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# Flickering 60-Hz white light stimulation for major depressive disorder: results from a phase two open-label clinical trial

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**Flickering 60-Hz white light stimulation for major depressive disorder: results from a phase two open-label clinical trial**

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**ABSTRACT**

**Objective**: Non-invasive sensory stimulation offers a potentially scalable way to modulate brain activity in depression. We evaluated the safety, tolerability, and feasibility of repeated 60 Hz flickering white-light stimulation, delivered via a wearable headset, as an adjunct to stable pharmacotherapy in adults with mild-to-moderate major depressive disorder (MDD).

**Methods**: In this single-centre, open-label, single-arm feasibility trial, 31 adults meeting DSM-5 criteria for a current mild-to-moderate depressive episode (27 comprising the full analysis set) received ten 30-minute sessions of 60 Hz flickering white light over two weeks. The primary outcomes were safety and tolerability, assessed by a per-session adverse-event questionnaire, monitoring for (hypo)mania, and formal ophthalmological examination including optical coherence tomography. Depressive and anxiety symptoms were exploratory outcomes, analysed with linear mixed-effects models.

**Results**: No serious adverse events, seizures, or (hypo)manic switches occurred, and ophthalmological examination showed no structural change attributable to the intervention. The most common adverse events — eye strain, drowsiness, and dry eyes — were transient and declined from Week 1 to Week 2; retention was 85% (23/27), all withdrawals unrelated to the intervention. As exploratory outcomes, depressive and anxiety symptoms decreased across all scales from baseline to session 10 (all $p < 0.0001$); HDRS-17 response and remission were each 55.5% at session 10. Continuous scores were largely maintained at follow-up, although categorical remission declined (HDRS-17 33.3% at 6 weeks).

**Conclusions**: Adjunctive 60 Hz flickering white-light stimulation was safe, well-tolerated, and feasible in mild-to-moderate MDD. The exploratory symptom improvements cannot be attributed to the intervention in this uncontrolled design and require confirmation in randomized, sham-controlled trials. ClinicalTrials.gov NCT06922812.

Key Words: major depressive disorder; flickering light stimulation; neuromodulation; safety; feasibility; adjunct treatment

## 1. Introduction

Major depressive disorder (MDD) ranks second among causes of years lived with disability worldwide [1]. First-line pharmacotherapy achieves remission in fewer than one third of patients after an adequate trial, requires several weeks to take effect, and carries adverse effects that limit adherence [2]. Non-invasive brain stimulation has since entered the treatment repertoire - repetitive transcranial magnetic stimulation, transcranial direct-current stimulation, and electroconvulsive therapy among them (Janicak et al., 2010; Brunoni et al., 2017) - yet each remains constrained in efficacy, which varies across patients and settings; in safety, as electroconvulsive therapy is delivered under general anaesthesia and the remaining methods have their own tolerability and contraindication profiles; and in accessibility, as delivery depends on dedicated devices, clinical facilities, and trained operators. These issues motivate the development of mechanistically distinct, non-pharmacological adjuncts.

Non-invasive sensory stimulation has emerged as one such approach. Rhythmic external stimuli can entrain endogenous neural oscillations, particularly in the gamma band (30–80 Hz), which is implicated in attention, executive function, and the pathophysiology of several neuropsychiatric disorders [3–5]; ., For instance, 40 Hz multi-modal audiovisual stimulation reduces amyloid burden and rescues memory through microglia-mediated mechanisms [6, 7]in Alzheimer's disease models. In MDD, Venturino and colleagues demonstrated that 60 Hz - but not 8 Hz, 40 Hz, or constant - light entrainment triggers microglia-dependent disassembly of perineuronal nets surrounding parvalbumin interneurons, reinstating juvenile-like cortical plasticity in adult mice through a mechanism that parallels the effects of ketamine [8]. Restoration of cortical plasticity is a central candidate mechanism of rapid-acting antidepressant response, raising the possibility that 60 Hz visual entrainment could engage a therapeutically relevant pathway non-invasively.

However, evidence in clinical populations is scarce. To date, a recent study using a wearable headset documented robust, widespread cortical entrainment and inter-regional synchronisation during 60 Hz flickering white-light stimulation in healthy volunteers, with preliminary signs of post-stimulation neuroplastic change [9], with absent clinical data in MDD samples. We therefore conducted an open-label study evaluating the safety, tolerability, and feasibility of ten sessions of 60 Hz flickering white-light stimulation, delivered via a wearable headset over two weeks as an adjunct to stable antidepressant pharmacotherapy in adults with mild-to-moderate MDD. The primary endpoints were safety and tolerability, including formal ophthalmological assessment; changes in depressive and anxiety symptoms, response, and remission were evaluated as exploratory outcomes.

## 2. Methods

### *2.1. Study Design*

The LUX trial was a single-centre, open-label, single-arm feasibility study conducted at the Instituto de Psiquiatria do Hospital da Clínicas da Faculdade de Medicina da Universidade de São Paulo (IPq-HCFMUSP), São

Paulo, Brazil, from May 2025 to January 2026. The study was approved by the local Institutional Review Board and the Brazilian National Ethics Committee (CAAE 84990324.7.0000.0068) and was registered at ClinicalTrials.gov (NCT06922812). All participants provided written informed consent prior to enrollment. The trial was conducted in accordance with the Declaration of Helsinki and Brazilian data protection law.

Volunteers enrolled through an online platform, were screened by a psychiatrist against the eligibility criteria and, if eligible, underwent an ophthalmological evaluation; those without contraindications proceeded to baseline assessment and then to the ten-session protocol. Assessments were repeated at sessions 5 and 10 and at 4- and 6-week follow-up. The protocol (Supplementary Material) was followed without major changes.

*2.2. Participants*

Eligible participants were adults aged 18-59 years with a DSM-5 [10] diagnosis of a current mild-to-moderate major depressive episode, confirmed by a certified psychiatrist using the Mini International Neuropsychiatric Interview (MINI) (Amorim, 2000). As an inclusion criterion, patients were required to have scores ranging from 8 to 23 on the Hamilton Depression Rating Scale (HDRS-17) [11]. Participants were on a stable pharmacological regimen for at least six weeks before enrollment, unchanged during the trial.

Exclusion criteria were treatment-resistant depression (two or more failed adequate antidepressant trials in the current episode) , current suicide ideation, other psychiatric disorders (bipolar disorder, schizophrenia, substance use disorders, dementia), personality disorders, neurological conditions, pregnancy, and contraindications specific to flickering light (personal or family history of epilepsy or photosensitive seizures, migraine, photosensitivity, and tinnitus). Ophthalmological exclusions comprised history of ocular changes that predispose to light toxicity, such as retinal and optic neuropathies, as well as conditions that might reduce light transmission to the retina, such as corneal opacities, dense cataracts and vitreous opacities. Regular use of anti-inflammatory agents or clopidogrel was also exclusionary, as these may interfere with microglial activation, a postulated mechanism of the intervention.

*2.3. Intervention*

Participants received 10 30-minute sessions of 60 Hz flickering white-light stimulation, delivered once daily on consecutive weekdays. Each session was held in a dimly lit room with a staff member present; participants sat in a neck-supported chair and kept their eyes open, fixating a wall marker.

Stimulation was delivered via the LENS v1.0 system, a custom wearable device comprising an open-frame ocular headset and an external controller, powered by a 10 Ah portable battery. The light source was a white LED strip (correlated colour temperature ≈ 4259 K, nominal 4500 K) mounted in the headset behind a transparent

cover, with the open frame preserving direct line of sight during stimulation. Stimulation was delivered at 60 Hz with a 50% duty cycle (rise time 2 ms, fall time 3 ms). Optical characterisation at maximum brightness, performed at a 2 cm eye distance with a calibrated GL Optic Spectis 1.0 Touch + Flicker spectrometer, yielded a peak irradiance of $1.13 \times 10^{-2}$ W·m$^{-2}$ and a radiance of $5.76 \times 10^{-2}$ W·m$^{-2}$·sr$^{-1}$. The estimated corneal-plane illuminance was approximately 3.4 lux, reflecting the device geometry rather than the intrinsic LED brightness. Full hardware and firmware specifications are provided in the Supplementary Material.

*2.4 Assessments*

Depressive symptoms were measured with HDRS-17 [11], Montgomery–Åsberg Depression Rating Scale [12], and Beck Depression Inventory-II [13] anxiety with the Hamilton Anxiety Rating Scale [13] global severity with the Clinical Global Impression-Severity [14] treatment-emergent (hypo)mania with the Young Mania Rating Scale [15] and sleep quality with the Pittsburgh Sleep Quality Index [16], with PSQI >5 indicating clinically significant disturbance.

Tolerability was assessed after each session with a structured 11-item adverse-event questionnaire rated on a 4-point severity scale (adapted from Brunoni et al., 2011), because no validated adverse event questionnaire is currently available for light stimulation, we adapted the standardized adverse event questionnaire originally developed for transcranial direct current stimulation (tDCS). This instrument has been previously used by our research group and provides a comprehensive assessment of a wide range of potential adverse effects associated with NIBS.

An experienced ophthalmologist assessed best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure, dilated fundoscopy, fundus autofluorescence (FAF) of the posterior pole, and optical coherence tomography (OCT; sectoral retinal nerve fibre layer thickness, macular central thickness, macular volume, ganglion cell layer thickness). Ocular-surface symptoms were measured with the Ocular Surface Disease Index (OSDI) [17]; scores >12 indicate clinically significant ocular surface disease.

Assessments were administered at baseline, sessions 5 and 10, and 4- and 6-week post-treatment follow-up, except: OSDI at baseline, session 10, and 6-week follow-up; PSQI at baseline and 4-week follow-up; ophthalmological examination and OCT at baseline and 6-week follow-up; and the adverse-event questionnaire after each of the ten sessions. Trained raters administered all scales, with CGI-S scored blinded to session number. Data were captured in REDCap [18, 19]

*2.5 Outcomes*

The primary outcomes were safety and tolerability. Safety was operationalised as the occurrence of serious adverse events, treatment-emergent seizures, treatment-emergent (hypo)manic switches (monitored by YMRS at every assessment timepoint), structural ophthalmological change (best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure, dilated fundoscopy, fundus autofluorescence, and OCT-derived RNFL, macular central thickness, macular volume, and GCL thickness), and treatment discontinuation due to adverse events. Tolerability was operationalised as (i) the occurrence and severity (mild, moderate, severe) of eleven prespecified adverse-event items, evaluated at the session level. This analysis was restricted to events deemed at least possibly related to the intervention (relatedness score ≥ 2 on a 0–4 scale); (ii) the within-patient incidence of these related events comparing Week 1 versus Week 2 of treatment; (iii) the mean number of distinct treatment-related adverse events per participant per session, characterising within-session burden over the treatment course; and (iv) change in the OSDI score from baseline, with abnormal ocular-surface status defined a priori as OSDI >12.

The exploratory efficacy outcomes were the change from baseline to session 10 in HDRS-17 (principal efficacy outcome), MADRS, BDI-II, HAM-A, and CGI-S, with the same contrasts evaluated at the 4- and 6-week post-treatment follow-ups. Clinical response was defined a priori as a ≥50% reduction from baseline on the HDRS-17 or MADRS, and remission as HDRS-17 ≤7 or MADRS ≤10. Sleep quality was evaluated as the change in PSQI Global Score from baseline to 4-week follow-up, with the proportion of poor sleepers (PSQI >5) reported as a complementary categorical endpoint.

*2.6 Statistical analysis*

Analyses used the full analysis set and were conducted in R (v4.5); all tests were two-sided with $\alpha = 0.05$. As a feasibility pilot, no formal sample-size or power calculation was performed; the target enrollment was determined by feasibility considerations. Baseline characteristics of completers and non-completers were compared with Wilcoxon rank-sum and Fisher's exact tests. Missingness was evaluated with Little's MCAR test and robustness to the missing-data mechanism was assessed through the multiple-imputation sensitivity analysis, which relies on the missing-at-random assumption. Safety outcomes were summarised descriptively. Paired Wilcoxon signed-rank tests,

applied to per-participant eye averages, compared baseline and end-of-study OCT and OSDI values; Spearman correlations related baseline OSDI to eye-related adverse-event severity.

*Efficacy.* Change in each clinical scale was modelled with linear mixed-effects models (LMM) including timepoint as a fixed effect and a random intercept per participant (REML; bobyqa optimiser), with Holm step-down correction of timepoint contrasts within each scale and Kenward–Roger degrees-of-freedom adjustment. The primary effect metric was the raw mean change from baseline at each timepoint. Standardised effect sizes (Cohen's d) were reported secondarily and computed using emmeans [20], scaling each baseline-versus-timepoint contrast by the total model-implied standard deviation, $\sigma_total = \sqrt{(\sigma^2_participant + \sigma^2_residual)}$, rather than the residual SD alone. Confidence intervals are inherited from the underlying contrast standard errors via the Kenward-Roger adjustment. Friedman tests with paired Wilcoxon post-hocs provided non-parametric verification in the complete-case subset. PSQI change was analysed by paired Wilcoxon signed-rank test and the proportion of poor sleepers by McNemar's test.

*Sensitivity.* Four prespecified sensitivity analyses assessed robustness of the efficacy results: LMM restricted to completers; baseline-covariate-adjusted LMM (including baseline HDRS-17 as a fixed effect) to address regression to the mean; and multiple imputation (MICE, m = 20, predictive mean matching) to evaluate sensitivity to the missing-at-random assumption; and refitting each model with an unstructured (MMRM-type) within-participant covariance and, where estimable, an additional random slope for time, to verify insensitivity to the assumed covariance structure.

*Exploratory.* Prespecified hypothesis-generating analyses comprised Spearman correlations among baseline scales, sex-by-timepoint LMM interactions for HDRS-17 and MADRS, a logistic regression of session-10 HDRS-17 response on sex, age, baseline severity, and history of prior episodes, and generalised estimating equations testing whether eight baseline ophthalmological predictors (RNFL Superior and Inferior, macular central thickness, macular volume, GCL Superior and Inferior, optic-nerve abnormality as a binary variable, baseline OSDI) moderated the antidepressant trajectory (64 interaction tests; Benjamini–Hochberg FDR correction). Given small subgroup sizes and multiplicity, GEE results are reported in the Supplementary Material.

## 3. Results

### *3.1. Participants*

Of 183 prescreened volunteers, 31 participants were enrolled between May 2025 and January 2026 (Figure 1). Two participants were excluded after the ophthalmological evaluation due to a retinal tear and amblyopia and two

withdrew from the study prior to baseline assessment. Four participants did not complete the study; all withdrew for personal reasons (e.g., scheduling conflicts, relocation) unrelated to the intervention.

The final full analysis sample included 27 participants (mean age 37.56 years; 74% female; 85% White), of whom 23 (85.19%) completed all study visits (Table 1). Mean baseline HDRS-17 was 16.89 (SD 3.14), MADRS 23.07 (SD 5.62), and BDI-II 22.19 (SD 6.99); mean HAM-A was 22.85 (SD 9.08). The number of observations contributing to each analysis varied by timepoint and instrument owing to the study design and ordinary attrition. Assessments on reduced schedules contributed fewer observations: PSQI (baseline and 4-week follow-up only), OSDI (baseline, Session 10, and 6-week follow-up only), and the ophthalmological/OCT examination (baseline and 6-week follow-up only). Paired ophthalmological analyses were further limited to participants with complete baseline and end-of-study eye data (OCT n = 21; paired OSDI n = 17). Completers and dropouts did not differ on any baseline measure (Table S1). Missing data were compatible with missing-completely-at-random (Little's MCAR $\chi^2(111) = 107$, $p = 0.59$).

*3.2. Safety and Tolerability*

*Adverse events:* The intervention was well-tolerated. No serious adverse events (AEs) were reported. No seizures were reported in any participant across any of the 10 sessions. No (hypo)manic switches occurred on the YMRS throughout the study. The most commonly reported adverse events during the first week of treatment were eye strain (59.3%), session-related somnolence (59.3%), headache (44.4%), and dry eyes (44.4%). The incidence of ocular side effects decreased across sessions: patient-reported eye strain fell from 59.3% in Week 1 to 26.1% in Week 2 ($p = 0.013$), and dry eyes decreased from 44.4% to 21.7% ($p = 0.041$). Other common events, such as headache and session-related somnolence, remained statistically stable across the two weeks (Table 2, Figure 3). Mean number of distinct AEs per patient per session ranged from 1.78 to 2.50, without upward trend across the 10 sessions (Figure S3), suggesting no cumulative tolerability burden.

*Ophthalmological safety - OCT:* Twenty-one patients had paired baseline and end-of-study OCT and no structural changes were noted on qualitative clinical review (0/21) (Table 3). Retinal nerve fibre layer thickness, macular central thickness, and macular volume were unchanged (all $p \geq 0.066$). Ganglion-cell layer inferior thickness showed a small statistically significant increase (98.5 → 100.3 µm; $d = 0.49$, $p = 0.034$), a finding of the opposite direction to neurodegeneration and well within published test-retest variability. There were no changes in ophthalmological examination such as BCVA, biomicroscopy, FO and FAF, at 6-week timepoint. Intraocular pressure showed a small but statistically significant decrease, likely reflecting measurement variability rather than a clinically meaningful change. Four patients (14.8) had idiopathic mild temporal optic-nerve pallor with no visual repercussion (incidental finding) at baseline fundoscopy, no changes after the treatment were observed. *Ocular surface - OSDI:* Mean OSDI scores decreased across timepoints (baseline 12.80, Session 10 9.49,

6-Week FU 4.72), with abnormal values (> 12) falling from 40.0% to 11.0% of patients (Figure 2). The paired comparison BL vs Session 10 was not statistically significant (W = 41.0, p = 0.91, d = 0.04), reflecting both the small paired sample (n = 17) and the fact that the steeper decline occurred by the 6-week follow-up. Baseline OSDI was correlated with eye-related adverse-event severity (Spearman ρ = 0.49, p = 0.012), suggesting patients with pre-existing ocular surface disease were more likely to report eye strain or dry eyes during stimulation.

*3.3. Efficacy*

Shapiro–Wilk testing indicated that 7 of 27 outcome–timepoint distributions deviated from normality (Supplementary Figure S6), most notably the CGI-S (an ordinal scale with few discrete levels) and later-timepoint depression scores affected by floor effects as symptoms remitted. Because deviations were limited and the primary depression scales (HDRS-17, MADRS) were approximately normal at all timepoints, the mixed-effects models were retained as the primary analysis, with non-parametric Friedman and Wilcoxon tests serving as a confirmatory check. Linear mixed-effects models showed symptom reductions across HDRS-17, MADRS, BDI-II, HAM-A, and CGI-S (Table S2; Figure S2), while sleep quality (PSQI), analyzed separately using a paired Wilcoxon test, also showed a significant improvement at follow-up (Table S2; Figure S2). On HDRS-17, mean score fell from 16.89 at baseline to 6.65 at Session 10 (Δ = −10.09, SE = 0.91, $t(91) = -11.03$, Holm $p < 0.0001$; Cohen's d = 2.35, 95 % CI [1.82, 2.89]). Comparable reductions were observed for MADRS (Δ = −14.43, d = 2.26 [1.75, 2.76]), BDI-II (Δ = −11.61, d = 1.69 [1.28, 2.10]), HAM-A (Δ = −13.51, d = 1.77 [1.32, 2.22]), and CGI-S (Δ = −1.35, d = 1.31 [0.80, 1.81]). All follow-up contrasts remained significant at $p < 0.0001$ with no evidence of relapse between Session 10 and Week 6 (all pairwise |d| ≤ 0.59). PSQI Global Score decreased from 8.91 (SD 3.04) at baseline to 6.17 (SD 2.35) at 4-week follow-up (Wilcoxon signed-rank W = 32.5, p = 0.004; Cohen's d = 1.01, 95% CI [0.37, 1.64]). The proportion of poor sleepers (PSQI > 5) fell from 87.0% to 56.5% (McNemar's $\chi^2 = 5.00$, p = 0.025). PSQI at baseline correlated with baseline HAM-A (ρ = 0.63, p = 0.001), HDRS-17 (ρ = 0.48, p = 0.021) and BDI-II (ρ = 0.44, p = 0.034), supporting a sleep-anxiety-depression triad.

At Session 10, 55.5% of patients met HDRS-17 response criteria (95% CI 37.3–72.4) and 55.5% met remission (95% CI 37.3–72.4); corresponding MADRS rates were 62.9% (95% CI 44.2–78.5) and 59.2% (95% CI 40.7–75.5). At the 6-week follow-up, response rates were 40.7% (HDRS-17, 95% CI 24.5–59.3) and 44.4% (MADRS, 95% CI 27.6–62.7), with remission rates of 33.3% (95% CI 18.6–52.2) on both scales.

Gains achieved at session 10 were sustained at follow-up visits. The differences between session 10 and 4-week follow-up (HDRS-17 −0.1 points) and between session 10 and 6-week follow-up (+1.3 points) were not statistically significant (both 95% CIs crossing zero), indicating no statistically meaningful relapse during the 6-week observation period. Categorical outcomes, however, showed some attenuation over

the same interval: HDRS-17 remission declined from 55.5% at Session 10 to 33.3% at 6 weeks, and MADRS response from 62.9% to 44.4%. Thus, while mean symptom levels were maintained, the proportion of participants meeting response and remission thresholds decreased at later follow-up.

*3.4. Sensitivity Analyses*

Results from the completers set analysis (n = 23 completers) were consistent with the intent-to-treat LME in both direction and magnitude across all five scales. The estimated HDRS-17 reductions from baseline in the completers-only model were −10.22 (SE = 0.91) at Session 10 and −10.28 (SE = 0.92) at the 4-week follow-up (both p < 0.0001), closely mirroring the primary analysis. The baseline-covariate-adjusted model (including HDRS-17 at baseline as a fixed effect) yielded estimates virtually identical to the unadjusted model, indicating that baseline severity did not confound the primary findings. Multiple imputation-based pooled means were indistinguishable from observed-case means (HDRS-17: 6.73 [SD 0.36] at session 10; 8.29 [SD 0.67] at 6 weeks), further supporting robustness to missing data. Finally, refitting each model with an unstructured (MMRM) within-participant covariance left the baseline-versus-timepoint estimates essentially unchanged (maximum absolute difference 0.40 points across all scales and timepoints), with comparable standard errors (ratio 0.83–1.39 relative to the primary model) and no change to the statistical significance of any contrast; random-slope specifications were singular for HDRS-17 and CGI-S and non-estimable for PSQI, consistent with the limited sample size.

**Baseline Scale Intercorrelations and Subgroup Analyses**

Spearman correlations among baseline scale scores were moderate to strong for the four depression/anxiety instruments (r = 0.47–0.67, all p < 0.05), with the exception of the correlation between the HDRS-17 and BDI-II (r = 0.32, p = 0.14), confirming adequate convergent validity overall. The CGI-S showed weaker, non-significant correlations with the other measures (r = 0.12–0.40, all p > 0.05), consistent with the known clinician-versus-patient perspective gap. No significant sex-by-timepoint interaction was identified for either HDRS-17 (F[4, 83.1] = 0.53, p = 0.72) or MADRS (F[4, 84.1] = 1.01, p = 0.41), suggesting that the intervention effect did not differ by sex. A logistic regression model predicting HDRS-17 response at session 10 from sex, age, baseline severity, and history of prior episodes showed no statistically significant predictors (all p > 0.30), though the analysis was limited by sample size (n = 24).

**Discussion**

To date, the LUX study provides an early evaluation of the safety and feasibility of 60 Hz flickering white light stimulation in mild-to-moderate MDD. The treatment was safe and well-tolerated overall, and side effects were mild to moderate, with no severe or life-threatening events. Exploratory efficacy analyses showed reductions in depressive and anxiety symptoms with high response and remission rates; given the uncontrolled design, these signals cannot be attributed to the intervention. The primary safety and tolerability outcomes were favourable. The findings show a consistent pattern of clinical improvement alongside a favourable safety profile, documented by dedicated ophthalmological assessment.

Because the intervention delivers repeated flickering light to the retina, ocular safety was a primary concern and was assessed with dedicated ophthalmological examination and optical coherence tomography at baseline and after treatment. No clinically relevant structural change was attributable to the stimulation. The few statistically significant findings - a small increase in inferior ganglion-cell-layer thickness and a small decrease in intraocular pressure - fell within the published test–retest variability and, for the retinal measure, ran opposite to the direction expected of injury.

Research leveraging the visual system to probe the pathophysiology of neuropsychiatric disorders [21] and to identify biomarkers [22] has become increasingly common, and visual interventions are increasingly explored as potential treatments.Studies using bright light therapy (BLT) have demonstrated efficacy in the treatment of seasonal depression [23, 24]. BLT primarily targets the circadian system by activating specific retinal photoreceptors, reducing melatonin secretion, and elevating serotonin levels; it may also modulate amygdala-thalamocortical circuits and serotonergic pathways [23, 25]. Nevertheless, its effectiveness in non-seasonal depression appears to be more modest [26, 27].

Beyond conventional bright light therapy, interest is growing in intermittent sensory stimulation approaches designed not only to modulate circadian rhythms, but also to directly entrain neural activity and induce neuroplasticity. However, clinical data on flickering light stimulation in non-seasonal depression remain scarce.

Recently, Sakalauskaitė et al. published the FELIX study design that will use 40 Hz masked flickering light for patients diagnosed with MDD [28],although efficacy results are not yet available. The rationale for 60 Hz frequency-specific flickering stimulation is supported by preclinical studies linking gamma-frequency entrainment to cortical plasticity mechanisms implicated in antidepressant response. Venturino et al. (2021) demonstrated that repeated anesthetic-dose ketamine causes rapid, widespread loss of perineuronal nets (PNNs) around parvalbumin-positive interneurons and reinstates juvenile-like cortical plasticity in adult mice; this PNN removal is mediated by microglia.The authors further demonstrate that entraining cortical activity with 60 Hz light flicker reproduces the microglia-dependent PNN dismantling, but 8 Hz, 40 Hz or constant light do not. Microglial depletion or blocking microglial nucleotide sensing prevents PNN loss, supporting a causal role for microglia in activity-driven extracellular matrix remodeling [8]. These findings suggest that ketamine’s rapid antidepressant effects may partly arise from

reopening windows of cortical plasticity and that 60 Hz sensory entrainment could represent a non-pharmacological strategy to engage similar neuroplastic mechanisms without the systemic risks of ketamine.
Supporting this mechanistic framework, a recent in vivo electrophysiology study demonstrated that 60 Hz light flickering promotes ocular dominance plasticity through a reduction in synaptic strength mediated by microglia-dependent remodeling of PNN in mice. In contrast, 40 Hz entrainment induced synaptic strengthening via a distinct unknown mechanism that appears to be independent of microglia-mediated PNN remodeling [29]

These observations motivate light-based interventions that extend beyond conventional circadian mechanisms to directly target neural activity. In particular, 60 Hz light flicker stimulation has emerged as a promising approach to modulate brain oscillations and associated cognitive and affective processes.

**Limitations**

The present study limitations include: (1) due to the open label design and the absence of a control group, we cannot exclude response bias and placebo effects (2) our study was single-centre, limiting the generalization of the findings (3) small sample size limits statistical power and precision, particularly for subgroup and exploratory analyses. Nevertheless, regarding the safety data, the treatment did not cause any structural eye damage and the side effects such as eye dryness and eye strain were transient. While the open-label design precludes disentangling the intervention effect from expectancy and therapeutic attention, several features argue against a purely placebo-driven response: rapid onset by session 5, sustained gains at 6-week follow-up, and convergence across clinician-rated and self-report measures. These features are encouraging but do not exclude expectancy or spontaneous improvement; a sham-controlled trial is required to estimate the true effect.Most patients had at least mild dry eye according to the OSDI scale before the treatment. We did not mandate routine use of artificial tears to avoid introducing bias; their use was left to clinicians' discretion for individual cases. For future studies, however, we will recommend artificial tears for participants with a prior history of dry eye.

**Conclusion**

This protocol, which was intended to be applicable in real-world settings of mental health care, was safe in adults with mild-to-moderate depression. Our study introduces a possible new non-invasive brain stimulation (NIBS) treatment, expanding the strategies available for MDD. For this trial, patients underwent treatment under the supervision of the clinical team; however, the device is portable and could, in principle, be used as a home-based therapy. Also, the protocol is compatible with most outpatient routines, allowing patients to maintain their daily activities while attending only a 30-minute session per day.

By establishing the safety and tolerability of the protocol, this study supports larger, placebo-controlled, multicentre trials.

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**Authors contributions**

The first and last author, Pelosof and Vidal, vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first and second author initially drafted and later wrote the manuscript with contributions from all the authors. Authors Carneiro, Vidal, Silva, Fontenelle, Pelosof, Malfatti, Gruenwald, Batista and Tolentino contributed to the acquisition of data and evaluations of participants throughout the study; authors Gruenwald, Tolentino, Pelosof, Batista and Fontenelle contributed with the application of the stimulation procedures; statistical analysis was conducted by Santos and Brunoni. The study design was conceived by author Vidal. All authors provided critical feedback and agreed with the final version of the manuscript.

**Competing interests**

**Role of the Funder**

Syntropic Medical GmbH provided financial support for this study. The funder had no role in the study design, data collection, statistical analysis, interpretation of the results, or the decision to publish the manuscript. Statistical analyses were performed independently by the academic authors. The funder reviewed the study and the manuscript but did not influence the scientific conclusions.

No promotional content is intended. The authors report no relevant equity interests or consulting relationships, unless otherwise disclosed. MA, FL, and MTF are employees of Syntropic Medical. AV disclosed an international patent application (PCT/EP2020/079365). AV is a co-founder of Syntropic Medical GmbH. MTF has received consulting and speaking fees from Angelini Pharma and Prodeco in the previous two years, unrelated to the current project.

**Data Availability Statement**

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to participant privacy and confidentiality considerations.


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## Figures and Tables

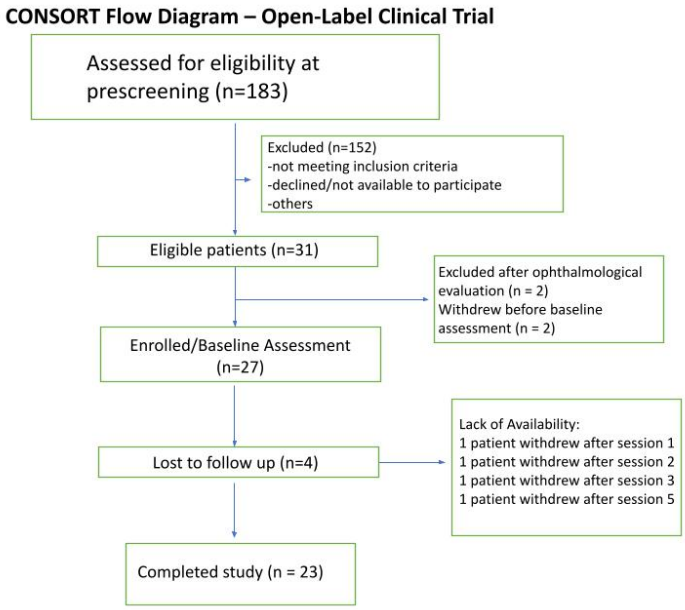



**Figure 1. CONSORT flow Diagram - Open Label Clinical Trial**

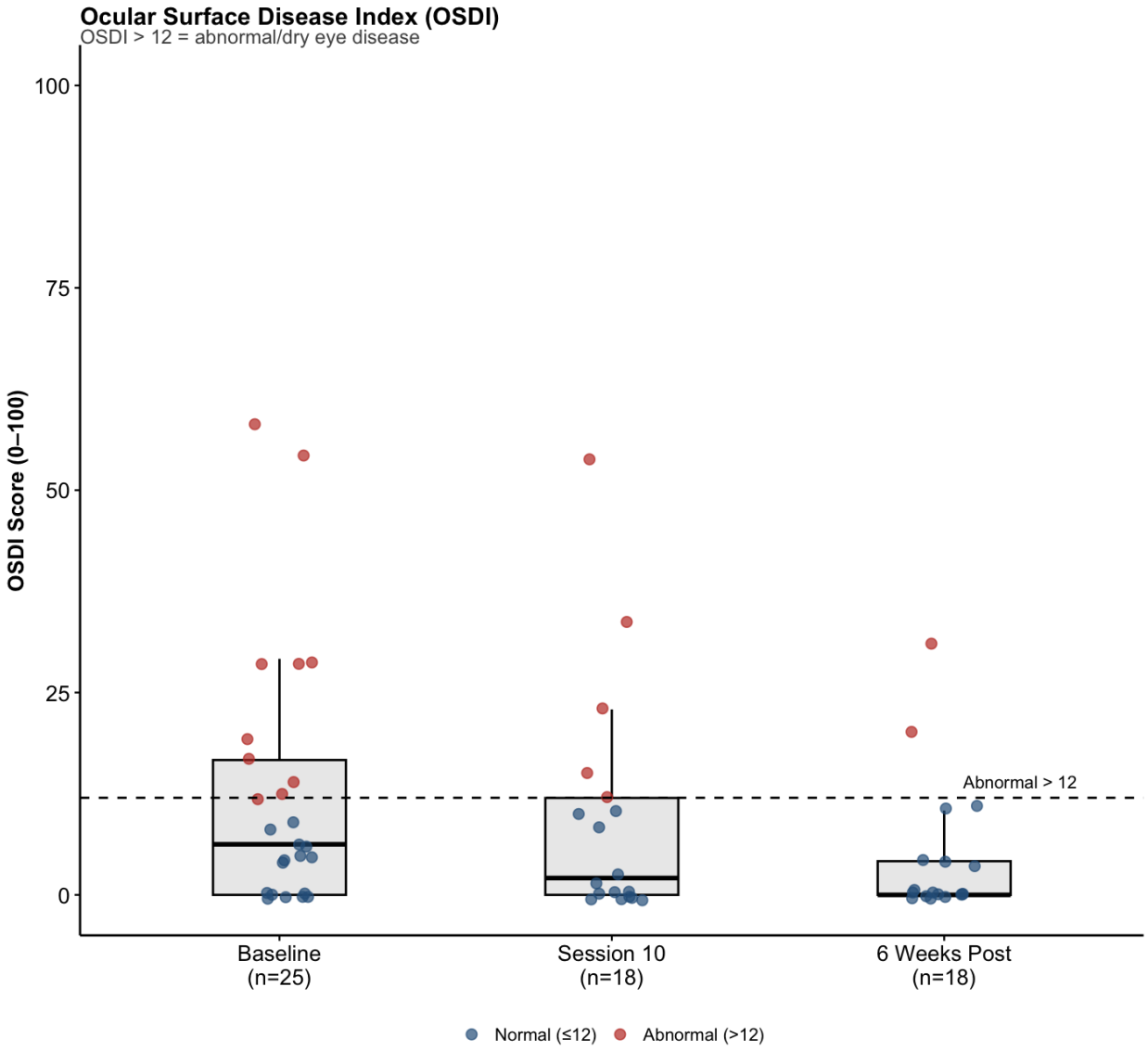



**Figure 2. Ocular Surface Disease Index (OSDI) across study timepoints.**

Box-and-whisker plots show OSDI Global Score distributions at Baseline (n = 25), Session 10 (n = 18), and 6-Week Follow-Up (n = 18). Boxes indicate the median and interquartile range; whiskers extend to 1.5 × IQR. Individual patients are shown as jittered points and colour-coded by ocular-surface status: blue, normal (≤ 12); red, abnormal (> 12). The horizontal dashed line marks the OSDI cut-off of 12, above which scores indicate clinically significant ocular surface disease.[1] The

proportion of patients with abnormal OSDI declined progressively across timepoints (40.0 % at Baseline, 28.0 % at Session 10, 11.0 % at 6-Week FU). The paired comparison Baseline vs Session 10 (n = 17) was not statistically significant (Wilcoxon W = 41.0, p = 0.91, Cohen's d = 0.04), reflecting the small paired sample and the fact that the larger reduction emerged only at the 6-week follow-up.

[1] OSDI severity bands: 0–12 normal, 13–22 mild, 23–32 moderate, > 32 severe (Schiffman et al., Arch Ophthalmol 2000).

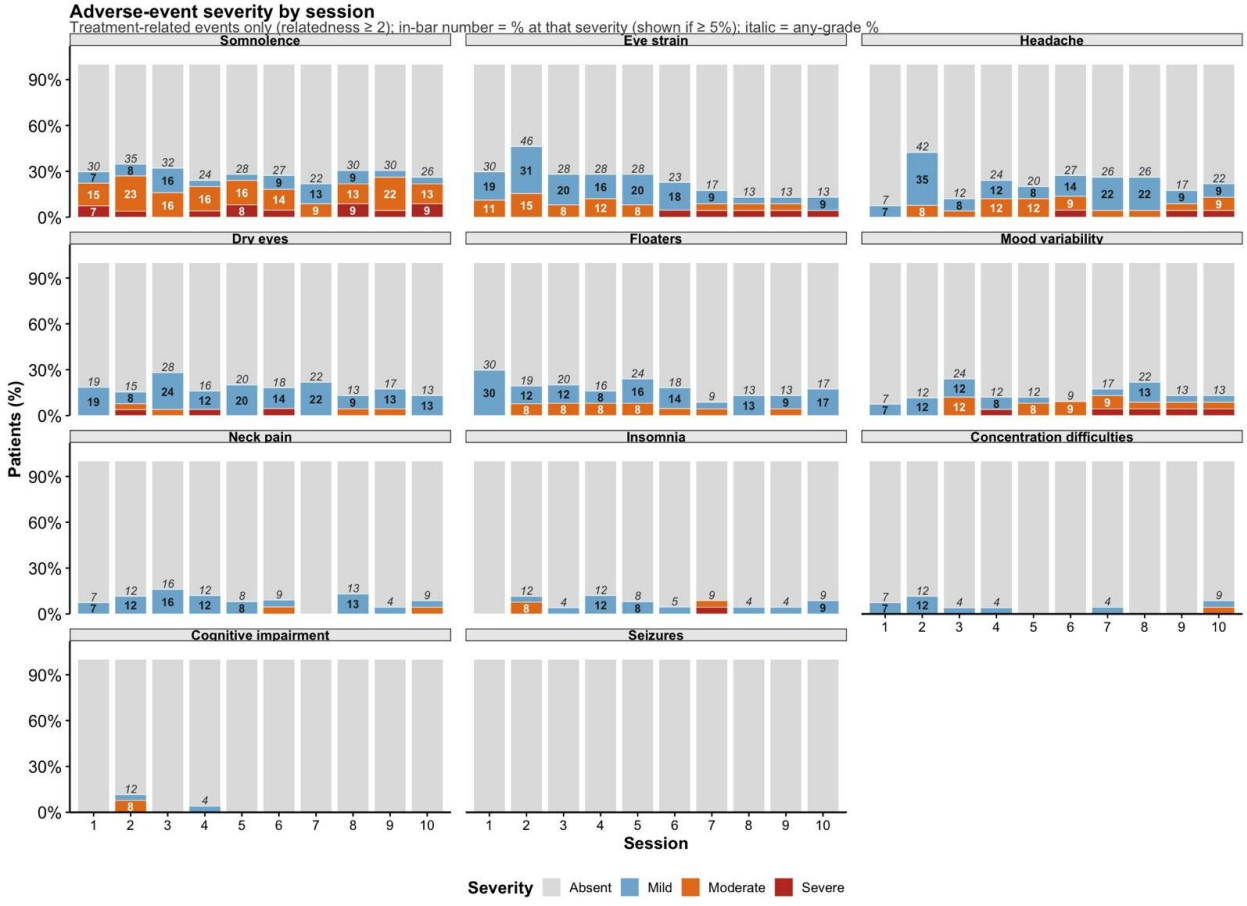


**Figure 3. Trajectory and severity of treatment-related adverse events across the 10 stimulation sessions.**

Stacked bar charts displaying the daily percentage of patients reporting specific adverse events following each 30-minute 60 Hz flickering light session. To isolate the effects of the intervention, the data represents only events that patients rated as at least possibly related to the treatment (relatedness score ≥ 2 on a 0–4 scale). Colors indicate the maximum severity of the event reported by the patient for that session (blue = mild, orange = moderate, red = severe). Bold numbers within the colored segments denote the specific percentage of patients experiencing that severity level (displayed only for values ≥ 5% for visual clarity). The italicized number positioned above each bar indicates the total, cumulative percentage of patients experiencing any grade of the adverse event during that specific session.

**TABLE 1. Baseline Characteristics of the Study Sample**

| **Characteristic** | **N = 27** |
|---|---|
| Age, mean (SD), years | 37.56 (9.14) |
| Female sex, n (%) | 20 (74) |
| **Race, n (%)** | |
| White | 23 (85) |

| | |
|---|---|
| Non-White | 4 (15) |
| Previous depressive episodes, n (%) | 22 (81) |
| History of suicide attempts, n (%) | 4 (16) |
| **Physical activity level, n (%)** | |
| Low | 16 (59) |
| Moderate | 7 (26) |
| High | 4 (15) |
| Comorbid medical conditions, n (%) | 4 (14.81) |
| **Baseline clinical scores, mean (SD)** | |
| HDRS-17 | 16.89 (3.14) |
| MADRS | 23.07 (5.62) |
| BDI-II | 22.19 (6.99) |
| HAM-A | 22.85 (9.08) |
| **CGI-S, n (%)** | |
| 2 (borderline mentally ill) | 1 (3.7) |
| 3 (mildly ill) | 3 (11) |
| 4 (moderately ill) | 21 (78) |
| 5 (markedly ill) | 2 (7.4) |
| Dropout (did not complete study), n (%) | 4 (14.81) |

BDI-II = Beck Depression Inventory-II; CGI-S = Clinical Global Impression-Severity; HAM-A = Hamilton Anxiety Rating Scale; HDRS-17 = 17-item Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; SD = standard deviation.

**TABLE 2. Adverse Events by Week of Treatment[1]**

**Number (%) of patients reporting each treatment-related event (relatedness ≥ 2) within each week**

| Adverse Event | Week 1, n (%) (N = 27) | Week 2, n (%) (N = 23) | P value |
|---|---|---|---|
| Eye strain | 16 (59.3) | 6 (26.1) | 0.013* |
| Somnolence | 16 (59.3) | 10 (43.5) | 0.343 |
| Dry eyes | 12 (44.4) | 5 (21.7) | 0.041* |
| Headache | 12 (44.4) | 12 (52.2) | 1.000 |

| | | | |
|---|---|---|---|
| Floaters | 11 (40.7) | 6 (26.1) | 0.221 |
| Mood variability | 11 (40.7) | 7 (30.4) | 0.505 |
| Concentration difficulties | 7 (25.9) | 3 (13.0) | 0.343 |
| Neck pain | 7 (25.9) | 4 (17.4) | 0.371 |
| Insomnia | 5 (18.5) | 3 (13.0) | 0.617 |
| Cognitive impairment | 4 (14.8) | 0 (0) | - |
| Seizures | 0 (0) | 0 (0) | - |

1 Week 1 = sessions 1–5; Week 2 = sessions 6–10. Denominators reflect the number of patients with at least one session attended in that week. A patient was counted as having an event if at least one episode at any severity (mild, moderate, or severe) rated as at least possibly related to the intervention (relatedness ≥ 2 on a 0–4 scale) was reported during the week. p values from McNemar's test for paired binary data comparing within-patient incidence Week 1 vs Week 2 (restricted to patients with sessions in both weeks). '—' indicates the test was not estimable due to constant outcome (e.g., zero events in both weeks). * p < .05, ** p < .01, *** p < .001.

**TABLE 3. Ophthalmological Safety Outcomes - Baseline vs. End of Study**

**Quantitative measures: paired Wilcoxon signed-rank test, two eyes averaged per patient (n = 21). Qualitative findings: number of patients with the alteration at each timepoint.**

| Ophthalmological Variable | Baseline | End of Study | Cohen's d | p value |
|---|---|---|---|---|
| **Quantitative Measures, mean (SD)** | | | | |
| RNFL Superior (µm) | 139.3 (30.6) | 130.3 (12.0) | -0.296 | 0.896 |
| RNFL Inferior (µm) | 132.3 (25.2) | 133.0 (16.4) | 0.035 | 0.154 |
| RNFL Temporal (µm) | 84.0 (31.9) | 75.0 (11.5) | -0.314 | 0.862 |
| RNFL Nasal (µm) | 90.4 (38.9) | 76.2 (13.9) | -0.325 | 0.926 |
| Macular CT (µm) | 263.1 (19.1) | 264.9 (22.1) | 0.206 | 0.913 |
| GCL Superior (µm) | 95.8 (5.8) | 97.0 (5.4) | 0.391 | 0.066 |

| | | | | |
|---|---|---|---|---|
| GCL Inferior (μm) | 98.5 (6.0) | 100.1 (6.3) | 0.490 | **0.034** |
| Macular Volume ($mm^3$) | 8.7 (0.3) | 8.7 (0.3) | 0.153 | 0.498 |
| Intraocular Pressure (mmHg) | 13.3 (1.2) | 12.2 (3.0) | -0.396 | **0.022** |
| **Qualitative Findings, n** | | | | |
| *Anterior segment biomicroscopy* | | | | |
| Hordeolum | 1 | 0 | - | - |
| *Macular fundoscopy* | | | | |
| Any alteration | 0 | 0 | - | - |
| *Optic-nerve fundoscopy* | | | | |
| Mild Temporal Pallor | 4 | 2 | - | - |
| Asymmetric Escavation | 1 | 0 | - | - |
| *Posterior-pole fundoscopy* | | | | |
| Small Choroidal Nervus | 1 | 1 | - | - |
| *Fundus autofluorescence (posterior pole)* | | | | |
| Any alteration | 0 | 0 | - | - |

Abbreviations: CT = central thickness; GCL = ganglion cell layer; RNFL = retinal nerve fiber layer; SD = standard deviation. Bold p values significant at $\alpha = 0.05$. Quantitative measures were compared with the paired Wilcoxon signed-rank test (two eyes averaged per patient, n = 21); Cohen's d is the standardized magnitude of the mean paired baseline-to-endpoint change. Because the Wilcoxon test ranks within-patient differences and is sensitive to the consistency of their direction rather than to the mean magnitude, the two measures can diverge-a large but heterogeneous change may yield a high p value (e.g., RNFL Superior), while a small but directionally consistent change may yield a lower one (e.g., RNFL Inferior). A Cohen's d of opposite sign to neurodegeneration (positive for thickness measures) indicates that the direction of change favors the intervention or reflects no harm; observed differences fall within published OCT test–retest variability and were not accompanied by qualitative structural findings on clinical review.

**Supplementary Material**

**Supplementary Methods S1. LENS v1.0 device specifications**

**S1.1 Ocular frame.** The headset comprised 3D-printed components (light-source housing, facial interface, transparent LED cover) assembled with conformable foam and adjustable silicone straps. The frame used an open design that preserved the participant's direct line of sight during stimulation, and the foam interface and straps allowed adaptation to different head sizes. The LED strip was mounted within the light-source housing via an adhesive backing and shielded by the transparent cover to limit direct ocular contact and exposure to external agents.

**S1.2 Light source.** A white LED strip (nominal correlated colour temperature 4500 K; 120 LEDs/m) was mounted in the ocular frame and used as the sole light source. Optical characterisation under maximum-brightness intended-use conditions yielded a measured correlated colour temperature of approximately 4259 K (Section S1.6).

**S1.3 Controller hardware.** Stimulation was driven by a custom printed circuit board housed in an ABS enclosure with USB interfaces, built around an ESP32 microcontroller. The 60 Hz flickering signal was generated using the microcontroller's LED controller / pulse-width modulation (PWM) module at 10-bit resolution. Light output was adjusted electronically through an SPI-controlled digital potentiometer. A MOSFET gate driver in combination with P-channel and N-channel MOSFETs was used to switch and regulate the LED strip, and a DC–DC boost converter increased the supply voltage from 5 V to 12 V to meet the operating requirements of the LED strip.

**S1.4 Power supply.** Power was supplied by an external 10 Ah (10,000 mAh) lithium-ion power bank with a digital battery-level indicator. The power bank was sufficient to deliver multiple consecutive 30-minute sessions on a single

charge.

**S1.5 Mobile application and firmware.** The device was operated through a dedicated cross-platform mobile application developed in Flutter and deployed on Android 12+ and iOS 14+ devices. The application communicated with the controller via Bluetooth Low Energy (BLE) and allowed the operator to start and stop stimulation, adjust light intensity, and set session duration. Embedded controller firmware was written in C++ and executed under FreeRTOS, a lightweight real-time operating system designed for embedded devices, with separate tasks assigned to BLE communication and PWM control on dedicated processor cores to support stable real-time operation.

**S1.6 Optical characterisation.** Optical measurements were obtained at full brightness under maximum-brightness intended-use conditions, with a minimum eye distance of 2 cm reflecting realistic in-use geometry. Measurements were performed with a calibrated GL Optic GL Spectis 1.0 Touch + Flicker spectrometer (GL Optic Lichtmesstechnik GmbH, Puszczykowo, Poland). Stimulation parameters and measured optical output are summarised in Table S1.6.

**Table S1.6. Stimulation parameters and optical output of the LENS v1.0 device.**

| Parameter | Value |
|---|---|
| Light source | White LED strip |
| Nominal correlated colour temperature | 4500 K |
| Measured correlated colour temperature | ~4259 K |
| Stimulation frequency | 60 Hz |
| Duty cycle | 50% |

| | |
|---|---|
| Rise time | 2 ms |
| Fall time | 3 ms |
| PWM resolution | 10-bit |
| Measured peak irradiance (at 2 cm) | $1.13 \times 10^{-2}$ W·m$^{-2}$ |
| Measured radiance (at 2 cm) | $5.76 \times 10^{-2}$ W·m$^{-2}$·sr$^{-1}$ |
| Session duration | 30 min |
| Sessions per participant | 10 (consecutive weekdays) |
| Power supply | 10 Ah external lithium-ion power bank |
| Wireless control | Bluetooth Low Energy (BLE) |


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**Figure S1. Prototype of the device used in the study**

**Supplementary Results**

*OCT correlations with clinical outcomes:* A pre-specified generalized-estimating-equations analysis tested whether baseline ophthalmological characteristics moderated the magnitude or time course of clinical response (Figure S4). Across 64 interaction tests, only baseline optic-nerve pallor significantly and consistently moderated HDRS-17 trajectory after FDR correction: at every post-baseline timepoint, patients with pallor showed a smaller reduction than those without at every post-baseline timepoint, surviving FDR correction at Session 5 (beta = +7.44, SE 1.59, p_FDR < 0.001), Session 10 (beta = +6.63, SE 1.45, p_FDR < 0.001), and the 6-week follow-up (beta = +5.15, SE 1.62, p_FDR = 0.023); the 4-week contrast was significant before but not after correction (beta = +4.40, SE 1.53, p = 0.004, p_FDR = 0.051). Expressed clinically, pallor-positive patients improved by approximately 4–7 HDRS points less than pallor-negative patients at each assessment. Given the small pallor-positive subgroup, this finding is hypothesis-generating and requires replication. No continuous OCT thickness variable survived FDR correction; at the unadjusted level, trends suggested that larger macular volume (beta = −1.72, p = 0.028 at Session 10) and thicker inferior GCL (beta = −2.07, p = 0.013 at Session 10) were associated with greater HDRS improvement, but neither remained significant after correction for multiple testing. For MADRS, one interaction term reached significance after FDR correction (macular CT at 4-week follow-up, beta = +3.68, p_FDR = 0.008) in a direction opposite to the HDRS signal and isolated to a single timepoint; we interpret it cautiously as likely exploratory.

Taken together, clinical efficacy was broadly uniform across baseline ocular phenotypes, with the important exception that mild idiopathic optic-nerve pallor predicted an attenuated antidepressant response - a potentially clinically useful, hypothesis-generating finding, that warrants replication.

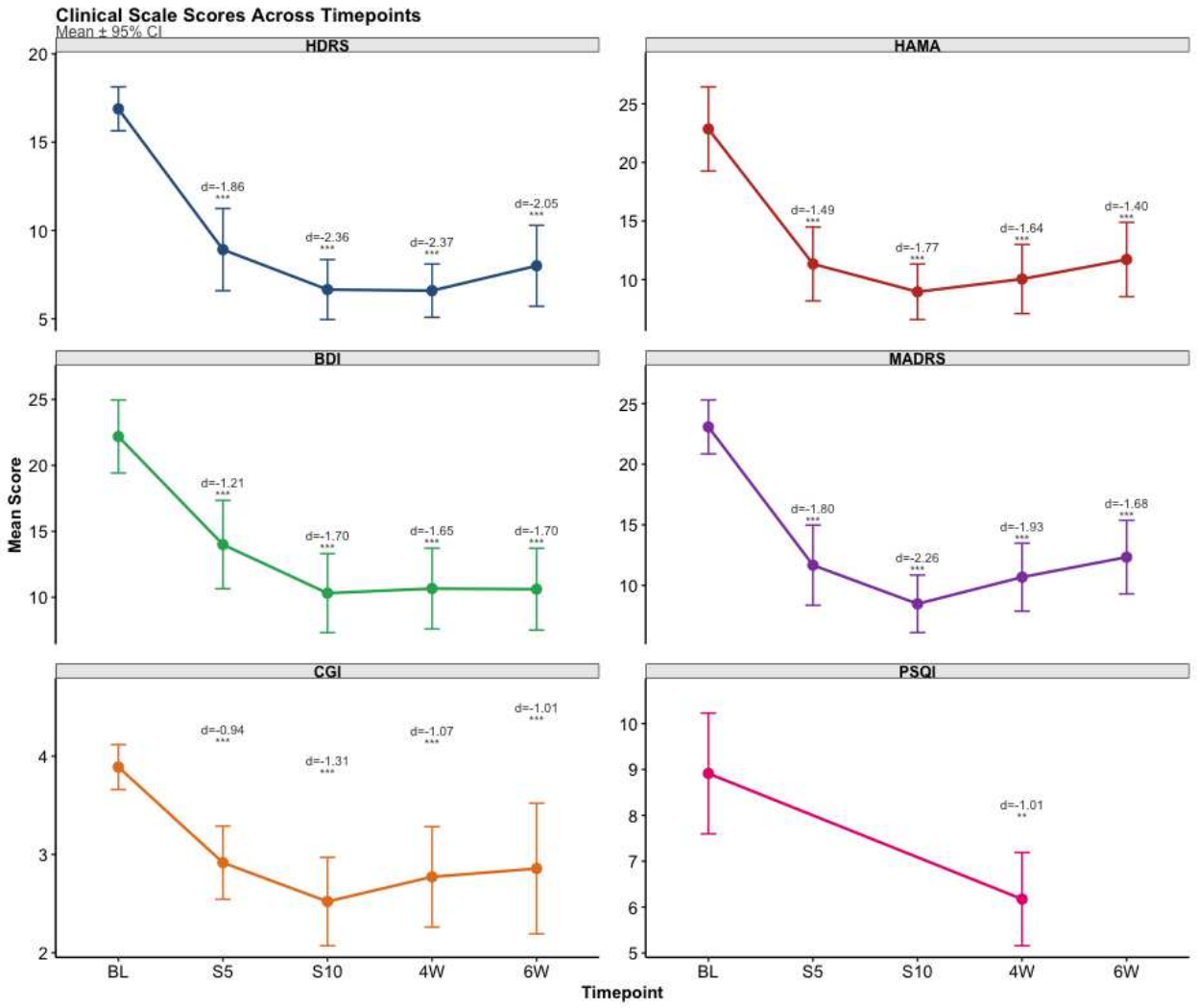



**Figure S2. Clinical Scale Scores Across Timepoints**

Mean scores (±95% confidence interval) on the HDRS-17, MADRS, BDI-II, HAM-A, CGI-S and PSQI at each study timepoint (Baseline, Session 5, Session 10, 4-Week Follow-Up, 6-Week Follow-Up). . N varies slightly across timepoints due to missing data. BL = baseline; S5/S10 = session 5 and 10 evaluation; 4W/6W = 4- and 6-week post-treatment follow-up. *** $p < 0.001$, ** $p < 0.01$.

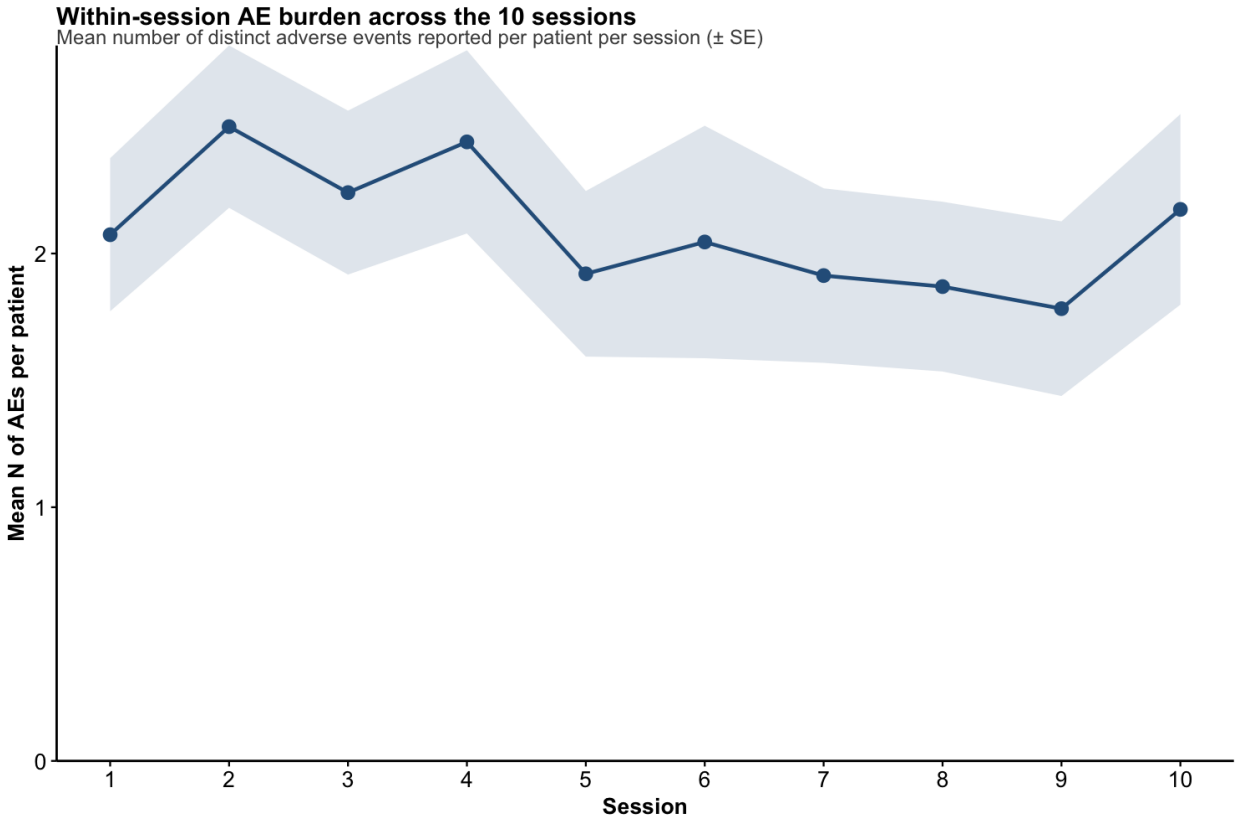



**Figure S3. Adverse-event burden across the 10 stimulation sessions.**

Mean number of distinct adverse events reported per patient per session, plotted across the 10 daily sessions of 60 Hz flickering light stimulation.[1] The line is flat across the treatment course (range 1.78–2.50 events per patient per session), with no upward drift.

[1] Counts are based on adverse-event questionnaires administered after each session. Variation in the per-session denominator reflects scheduled withdrawals and missed assessments rather than treatment-related drop-out (no participant withdrew because of an adverse event). The y-axis is the within-session mean of distinct adverse events endorsed at any severity (≥ 1).

*Abbreviations:* AE = adverse event; N = total sample with at least one session attended.

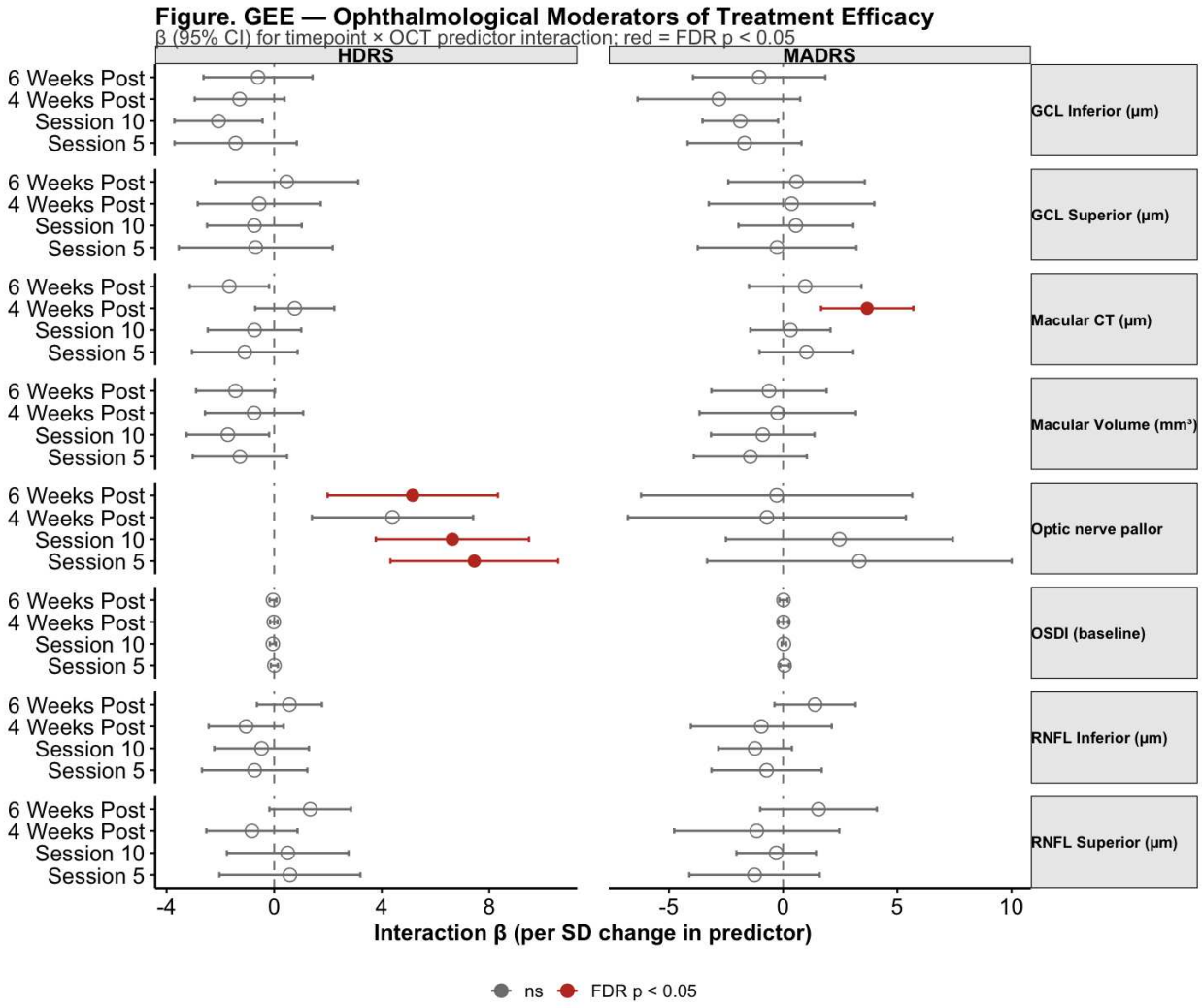



**Figure S4. Generalized estimating equations: ophthalmological moderators of treatment efficacy.**

Forest plot of timepoint × predictor interaction coefficients (β, 95% CI) from GEE models testing whether baseline ophthalmological characteristics modify the antidepressant trajectory of 60 Hz flickering light stimulation. Rows correspond to eight pre-specified baseline predictors (continuous OCT measures, the binary optic-nerve pallor flag, and baseline OSDI); columns separate the two clinical outcomes (HDRS-17 and MADRS); the four points within each panel correspond to the four post-baseline timepoints (Session 5, Session 10, 4-Week FU, 6-Week FU). The vertical dashed line at β = 0 represents no moderation. Filled red points denote interactions reaching FDR-adjusted $p < 0.05$; open grey points denote non-significant interactions.[1,2]Across 64 interaction tests, baseline optic-nerve pallor (n = 4 pallor-positive patients) was the only predictor reaching FDR significance for HDRS-17, doing so at Session 5,

Session 10, and the 6-week follow-up (the 4-week contrast was significant before but not after FDR correction); positive β values indicate that pallor-positive patients improved by approximately 4.4–7.4 HDRS points less than pallor-negative patients. For MADRS, a single interaction term (Macular CT × 4-Week FU, β = +3.68, FDR p = 0.008) reached significance in the opposite direction to the HDRS pattern and is interpreted as exploratory. Findings for the remaining predictors were null after correction, supporting broadly uniform efficacy across baseline retinal phenotypes, with the exception of the small-subgroup pallor signal noted above.[1] All models used GEE with an exchangeable working correlation structure and robust sandwich standard errors (geepack); the model form was score ~ timepoint × predictor. Continuous OCT predictors (RNFL Superior, RNFL Inferior, Macular Central Thickness, Macular Volume, GCL Superior, GCL Inferior, baseline OSDI) were z-standardised so that β represents the change in treatment effect (relative to baseline) per one standard deviation of the predictor. Optic-nerve pallor was modelled as a binary indicator (0 = absent, 1 = present); its β represents the additional points of HDRS/MADRS in pallor-positive vs pallor-negative patients at each timepoint.[2] Positive β = attenuated improvement (less benefit); negative β = enhanced improvement (greater benefit). The Benjamini–Hochberg false-discovery rate (FDR) correction was applied across all 64 predictor × outcome × timepoint combinations.Abbreviations: CT = central thickness; FDR = false discovery rate; GCL = ganglion cell layer; GEE = generalized estimating equations; HDRS-17 = 17-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; OCT = optical coherence tomography; OSDI = Ocular Surface Disease Index; RNFL = retinal nerve fibre layer; SD = standard deviation; SE = standard error.

**Figure S5. Comprehensive ophthalmological examinations, fundus photography and optical coherence tomography (OCT)**

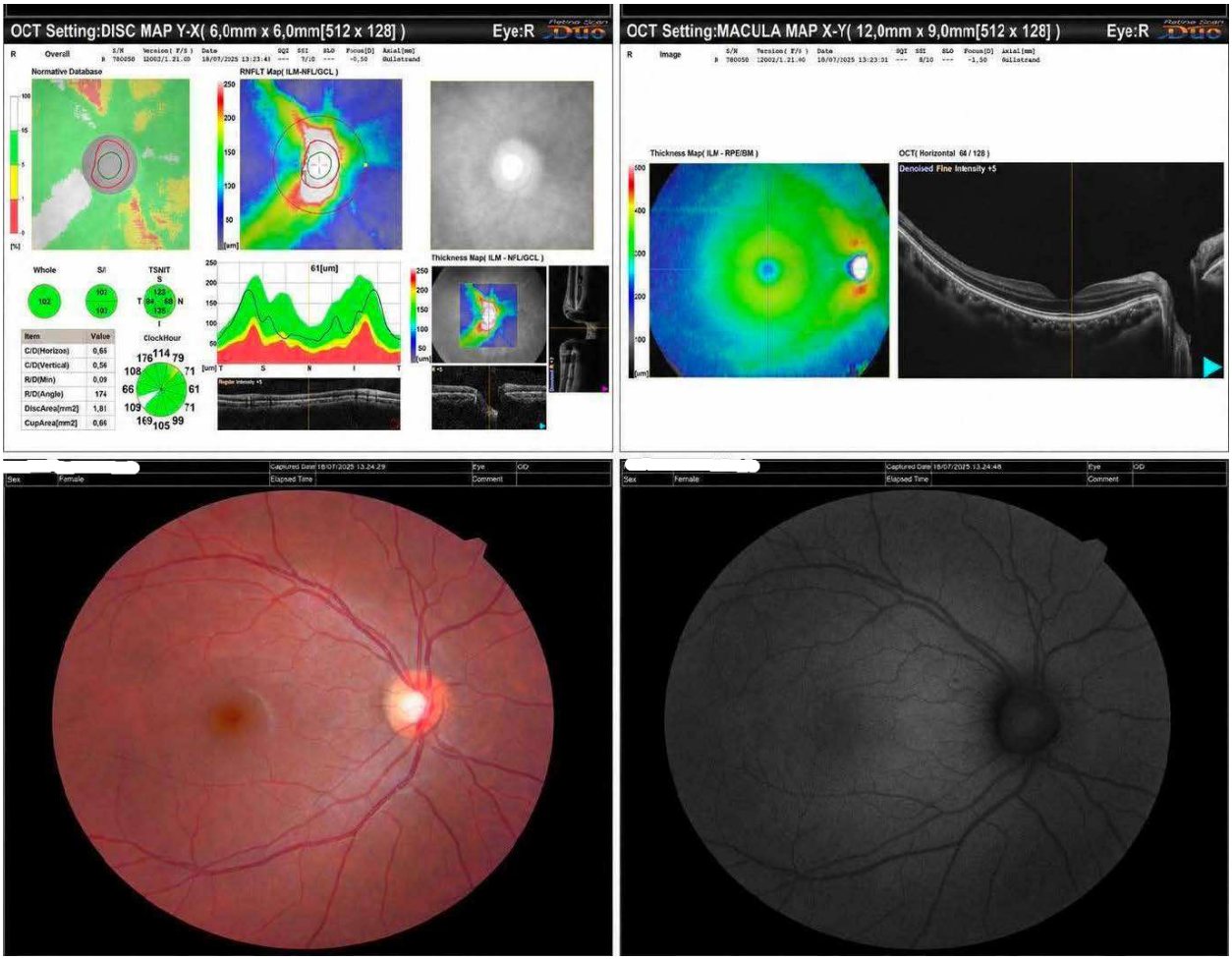



**Figure S6. Distribution of Outcome Variables (Editor's note: Image redaction applied on 16 October, 2026)**

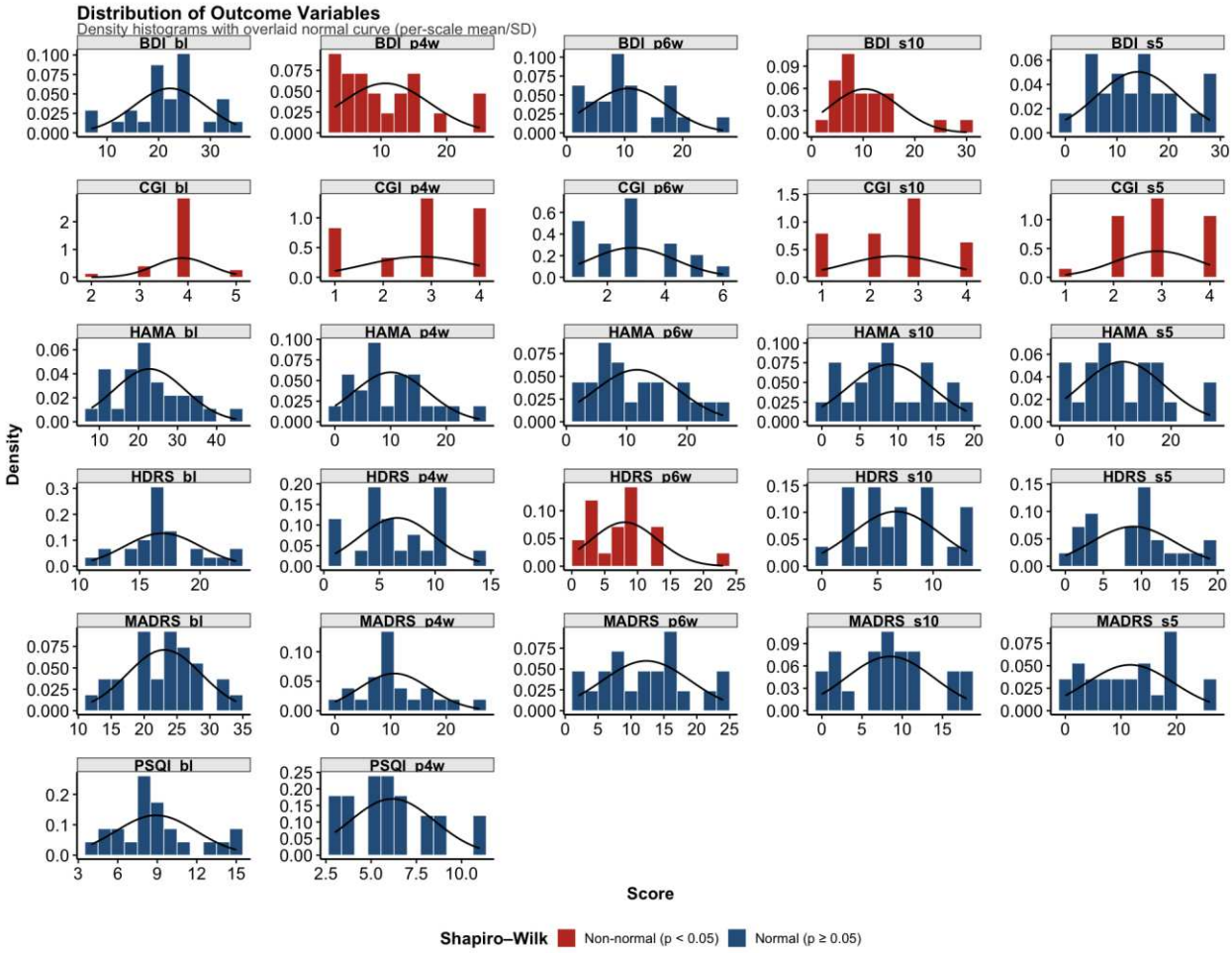



**TABLE S1. Baseline Characteristics - Completers x Dropouts**

| Characteristic | Overall N = 27 | Completer N = 23 | Dropout N = 4 | p-value |
|---|---|---|---|---|
| Age, mean (SD), years | 37.56 (9.14) | 36.52 (8.57) | 43.50 (11.39) | 0.2 |

| | | | | |
|---|---|---|---|---|
| Female sex, n (%) | 20 (74) | 16 (70%) | 4 (100%) | 0.5 |
| **Race, n (%)** | | | | >0.9 |
| White | 23 (85) | 19 (83%) | 4 (100%) | |
| Non-White | 4 (15) | 4 (17%) | 0 (0%) | |
| Previous depressive episodes, n (%) | 22 (81) | 19 (83%) | 3 (75%) | >0.9 |
| History of suicide attempts, n (%) | 4 (16) | 3 (13%) | 1 (25%) | 0.3 |
| **Physical activity level, n (%)** | | | | |
| Low | 16 (59) | 13 (57%) | 3 (75%) | >0.9 |
| Moderate | 7 (26) | 6 (26%) | 1 (25%) | |
| High | 4 (15) | 4 (17%) | 0 (0%) | |
| Comorbid medical conditions, n (%) | 4 (14.81) | 4 (17%) | 0 (0%) | >0.9 |
| **Baseline clinical scores, mean (SD)** | | | | |
| HDRS-17 | 16.89 (3.14) | 16.87 (2.97) | 17.00 (4.55) | >0.9 |
| MADRS | 23.07 (5.62) | 23.13 (6.02) | 22.75 (2.75) | 0.8 |
| BDI-II | 22.19 (6.99) | 22.35 (7.51) | 21.25 (2.87) | 0.6 |
| HAM-A | 22.85 (9.08) | 22.70 (8.26) | 23.75 (14.57) | 0.7 |
| **CGI-S, n (%)** | | | | >0.9 |
| 2 (borderline mentally ill) | 1 (3.7%) | 1 (4.3%) | 0 (0%) | |
| 3 (mildly ill) | 3 (11) | 3 (13%) | 0 (0%) | |
| 4 (moderately ill) | 21 (78) | 17 (74%) | 4 (100%) | |
| 5 (markedly ill) | 2 (7.4) | 2 (8.7%) | 0 (0%) | |

BDI-II = Beck Depression Inventory-II; CGI-S = Clinical Global Impression-Severity; HAM-A = Hamilton Anxiety Rating Scale; HDRS-17 = 17-item Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; SD = standard deviation.
[1] n (%)
[2] Wilcoxon rank sum test; Fisher's exact test

**TABLE S2. Efficacy Outcomes Across Timepoints (N = 27, Intent-to-Treat)**

| Scale | Baseline | Session 5 | Session 10 | 4-Week FU | 6-Week FU |
|---|---|---|---|---|---|
| **HDRS-17** | 16.89 (3.14) | 8.92 (5.51) | 6.65 (3.93) | 6.59 (3.40) | 8.0 (5.04) |

| | | | | | |
|---|---|---|---|---|---|
| Δ from BL | — | −7.96*** | −10.09*** | −10.15*** | −8.79*** |
| Cohen's d | — | 1.86 | 2.35 | 2.37 | 2.05 |
| **MADRS** | 23.07 (5.62) | 11.67 (7.83) | 8.48 (5.49) | 10.68 (6.32) | 12.33 (6.67) |
| Δ from BL | — | −11.50*** | −14.43*** | −12.35*** | −10.72*** |
| Cohen's d | — | 1.80 | 2.26 | 1.93 | 1.67 |
| **BDI-II** | 22.19 (6.99) | 14 (7.92) | 10.32 (6.74) | 10.67 (6.71) | 10.62 (6.81) |
| Δ from BL | — | −8.26*** | −11.61*** | −11.29*** | −11.65*** |
| Cohen's d | — | 1.20 | 1.69 | 1.64 | 1.70 |
| **HAM-A** | 22.85 (9.08) | 11.33 (7.47) | 8.96 (5.48) | 10.05 (6.65) | 11.71 (6.97) |
| Δ from BL | — | −11.31*** | −13.51*** | −12.45*** | −10.66*** |
| Cohen's d | — | 1.48 | 1.77 | 1.63 | 1.40 |
| **PSQI** | 8.91 (3.04) | — | — | 6.17 (2.35) | — |
| Δ from BL | — | — | — | −2.73** | — |
| Cohen's d | — | — | — | 1.01 | — |
| **HDRS response, n (%)[U]** | — | — | 15 (55.5) | 15 (55.5) | 11 (40.7) |
| **HDRS remission, n (%)[b]** | — | — | 15 (55.5) | 13 (48.14) | 9 (33.3) |
| **MADRS response, n (%)[U]** | — | — | 17 (62.9) | 13 (48.14) | 12 (44.4) |
| **MADRS remission, n (%)[b]** | — | | 16 (59.2) | 14 (51.8) | 9 (33.3) |

All values are mean (SD) unless otherwise indicated. Contrasts from linear mixed-effects models versus baseline; Holm-corrected. [U]Response: ≥50% reduction from baseline. [b]Remission: HDRS-17 ≤7 or MADRS ≤10. FU = follow-up; *** $p < 0.001$, ** $p < 0.01$.