insignificant increase in the overall diastolic blood pressure [28].

Our prior findings relate to the benign side effects for repeated sessions of NIR t-PBM—when low doses were delivered—and are similar to the findings of three large trials testing
safety and tolerability for a single session of t-PBM, at high dose, in patients with acute stroke [17,25,39].

For example, Lampl et al. used t-PBM for improving 90-day outcomes in patients with acute ischemic stroke. In their double-blind trial on 120 patients with acute ischemic stroke, no device-related severe adverse effects were reported [24]. Additionally, Hacke et al. studied 1000 patients with acute ischemic stroke treated with laser t-PBM; the authors considered five adverse events as likely related to the investigational treatment (0.5%) and three events (0.25%) likely related to sham treatment. These events included pain at the application site or related to the procedure, skin laceration, or erythema. Rates of serious adverse events were almost the same in both groups: 21% in t-PBM and 28% in the sham group [27]. Furthermore, Zivin et al. evaluated the t-PBM in 660 patients with acute ischemic stroke (t-PBM or sham) in a double-blind, randomized study. They used an 808 nm wavelength. The mortality rates, serious adverse events, and adverse events were nearly identical. No serious adverse events were directly attributable to t-PBM. No difference in the safety outcomes between the two groups was found [40].

The present paper, over three cohorts of patients with mood and anxiety disorders, further suggests the good tolerability and safety of t-PBM and extends this notion to repeated sessions with low-dose t-PBM. This is an important finding given the concern that repeated sessions of t-PBM could lead to dose-dependent side effects over time [23]. This is an especially meaningful finding, as clinical improvements for mood and anxiety disorders are more likely to be achieved and maintained with multiple and regular sessions. Overall, very few side effects were reported frequently; some were reported once or twice, such as headaches, strange tastes in the mouth, abnormal sensations, and dizziness when standing up. Interestingly, no impairment in sexual functioning was observed from t-PBM, which is superior to most antidepressant medications from this standpoint [3]. Furthermore, a beneficial effect of t-PBM for sexual functioning has been suggested by our group [41,42].

Our conclusions on the good tolerability of repeated sessions of t-PBM could also extend to high-dose t-PBM, as suggested by a recent RCT on t-PBM for opioid use disorder. In a relatively small sample of 39 subjects with active opioid cravings, despite the high-dose of t-PBM—4 min twice weekly (every 3 to 4 days), 810 nm, with an irradiance of 250 mW/cm² and a fluence of 60 J/cm² to the forehead—no adverse effects were reported [43].

Our study presents several limitations. (1) Age of participants: A statistically significant but not clinically meaningful difference was observed in terms of age. However, the sample was still within a close enough age range (mid 30s to 40s) that analysis could be warranted. Additionally, in regressions controlled for age to determine the impact of variables of interest, age did not significantly account for any variances in either the frequency of adverse events or the probability of occurrence. (2) The wide spectrum in depression severity: This follows the inclusion of participants who had clinical anxiety, but not necessarily clinical depression (LIGHTEN GAD). As such, their information was not included in the calculations of how the change in HAM-D17 scores could affect the number of adverse events or the probability of adverse events occurring. (3) Our sample was fairly homogeneous both racially and ethnically. More research should be performed to investigate the tolerability and safety of t-PBM in a more diverse sample. (4) As current studies on t-PBM for depression and anxiety have included a small number of participants, the absence of statistically significant differences between active and sham treatments could result from limited power to detect these differences. Aiming to address this limitation, we combined data from three studies. However, the total sample size for the current study was still relatively small, and this limitation should be considered when interpreting our results.

5. Conclusions

Our overall finding is that repeated sessions with transcranial NIR for mood and anxiety disorders, delivered at a low dose, appear to be safe and well-tolerated. At low irradiance and a low dose of t-PBM per session, an increase in the total number of sessions (up to daily)—which is potentially necessary to achieve antidepressant and anxiolytic
response—did not translate into higher occurrences of adverse events or a higher probability of experiencing an adverse event.

**Author Contributions:** Conceptualization, P.C. and D.I.; methodology, R.N. and M.A.C.; software, and analysis, P.C., R.N. and M.A.C.; investigation, writing, draft preparation, F.V. (Farzan Vahedifarid), F.V. (Fernando Vizcaino), K.M.M.; —review and editing, P.C. and F.V. (Farzan Vahedifarid); supervision, P.C. and D.I.; project administration, K.M.M.; funding acquisition, P.C. and D.I. All authors have read and agreed to the published version of the manuscript.

**Funding:** There is no specific funding for this study. ELATED-2 was funded by the Harvard Psychiatry Department (Dupont-Warren Fellowship and Livingston Award) and the Brain and Behavior Research Foundation (NARSAD Young Investigator Award; Grant No. 19159. ELATED-3 was funded by LiteCure LLC, and LIGHTEN GAD by Cerebral Sciences Inc.

**Institutional Review Board Statement:** There was no need for IRB approval to conduct an analysis of existing datasets, since the data were deidentified. All used studies were conducted under their IRB approval.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author.

**Conflicts of Interest:** Cassano consulted for Janssen Research and Development and for Niraxx Light Therapeutics Inc. Cassano was funded by PhotoThera Inc., LiteCure LLC, and Cerebral Sciences Inc. to conduct studies on transcranial photobiomodulation. Cassano is a co-founder, shareholder, and board director of Niraxx Light Therapeutics Inc. Cassano has filed several patents related to the use of near-infrared light in psychiatry. Dr. Caldieraro received a research grant from Janssen, unrelated to the current study.

**References**

1. Kessler, R.C.; Berglund, P.; Demler, O.; Jin, R.; Koretz, D.; Merikangas, K.R.; Rush, A.J.; Walters, E.E.; Wang, P.S. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003, 289, 3095–3105. [CrossRef]

2. Ferrari, A.J.; Charlson, F.J.; Norman, R.E.; Patten, S.B.; Freedman, G.; Murray, C.J.; Vos, T.; Whiteford, H.A. Burden of depressive disorders by country, sex, age, and year: Findings from the global burden of disease study 2010. *PLoS Med.* 2013, 10, e1001547. [CrossRef]

3. Cassano, P.; Fava, M. Tolerability issues during long-term treatment with antidepressants. *Ann. Clin. Psychiatry* 2004, 16, 15–25. [CrossRef]

4. Kennedy, S.H.; Lam, R.W.; McIntyre, R.S.; Tourjman, S.V.; Bhat, V.; Blier, P.; Hasnain, M.; Jollant, F.; Levitt, A.J.; MacQueen, G.M.; et al. 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* 2016, 61, 540–560. [CrossRef]

5. Rush, A.J.; Warden, D.; Wisniewski, S.R.; Fava, M.; Trivedi, M.H.; Gaynes, B.N.; Nierenberg, A.A. STAR*D: Revising conventional wisdom. *CNS Drugs* 2009, 23, 627–647.

6. Simoy, M.; Schaffer, A.; Levitt, A. The sequenced treatment alternatives to relieve depression (STAR*D) trial: A review. *Can. J. Psychiatry* 2010, 55, 126–135. [CrossRef]

7. Ferguson, J.M. SSRI antidepressant medications: Adverse effects and tolerability. *Prim. Care Companion J. Clin. Psychiatry* 2001, 3, 22–27. [CrossRef]

8. Bystritsky, A.; Khalsa, S.S.; Cameron, M.E.; Schiffman, J. Current diagnosis and treatment of anxiety disorders. *Pharm. Ther.* 2013, 38, 30–57.

9. Ruscio, A.M.; Hallion, L.S.; Lim, C.C.W.; Aguilar-Gaxiola, S.; Al-Hamzawi, A.; Alonso, J.; Andrade, L.H.; Borges, G.; Bremet, E.J.; Bunting, B.; et al. Cross-sectional comparison of the epidemiology of DSM-5 generalized anxiety disorder across the globe. *JAMA Psychiatry* 2017, 74, 465–475. [CrossRef]

10. Davidson, J.R. First-line pharmacotherapy approaches for generalized anxiety disorder. *J. Clin. Psychiatry* 2009, 70 (Suppl. 2), 25–31. [CrossRef]

11. Cvjetkovic-Bosnjak, M.; Soldatovic-Stajic, B.; Babovic, S.S.; Boskovic, K.; Jovicевич, M. Pregabalin versus sertraline in generalized anxiety disorder. An open label study. *Eur. Rev. Med. Pharmacol. Sci.* 2015, 19, 2120–2124.

12. Baldwin, D.S.; Waldman, S.; Allgulander, C. Evidence-based pharmacological treatment of generalized anxiety disorder. *Int. J. Neuropsychopharmacol.* 2011, 14, 697–710. [CrossRef]

13. Burstyn, O.; Shamir, A.; Abramovitz, N.; Doron, R. Patients' attitudes toward conventional and herbal treatments for depression and anxiety: A cross-sectional Israeli survey. *Int. J. Soc. Psychiatry* 2022, 68, 589–599. [CrossRef]
14. Cassano, P.; Petrie, S.R.; Hamblin, M.R.; Henderson, T.A.; Iosifescu, D.V. Review of transcranial photobiomodulation for major depressive disorder: Targeting brain metabolism, inflammation, oxidative stress, and neurogenesis. *Neurophotonics* 2016, 3, 031404. [CrossRef]

15. Salehpour, F.; Mahmoudi, J.; Kamari, F.; Sadigh-Eteghad, S.; Rasta, S.H.; Hamblin, M.R. Brain photobiomodulation therapy: A narrative review. *Mol. Neurobiol.* 2018, 55, 6601–6636. [CrossRef]

16. Cassano, P.; Cusin, C.; Mischoulon, D.; Hamblin, M.R.; De Taboada, L.; Pisoni, A.; Chang, T.; Yeung, A.; Ionescu, D.F.; Petrie, S.R.; et al. Near-infrared transcranial radiation for major depressive disorder: Proof of concept study. *Psychiatry J.* 2015, 2015, 352979. [CrossRef]

17. Schiffer, F.; Johnston, A.L.; Ravichandran, C.; Polcari, A.; Teicher, M.H.; Webb, R.H.; Hamblin, M.R. 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.* 2009, 5, 46. [CrossRef]

18. Karu, T.I. Molecular mechanism of the therapeutic effect of low-intensity laser irradiation. *Dokl. Akad. Nauk SSSR* 1986, 291, 1245–1249.

19. Mochizuki-Oda, N.; Kataoka, Y.; Cui, Y.; Yamada, H.; Heya, M.; Awazu, K. Effects of near-infra-red laser irradiation on adenosine triphosphate and adenosine diphosphate contents of rat brain tissue. *Neurosci. Lett.* 2002, 323, 207–210. [CrossRef]

20. Oron, U.; Ilic, S.; De Taboada, L.; Streeter, J. Ga-As (808 nm) laser irradiation enhances ATP production in human neuronal cells in culture. *Photomed. Laser Surg.* 2007, 25, 180–182. [CrossRef]

21. Nagafusa, Y.; Okamoto, N.; Sakamoto, K.; Yamashita, F.; Kawaguchi, A.; Higuchi, T.; Matsuda, H. Assessment of cerebral blood flow findings using 99mTc-ECD single-photon emission computed tomography in patients diagnosed with major depressive disorder. *J. Affect. Disord.* 2012, 140, 296–299. [CrossRef]

22. Calderaro, M.A.; Cassano, P. Transcranial and systemic photobiomodulation for major depressive disorder: A systematic review of efficacy, tolerability and biological mechanisms. *J. Affect. Disord.* 2019, 243, 262–273. [CrossRef]

23. Cassano, P.; Petrie, S.R.; Mischoulon, D.; Cusin, C.; Katnani, H.; Yeung, A.; De Taboada, L.; Archibald, A.; Bui, E.; Baer, L.; et al. Transcranial photobiomodulation for the treatment of major depressive disorder. The ELATED-2 pilot trial. *Photomed. Laser Surg.* 2018, 36, 634–646. [CrossRef]

24. Lampl, Y.; Zivin, J.A.; Fisher, M.; Lew, R.; Welin, L.; Dahlof, B.; Borenstein, P.; Andersson, B.; Perez, J.; Caparo, C.; et al. Infrared laser therapy for ischemic stroke: A new treatment strategy: Results of the NeuroThera effectiveness and safety trial-1 (NEST-1). *Stroke* 2007, 38, 1843–1849. [CrossRef]

25. Huisa, B.N.; Stemer, A.B.; Walker, M.G.; Rapp, K.; Meyer, B.C.; Zivin, J.A. Transcranial laser therapy for acute ischemic stroke: A pooled analysis of NEST-1 and NEST-2. *Int. J. Stroke* 2013, 8, 315–320. [CrossRef]

26. Hacke, W.; Schellinger, P.D.; Albers, G.W.; Bornstein, N.M.; Dahlof, B.L.; Fulton, R.; Kasner, S.E.; Shuaib, A.; Richieri, S.P.; Dilly, S.G.; et al. Transcranial laser therapy in acute stroke treatment: Results of neurothera effectiveness and safety trial 3, a phase III clinical end point device trial. *Stroke* 2014, 45, 3187–3193. [CrossRef]

27. Cassano, P.; Cassano, P.; Henderson, T.A. Reported side effects, weight and blood pressure, after repeated sessions of transcranial photobiomodulation. *Photomed. Photobiol. Laser Surg.* 2019, 37, 651–656. [CrossRef]

28. Morries, L.D.; Cassano, P.; Henderson, T.A. Treatments for traumatic brain injury with emphasis on transcranial near-infrared laser phototherapy. *Neuropsychiatr. Dis. Treat.* 2015, 11, 2159–2175.

29. Maiello, M.; Losiewicz, O.M.; Bui, E.; Spera, V.; Hamblin, M.R.; Marques, L.; Cassano, P. Transcranial photobiomodulation with near-infrared light for generalized anxiety disorder: A pilot study. *Photomed. Photobiol. Laser Surg.* 2019, 37, 644–650. [CrossRef]

30. Iosifescu, D.V.; Norton, R.J.; Tural, U.; Mischoulon, D.; Collins, K.; Rette, D.; de Taboada, L.; Foster, S.; Cusin, C.; Yeung, A.; et al. Very low-level transcranial photobiomodulation for major depressive disorder: The ELATED-3 multicenter, randomized, sham-controlled trial. *J. Clin. Psychiatry* 2022; in press.

31. Levine, J.; Schooler, N. A. General versus specific inquiry with SAFFEE. *J. Clin. Psychopharmacol.* 1992, 12, 448. [CrossRef]

32. Sheehan, D.V.; Lecrubier, Y.; Sheehan, K.H.; Amorim, P.; Janavs, J.; Weiller, E.; Hergueta, T.; Baker, R.; Dunbar, G.C. The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* 1998, 59 (Suppl. 20), 22–33.

33. Busner, J.; Targum, S.D. The clinical global impressions scale: Applying a research tool in clinical practice. *Psychiatry* 2007, 4, 28–37.

34. Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 1960, 23, 56–62. [CrossRef]

35. Jobbys-VanderVliet, F.F.; Piantadosi, C.A.; Sylvia, A.L.; Lucas, S.K.; Keizer, H.H. Near-infrared monitoring of cerebral oxygen sufficiency: I. Spectra of cytochrome c oxidase. *Neurol. Res.* 1988, 10, 7–17. [CrossRef]

36. Barrett, D.W.; Gonzalez-Lima, F. Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience* 2013, 230, 13–23. [CrossRef]

37. Fava, M.; Evins, A.E.; Dorer, D.J.; Schoenfeld, D.A. The problem of the placebo response in clinical trials for psychiatric disorders: Culprits, possible remedies, and a novel study design approach. *Psychother. Psychosom.* 2003, 72, 115–127. [CrossRef]

38. Morris, D.W.; Budhwar, N.; Husain, M.; Wisniewski, S.R.; Kurian, B.T.; Luther, J.F.; Kerber, K.; Rush, A.J.; Trivedi, M.H. Depression treatment in patients with general medical conditions: Results from the CO-MED trial. *Ann. Fam. Med.* 2012, 10, 23–33. [CrossRef]
39. Ma, Y.; Balasubramanian, R.; Pagoto, S.L.; Schneider, K.L.; Hebert, J.R.; Phillips, L.S.; Goveas, J.S.; Culver, A.L.; Olendzki, B.C.; Beck, J.; et al. Relations of depressive symptoms and antidepressant use to body mass index and selected biomarkers for diabetes and cardiovascular disease. *Am. J. Public Health* 2013, 103, e34–e43. [CrossRef]

40. Zivin, J.A.; Albers, G.W.; Bornstein, N.; Chippendale, T.; Dahlof, B.; Devlin, T.; Fisher, M.; Hacke, W.; Holt, W.; Ilic, S.; et al. Effectiveness and safety of transcranial laser therapy for acute ischemic stroke. *Stroke* 2009, 40, 1359–1364. [CrossRef]

41. Salehpour, F.; Khademi, M.; Vahedifard, F.; Cassano, P. Transcranial photobiomodulation therapy for sexual dysfunction associated with depression or induced by antidepressant medications. *Photonics* 2022, 9, 330. [CrossRef]

42. Cassano, P.; Dording, C.; Thomas, G.; Foster, S.; Yeung, A.; Uchida, M.; Hamblin, M.R.; Bui, E.; Fava, M.; Mischoulon, D.; et al. Effects of transcranial photobiomodulation with near-infrared light on sexual dysfunction. *Lasers Surg. Med.* 2019, 51, 127–135. [CrossRef]

43. Schiffer, F.; Khan, A.; Bolger, E.; Flynn, E.; Seltzer, W.P.; Teicher, M.H. An effective and safe novel treatment of opioid use disorder: Unilateral transcranial photobiomodulation. *Front Psychiatry* 2021, 12, 713686. [CrossRef]