Supplementary Material

Adjunctive delta-9-tetrahydrocannabinol during prolonged exposure therapy for PTSD: A randomized, double-blind feasibility pilot trial with mechanistic assessment of extinction recall

Supplementary Methods

S1. Eligibility Criteria

Following online prescreening and written informed consent, participants completed in-person diagnostic, safety, and eligibility evaluations. Participants were adults aged 18–60 years with a current diagnosis of PTSD as determined by the CAPS-5. Inclusion required exposure to at least one DSM-5 Criterion A traumatic event and clinically significant PTSD symptom severity at screening (total score ≥ 25).

Exclusion criteria included current psychotic or bipolar disorder; a current diagnosis of a mood, anxiety, or other psychiatric disorder determined by self-report or the MINI 7.0.2 to be more clinically salient than PTSD (e.g., major depressive disorder, obsessive-compulsive disorder, panic disorder, or generalized anxiety disorder); risk of harm to self or others requiring immediate clinical intervention; current severe alcohol or substance use disorder; current cannabis use and unwillingness to abstain throughout study participation; moderate or severe traumatic brain injury; lack of fluency in English; contraindicated medical conditions; pregnancy or breastfeeding; known hypersensitivity to cannabinoids or capsule constituents; use of medications with known clinically significant interactions with dronabinol; inability to tolerate MRI procedures (e.g., claustrophobia or ferromagnetic implants); insufficient memory of the traumatic event to engage in imaginal exposure; inability to comply with study procedures;

concurrent psychotherapy for PTSD; or prior exposure-based trauma therapy. Cannabis abstinence was verified by urine toxicology screening at study entry, with repeat testing conducted at the first medication session, prior to drug administration, to support continued abstinence. Participants receiving psychotropic medications were required to be on stable medication regimens prior to enrollment, and medication changes during the acute treatment phase were discouraged whenever clinically feasible.

S2. Randomization and Blinding

Following completion of PE sessions 1 and 2, eligible participants were randomized in a 1:1 ratio to receive placebo or 7.5 mg dronabinol. Randomization was performed using a covariate-adaptive procedure to promote balance across drug condition arms[1]. Stratification variables included biological sex, age, racial identity, and baseline CAPS-5 total score. Randomization occurred prior to the first medication-paired exposure session (Visit 6/PE Session 3).

The randomization sequence was generated by the principal investigator (C.A.R.), who was not involved in therapy delivery, outcome assessment, or data analysis. The allocation key was maintained in a secure, access-restricted file and was inaccessible to participants, therapists, assessors, and study staff involved in clinical care or outcome evaluation. Following randomization, study medication was assigned by the principal investigator according to the allocation schedule.

Study medication and placebo capsules were over-encapsulated by a research pharmacist to ensure identical appearance, taste, and packaging. Participants, study psychologists, assessors, and research staff remained blind to drug assignment throughout the study. Blinding integrity

was assessed at study completion for participants and research staff using structured questionnaires (see S5).

S3. Intervention Delivery and Fidelity

PE therapy was delivered via HIPAA-compliant telehealth platforms by doctoral-level licensed clinical psychologists serving as study psychologists trained in PE therapy and experienced in its delivery. Study psychologists were authorized to provide telehealth services to participants residing in Michigan. Sessions were video recorded for fidelity monitoring. Twenty percent of sessions were independently reviewed by a PE expert (S.R.), blinded to drug condition, and ongoing supervision meetings were conducted regularly to ensure protocol adherence.

PE therapy followed the standard therapist manual and patient workbook and consisted of 10 sessions delivered in a massed format of up to three sessions per week. Sessions 1 and 2 focused on psychoeducation, treatment rationale, breathing retraining, preparation for exposure, and development of an in vivo exposure hierarchy. Sessions 3 through 10 included imaginal exposure to the index trauma memory and systematic in vivo exposure exercises. Additional details regarding treatment procedures, therapist training, supervision, and fidelity monitoring are available in the published trial protocol[2].

S4. Clinical and Psychosocial Outcome Measures

PTSD Measures

The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[3] is a structured clinical interview assessing PTSD symptom severity across four symptom clusters (intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity). Symptoms are rated for frequency and intensity and summed to produce a total severity score. The CAPS-5

also includes dissociative symptom items and a global severity rating. The PTSD Checklist for DSM-5 (PCL-5)[4] is a 20-item self-report measure assessing PTSD symptom severity using a 5-point Likert scale. The standard version, referencing symptoms over the previous month, was administered at baseline and follow-up assessments (Table S1). A weekly version, referencing symptoms over the previous week, was administered during treatment to monitor symptom change across PE sessions. Total scores reflect overall PTSD symptom burden, with higher scores indicating greater severity.

Secondary Clinical Measures

Anxiety symptoms were assessed using the Hamilton Anxiety Rating Scale (HAM-A)[5], a clinician-administered measure consisting of 14 items rated on a 0–4 scale, with higher scores indicating greater anxiety severity. Depressive symptoms were assessed using the Hamilton Depression Rating Scale (HAM-D)[6], a clinician-rated measure evaluating depressive symptom severity, with higher scores indicating greater depressive symptom burden. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI)[7], a 19-item self-report questionnaire yielding a global sleep quality score, with higher scores indicating poorer sleep.

Psychosocial Measures

The Cognitive Avoidance Questionnaire (CAQ) is a self-report measure assessing cognitive strategies used to avoid distressing thoughts and trauma-related memories. Higher scores indicate greater reliance on cognitive avoidance strategies. The Posttraumatic Cognitions Inventory (PTCI) assesses trauma-related beliefs about the self, the world, and self-blame. Higher scores reflect more maladaptive trauma-related cognitions. The Posttraumatic Growth Inventory (PTGI) is a self-report measure assessing positive psychological change following trauma, including domains of personal strength, appreciation of life, and interpersonal

relationships. Higher scores indicate greater posttraumatic growth. The Connor–Davidson Resilience Scale (CD-RISC) assesses psychological resilience. Higher scores indicate greater resilience.

These measures were prespecified secondary outcomes included in the approved study protocol and were administered at baseline, post-treatment, and follow-up assessments (Table S1). Given the pilot nature of the study, analyses of these outcomes emphasized descriptive estimation of change scores and effect sizes and were considered exploratory.

S5. Subjective Drug Effects and Blinding

Drug Effects Questionnaire

Acute subjective drug effects were assessed using the Drug Effects Questionnaire (DEQ)[8] during medication-paired sessions. The DEQ assessed perceived drug effects ("Do you feel a drug effect right now?"), intoxication ("Are you high right now?"), negative subjective effects ("Do you dislike any of the effects you are feeling right now?"), positive subjective effects ("Do you like any of the effects you are feeling right now?"), and desire for additional drug ("Would you like more of the drug you took right now?"). DEQ items were rated on visual analog scales ranging from 0 to 100, with higher scores indicating greater endorsement. DEQ assessments were obtained at multiple time points during each medication-paired session and were subsequently averaged within participants across medication sessions to generate participant-level summary scores for descriptive comparison between drug conditions.

Blinding Integrity

Blinding integrity was assessed separately for participants and research staff. Participants completed an End-of-Session Questionnaire following each medication-paired session and indicated whether they believed they received THC or placebo during that session. For

descriptive analyses of blinding integrity, participant guesses from the final medication-paired session (Visit 9/PE Session 6) were used. Research staff completed a blinding integrity questionnaire at study completion for each participant. Response options included: “strongly believe THC,” “somewhat believe THC,” “somewhat believe placebo,” “strongly believe placebo,” and “don't know.” For descriptive analyses, THC-related responses and placebo-related responses were collapsed into THC and placebo categories, respectively, while “don't know” responses were retained as a separate category. Blinding assessments were summarized descriptively. For participant drug-assignment guesses, exact binomial tests were used to compare the proportion of correct guesses against chance performance (50%).

S6. Treatment Response and Remission

Treatment response was defined as a ≥50% reduction in CAPS-5 total severity from baseline to post-treatment or follow-up. Remission was defined as loss of PTSD diagnosis and a CAPS-5 total score <20 at the 3-month follow-up. Treatment response and remission outcomes were examined descriptively given the pilot nature of the study.

S7. Safety Monitoring and Adverse Events

Participant safety was monitored throughout the study in accordance with the approved protocol. Suicide risk was assessed at screening and monitored throughout treatment using the Columbia-Suicide Severity Rating Scale (C-SSRS)[9]. Adverse events were assessed at each study visit and recorded systematically. Medication use and potential drug-drug interactions were reviewed throughout the study. Participants completed urine toxicology screens, breath alcohol testing, and pregnancy testing at prespecified visits. Study medication tolerability was assessed during medication-paired sessions. An independent Data Safety & Monitoring Board (DSMB) reviewed safety events, study progress, and protocol adherence throughout the trial.

S8. Assessment Schedule

Clinical assessments were conducted at pre-treatment baseline, during treatment, immediately post-treatment, and at one- and three-month follow-up visits (Table S1). The CAPS-5 was administered at baseline, mid-treatment (following completion of the medication-paired exposure sessions; Visit 9/PE Session 6), post-treatment (following Visit 13/PE Session 10), and at the three-month follow-up. The primary clinical endpoint was post-treatment PTSD symptom severity assessed following completion of PE Session 10. The PCL-5 was administered repeatedly throughout treatment, including PE Sessions 1, 3, 5, 7, 9, and 10, to assess symptom change over time. Secondary clinical, psychosocial, and safety measures were administered according to the schedule shown in Table S1. Acute subjective drug effects were assessed during medication-paired sessions.

S9. Statistical Modeling Details

Longitudinal clinical outcomes were analyzed using linear mixed-effects models implemented in R (lme4 package). Fixed effects included drug condition, time, and the drug condition-by-time interaction, with participant-specific random intercepts included to account for within-subject correlation across repeated observations. Two complementary longitudinal modeling approaches were used. First, linear mixed-effects models treating assessment time as a continuous variable were used to estimate overall symptom trajectories across the study period. Second, piecewise mixed-effects models were specified to estimate separate rates of change from baseline to post-treatment and from post-treatment to the three-month follow-up assessment. Drug condition interactions with each slope term were examined descriptively given the pilot nature of the study. To facilitate interpretation of drug-related effects at individual assessment visits, additional visit-based mixed-effects models treating assessment as a categorical factor

were fit, and estimated marginal means and planned contrasts were computed using the emmeans package. Degrees of freedom for estimated marginal means and contrasts were estimated using the Kenward–Roger method. Consistent with the covariate-adaptive randomization procedure and pilot-trial design, demographic covariates were not included in primary models.

Models were estimated using maximum likelihood estimation, permitting inclusion of participants with incomplete longitudinal data under a missing-at-random assumption. Missing data were minimal and no data imputation procedures were applied. Supplementary analyses were intended to characterize symptom trajectories, effect sizes, and domain-level patterns in this pilot trial and should be interpreted primarily as estimates of longitudinal change and effect estimation rather than definitive tests of efficacy.

Sample Size Considerations

The study was originally designed to enroll 30 participants per treatment condition. Based on prior pharmacological augmentation studies of exposure-based therapy, this sample size was expected to provide at least 80% power to detect moderate-to-large between-group effects (Cohen's d = .43-1.18). As described in the published trial protocol[2], the study was conceived as an exploratory pilot trial intended primarily to estimate effect sizes and feasibility parameters to inform future efficacy studies.

S10. Fear Conditioning and Extinction Task Parameters

Participants completed an immersive virtual reality fear conditioning and extinction paradigm consisting of four phases: fear acquisition, extinction learning, extinction recall, and fear renewal. The task was administered during fMRI at pre-treatment and post-treatment assessments. Two versions of the task were available and were counterbalanced across participants. The paradigm was adapted from previous studies conducted by our group

examining fear extinction learning and extinction recall[10–12]. Unlike earlier versions of the task, which included a safety cue, the present paradigm incorporated a conditioned stimulus (CS) associated with avoidance behavior.

Three conditioned stimuli (CSs), designated as the extinguished conditioned stimulus (CS+E), avoidance-conditioned stimulus (CS+A), and unextinguished conditioned stimulus (CS+U), were represented by colored messenger bags. Stimulus color assignments were randomized across participants from six possible colors (blue, red, yellow, black, white, and gray). Four distinct virtual environments (garden, plaza, condominium, and lobby contexts) were available. Two contexts were randomly selected for each participant. Fear acquisition and renewal were conducted in one context, whereas extinction learning and extinction recall were conducted in a separate context.

The acquisition phase consisted of 60 trials presented across two runs (30 trials/run). During acquisition, all three CSs were paired with an aversive unconditioned stimulus (US) according to a 50% partial reinforcement schedule. The US consisted of an animated snake emerging from the messenger bag accompanied by an aversive snake-hissing sound. The extinction phase consisted of 40 trials presented across two runs (20 trials/run). During extinction, the CS+E and CS+A were each presented 20 times without reinforcement, whereas the CS_U was omitted from extinction learning. For the CS+A, participants could actively move away from the stimulus to prevent the messenger bag from opening, thereby providing an opportunity to engage in avoidance behavior. Extinction recall consisted of 60 trials presented across two runs (30 trials/run) and was conducted on the following day (~ 24 h later). During recall, the CS+E, CS+A, and CS+U were presented without reinforcement in the extinction

context. Fear renewal consisted of 60 trials presented across two runs (30 trials/run) and was conducted in the original acquisition context.

Each trial began with presentation of the virtual context (3–6 s), followed by CS presentation (~4.5 s). Intertrial fixation intervals were jittered between 3 and 6 s. Participants provided trial-by-trial US expectancy ratings using an MRI-compatible response device. To minimize carryover and familiarity effects, novel CS assignments and virtual contexts were used at the post-treatment assessment. Consistent with the primary mechanistic analyses, extinction recall was operationalized as differential responding to the extinguished and unextinguished conditioned stimuli (CS+E − CS+U) during early recall. Additional details regarding task development and implementation are available in the published trial protocol[2].

S11. US Expectancy Ratings

Participants were instructed to indicate whether they expected the US (a snake emerging from the bag) to occur on each trial. At the onset of each CS, participants selected one of three response options: “Yes, I think the US will occur,” “No, I do not think the US will occur,” or “I don’t know.” Responses were recorded using an MR-compatible response device, and only the first response made during each trial was retained for analysis.

Consistent with prior fear conditioning studies, US expectancy ratings were used as an index of conscious contingency awareness and behavioral expression of extinction memory. The primary behavioral analysis focused on post-treatment early extinction recall and compared expectancy ratings for the CS+E and the CS+U. Analyses were restricted to the early extinction recall trials, which have been shown to be most sensitive to drug-related differences in extinction memory retrieval. Expectancy ratings were analyzed using cumulative-link mixed-effects ordinal logistic regression. Responses were modeled as an ordered categorical outcome (“No,” “I don't

know," and "Yes"), with drug condition (THC vs. placebo), stimulus type (CS+E vs. CS+U), and their interaction included as fixed effects. Participant was included as a random intercept to account for repeated observations across trials.

S12. Skin Conductance Response Acquisition, Processing, and Quality Control

Data Acquisition

Skin conductance responses (SCRs) were recorded continuously during fear acquisition, extinction learning, extinction recall, and fear renewal using an MRI-compatible BIOPAC MP160 data acquisition system (BIOPAC Systems, Goleta, CA). Electrodermal activity was measured using gel-filled Ag/AgCl electrodes attached to the fingers of the hand not used for behavioral responding. Participants provided US expectancy ratings using the opposite hand. At study initiation, SCR recordings were acquired using a gain setting of 2 μΩ/V and an online 1-Hz high-pass filter. During data collection, the online high-pass filter was determined to introduce artifacts into a substantial proportion of recordings and was subsequently removed from the acquisition protocol. Recordings acquired after removal of the filter exhibited improved signal quality and reduced artifact contamination.

Signal Processing

SCR data were processed using custom MATLAB and Python pipelines incorporating functions from the Psychophysiological Modeling (PsPM) toolbox. Raw BIOPAC acquisition files were imported into MATLAB, trimmed relative to task markers, and converted into formats suitable for model estimation. Event timing files were generated from stimulus marker channels and used to model CS and outcome events.

All recordings underwent visual inspection prior to model fitting. Artifact-contaminated signal segments were manually identified and encoded as missing epochs. Recordings exhibiting

substantial low-frequency drift were processed using both high-pass and low-pass filtering, whereas recordings without appreciable drift were processed using low-pass filtering alone.

SCR amplitudes were estimated using a model-based approach implemented in the PsPM toolbox. This approach estimates latent sudomotor nerve activity underlying the observed electrodermal signal and generates trial-level estimates of conditioned responding through generative modeling of the continuous skin conductance time series. Consistent with prior work, this approach was used to quantify trial-wise SCR amplitudes rather than relying on conventional peak-detection methods[13]. Models were fit separately for each participant, task phase, and assessment session. Following model estimation, model fit and signal reconstruction were visually reviewed.

Quality Control

SCR recordings were available for 19 participants. Following preprocessing, model estimation, and review of model fit and SCR reconstruction, 12 participants (6 placebo, 6 THC) contributed usable post-treatment early extinction recall SCR data to the primary analyses. Baseline-adjusted SCR analyses were restricted to participants with usable pre- and post-treatment early extinction recall data (n = 6; placebo = 1, THC = 5) and should therefore be interpreted cautiously. Artifact-contaminated epochs were incorporated into the estimation procedure and excluded from model fitting when appropriate.

SCR Outcome Variables

The primary SCR measure was the model-derived anticipatory SCR amplitude estimate (aSCR), representing the estimated magnitude of the stimulus-evoked sudomotor response. To reduce positive skewness, aSCR values were square-root transformed prior to statistical analyses. Additional model-derived outputs included latency, dispersion, and evoked SCR parameters but

were not included in primary analyses. Transformed responses were averaged within participant separately by assessment (pre-treatment, post-treatment), task phase, run (early, late), and stimulus type. Differential SCR scores were calculated as SCR(CS+E) − SCR(CS+U), with positive values indicating greater responding to the CS+E relative to the CS+U. The primary SCR outcome was differential responding during post-treatment early extinction recall. Drug condition differences were evaluated using linear regression models with drug condition (THC vs. placebo) as the predictor. Secondary analyses examined differential SCR during extinction learning. Exploratory baseline-adjusted analyses included pre-treatment differential SCR as a covariate and were restricted to participants with usable pre- and post-treatment SCR data.

S13. Neuroimaging Data Acquisition

Functional MRI data were acquired on a Siemens MAGNETOM 3T scanner using a T2*-weighted multiband echo-planar imaging (EPI) sequence (TR = 2000 ms, TE = 30 ms, flip angle = 73°, 66 axial slices, voxel size = 2.0 × 2.0 × 2.0 mm, multiband acceleration factor = 3, GRAPPA acceleration factor = 2). High-resolution T1-weighted anatomical images were acquired using an MPRAGE sequence (TR = 1820 ms, TE = 3.52 ms, TI = 1100 ms, flip angle = 8°, voxel size = 0.9 × 0.9 × 1.5 mm). Opposing phase-encoded spin-echo field maps (AP/PA) were also acquired.

S14. Neuroimaging Preprocessing

Functional MRI data were preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing included realignment, slice-timing correction, coregistration to the participant's anatomical image, segmentation-based normalization to MNI space using VBM8/DARTEL warping, resampling to 2 × 2 × 2 mm voxel resolution, and spatial

smoothing using a 6-mm full-width-at-half-maximum Gaussian kernel. Identical preprocessing procedures were applied to baseline and post-treatment data.

S15. Neuroimaging Quality Control

Functional image quality was evaluated using both visual inspection and quantitative quality-control procedures. Co-registration quality was visually inspected for all participants. Motion and image-intensity outliers were identified using frame-level quality-control metrics. Image-intensity outliers were defined using a z-score threshold of 6. Framewise displacement (FD) was calculated from rigid-body realignment parameters using a 50-mm lever arm. Volumes with FD exceeding 0.8 mm were identified as motion outliers and censored along with one preceding and one subsequent image volume. Motion summaries included maximum displacement, mean displacement, maximum FD, mean FD, number of outlier volumes, and scrub ratio. Quality-control metrics were calculated from post-treatment extinction recall runs included in the primary fMRI analyses. All participants retained for neuroimaging analyses met prespecified image-quality criteria.

S16. First-Level fMRI Modeling

First-level analyses were conducted using the general linear model framework implemented in SPM8. Separate first-level models were estimated for each task phase (fear acquisition, extinction learning, extinction recall, and fear renewal) and assessment session (pre-treatment and post-treatment). For extinction recall, separate regressors were specified for CS+E, CS+U, and CS+A events and were convolved with the canonical hemodynamic response function. Motion parameters and censor regressors identified during quality control were included as nuisance covariates. Serial autocorrelation was modeled using an AR(1) structure and a 128-s high-pass filter was applied. Contrast images were generated for extinction recall

and related task conditions. The primary contrast of interest was differential extinction recall (CS+E − CS+U) during the early post-treatment extinction recall run, which was carried forward to second-level ROI and whole-brain analyses. Additional contrasts examining early and late recall phases were also generated.

S17. Second-Level fMRI Analysis

First-level contrast images were entered into second-level random-effects analyses to examine drug-related differences in neural responses during post-treatment early extinction recall. Extinction recall was operationalized as differential activation to the extinguished versus unextinguished conditioned stimuli (CS+E − CS+U). Primary neuroimaging analyses focused on the early extinction recall contrast, consistent with prior work indicating that early recall is most sensitive to extinction memory retrieval processes.

S18. Regions of Interest (ROI) Analyses

Based on a priori hypotheses regarding extinction memory retrieval, ROI analyses focused on the hippocampus (HPC), ventromedial prefrontal cortex (vmPFC), and amygdala. Anatomical ROI analyses were first performed using bilateral HPC and amygdala masks and an AAL-derived vmPFC mask based on the Automated Anatomical Labeling (AAL) atlas[14]. Statistical inference for anatomical ROI analyses was based on voxelwise family-wise error (FWE) correction within each anatomical search volume.

To complement anatomically defined ROI analyses, literature-based small volume correction (SVC) analyses were conducted within regions implicated in extinction memory retrieval and cannabinoid modulation of extinction processes. Coordinates were selected a priori from two sources. First, coordinates were derived from a quantitative meta-analysis of human extinction recall studies that identified consistent HPC and vmPFC engagement during extinction

memory retrieval[15]. Second, coordinates were selected from independent neuroimaging studies conducted prior to the current trial that examined the effects of THC on extinction learning and extinction memory retrieval in healthy adults and adults with PTSD[10,16,17]. These studies were selected because they tested the same cannabinoid-extinction mechanisms hypothesized to underlie drug effects in the present study. For HPC and amygdala coordinates, SVC analyses were performed within 5-mm-radius spheres centered on each a priori coordinate. For vmPFC coordinates, SVC analyses were performed within 10-mm-radius spheres centered on each a priori coordinate. Statistical significance was assessed using family-wise error correction within each search volume. A complete list of coordinates, source publications, associated experimental paradigms, and MNI locations is provided in Table S2.

To illustrate the direction and magnitude of significant drug effects, first eigenvariate estimates were extracted from spheres centered on the peak voxel of each significant cluster. For HPC and amygdala findings, values were extracted using 5-mm-radius spheres. For vmPFC findings, values were extracted using 10-mm-radius spheres. These extracted values were used solely for visualization and interpretation of significant effects and were not subjected to additional inferential statistical testing.

S19. Whole-Brain Analysis

Complementary whole-brain voxelwise analyses were conducted using the post-treatment early extinction recall contrast (CS+E − CS+U). First-level contrast images were entered into second-level random-effects analyses comparing THC- and placebo-treated participants. Statistical inference was based on voxelwise FWE correction across the whole brain.

Supplemental Results

S1. Subjective Drug Effects and Blinding

Participants receiving THC reported greater subjective drug effects and intoxication than participants receiving placebo. Ratings of liking and disliking the drug effects varied across assessment timepoints and were generally higher among THC-treated participants, particularly during active drug sessions. In contrast, ratings of desire for additional drug did not differ between drug conditions. Detailed DEQ results are presented in Table S4.

Blinding was generally preserved. Participant drug-assignment guesses obtained following the final medication-paired session did not differ significantly from chance performance. Correct identification occurred in 54.5% of THC-treated participants (binomial p = 1.00) and 75.0% of placebo-treated participants (binomial p = .146; Table S5). Research staff frequently reported uncertainty regarding drug assignment, selecting “don't know” in 13 of 23 assessments (56.5%). Among staff providing a directional guess, assignment accuracy was approximately at chance levels (Table S5). These findings provide no evidence of systematic unblinding.

S2. Skin Conductance Responses

Usable post-treatment extinction recall SCR data were available for 12 participants following preprocessing and quality-control procedures. SCR was used as a physiological index of conditioned fear expression during extinction memory retrieval. Analyses focused on early post-treatment extinction recall trials to assess retrieval of extinction memory prior to substantial within-session updating. Differential SCR, defined as the difference between responses to the extinguished and unextinguished conditioned stimuli [SCR(CS+E) − SCR(CS+U)], did not differ significantly between drug conditions (β = 0.03, SE = 0.12, p = .79). Mean differential SCR values were similar in the THC (M = −0.04, SD = 0.21) and placebo conditions (M = −0.07, SD

= 0.22). These findings provide no evidence that THC altered physiological indices of extinction memory retrieval.

S3. Neuroimaging Quality Control

Across the final post-treatment early recall fMRI sample (N = 19), mean framewise displacement (FD) was 0.16 mm (SD = 0.05) and the mean proportion of censored volumes (scrub ratio) was 0.02 (SD = 0.042). Across all post-treatment early recall runs included in the primary analyses, 177 volumes exceeded the FD threshold of 0.8 mm and were identified as motion outliers and censored. In the placebo condition (n = 10), mean FD was 0.15 mm (SD = 0.06) and the mean scrub ratio was 0.03 (SD = 0.05), with 106 supra-threshold volumes identified. In the THC condition (n = 9), mean FD was 0.17 mm (SD = 0.05) and the mean scrub ratio was 0.02 (SD = 0.03), with 71 supra-threshold volumes identified.

To evaluate potential drug condition differences in data quality, participant-level motion metrics were compared between drug conditions. No significant differences were observed in mean framewise displacement (t = -1.07, p = .30), mean scrub ratio (t = 0.42, p = .68), or the number of supra-threshold volumes identified for censoring (t = 0.42, p = .68). These findings indicate comparable levels of image quality and head motion across drug conditions.

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Table S1. Schedule of clinical, psychosocial, safety, and study assessments

Measure	Baseline	During Treatment	Post-Treatment (Visit 13/PE Session 10)	1-Month Follow-up	3-Month Follow-up
CAPS-5	X	Visit 9/PE Session 6	X	–	X
PCL-5	X	Visits 4, 6, 8, 10, 12/PE Sessions 1, 3, 5, 7, 9	X	X	X
HAM-A	X	–	X	X	X
HAM-D	X	–	X	X	X
PSQI	X	–	X	X	X
CAQ	X	–	X	X	X
PTCI	X	–	X	X	X
CD-RISC	X	–	X	X	X
PTGI	X	–	X	X	X
DEQ	–	Medication Visits 6-9/PE Sessions 3–6	–	–	–
C-SSRS	X	X	X	X	X

Adverse Events	–	Each Study Visit	X	X	X
Urine Drug Screen	X	Prior to First Medication Session (Visit 6/PE Session 3)	–	–	–
Breath Alcohol Test	As Scheduled	As Scheduled	–	–	–
Pregnancy Test[a]	X	As Scheduled	–	–	–

Note. CAPS-5 = Clinician Administered PTSD Scale for DSM-5; PCL-5 = PTSD Checklist for DSM-5; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; PSQI = Pittsburgh Sleep Quality Index; CAQ = Cognitive Avoidance Questionnaire; PTCI = Posttraumatic Cognitions Inventory; CD-RISC = Connor–Davidson Resilience Scale; PTGI = Posttraumatic Growth Inventory; DEQ = Drug Effects Questionnaire; C-SSRS = Columbia-Suicide Severity Rating Scale.

Table S2. Literature-derived coordinates used for small-volume correction analyses.

Region	MNI Coordinate (x, y, z)	Reference
HPC	20, -20, -22	[1]
	-30, -6, -16	[2]
	-26, -22, -10	[3]
vmPFC	-30, 46, -10	[1]
	-4, 34, -6	[1]
	4, 12, -14	[1]
	-4, 60, -12	[2]
	6, 58, -10	[4]
Amygdala	30, -4, -18	[4]

Note. Coordinates were selected a priori from a quantitative meta-analysis of human extinction recall and from independent neuroimaging studies examining THC modulation of extinction memory retrieval. Coordinates are reported in MNI space. HPC = hippocampus; vmPFC = ventromedial prefrontal cortex; MNI = Montreal Neurological Institute.

[1] Fullana et al. (2018) extinction recall meta-analysis.

[2] Rabinak et al. (2014) THC-enhanced extinction recall in healthy adults.

[3] Zabik et al. (2024) extinction recall one-week follow-up in adults with PTSD.

[4] Hammoud et al. (2019) one-week extinction memory retention test in healthy adults.

Table S3. Expanded index trauma categories.

Trauma Category	Description	Total Sample (N = 23), n (%)	PBO (n = 12), n (%)	THC (n = 11), n (%)
Interpersonal violence	Sexual assault, sexual abuse, or interpersonal physical violence (including serious injury events involving another individual)	12 (52.2%)	7 (58.3%)	5 (45.5%)
Traumatic loss	Sudden or traumatic death of a close other (e.g., suicide, overdose, acute medical events)	6 (26.1%)	4 (33.3%)	2 (18.2%)
Witnessed or threatened violence	Exposure to threatened harm, witnessing violence, or high perceived threat	2 (8.7%)	1 (8.3%)	1 (9.1%)
Occupational or community trauma	Work-related exposure to violence or community-level mass trauma (e.g., correctional work, mass casualty events)	2 (8.7%)	1 (8.3%)	1 (9.1%)

Trauma Category	Description	Total Sample (N = 23), n (%)	PBO (n = 12), n (%)	THC (n = 11), n (%)
Other high-intensity traumatic events	Other events meeting Criterion A (e.g., serious accidents, complex interpersonal stressors not classified above)	1 (4.3%)	0 (0%)	1 (9.1%)

Note. Trauma categories were derived from participant-reported index events and grouped to reflect shared characteristics. Although categories are not mutually exclusive conceptually, each participant was assigned to a single category based on the primary index trauma identified for treatment. Percentages are based on the number of participants within each drug condition. THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Table S4. Subjective drug effects assessed using the Drug Effects Questionnaire (DEQ)

DEQ Item	Timepoint	PBO Mean (± SD)	THC Mean (± SD)
Feel Drug Effect	Time 0	2.5 (5.6)	6.9 (10.6)
	Time 1	12.5 (16.8)	28.0 (25.2)
	Time 2	7.7 (9.4)	26.2 (28.5)
	Next Day	1.4 (4.8)	0.6 (1.3)
Feeling High	Time 0	1.7 (4.0)	4.4 (6.4)
	Time 1	7.1 (12.5)	21.6 (24.4)
	Time 2	3.7 (7.9)	21.0 (25.0)
	Next Day	0.7 (2.3)	5.0 (10.3)
Like Effects	Time 0	10.6 (15.4)	11.4 (17.4)
	Time 1	24.7 (19.5)	38.7 (21.9)
	Time 2	16.2 (17.1)	37.1 (24.4)
	Next Day	11.8 (16.6)	9.6 (16.1)
Dislike Effects	Time 0	2.5 (5.7)	7.6 (8.0)

DEQ Item	Timepoint	PBO Mean (± SD)	THC Mean (± SD)
	Time 1	3.2 (6.3)	26.2 (22.1)
	Time 2	2.4 (4.0)	23.3 (28.6)
	Next Day	5.5 (10.2)	3.3 (5.6)
Desire for Additional Drug	Time 0	14.9 (19.1)	8.5 (12.0)
	Time 1	21.4 (19.9)	14.6 (19.6)
	Time 2	15.1 (20.0)	14.3 (17.0)
	Next Day	12.9 (15.8)	7.3 (12.4)

Note. DEQ ratings were averaged within participants across medication-paired sessions (Visits 6–9) for each assessment timepoint. Time 0 = pre-dose assessment; Time 1 = midpoint assessment; Time 2 = end-of-session assessment; Next Day = approximately 24-hour follow-up assessment. Linear mixed-effects models demonstrated significant drug-related effects for Feel Drug Effect ($p = .036$), Feeling High ($p = .023$), and Dislike Effects ($p = .005$). Significant drug condition-by-timepoint interactions were observed for Like Effects ($p = .012$) and Dislike Effects ($p = .002$). No significant drug-related effects were observed for Desire for Additional Drug ($p = .438$). DEQ = Drug Effects Questionnaire; THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Table S5. Blinding Integrity Assessments

Assessor	Actual Assignment	Guess THC	Guess PBO	Accuracy (%)
Participant	THC (n=11)	6	5	54.5%
	PBO (n=12)	3	9	75.0%
Assessor	**Actual Assignment**	**Guess THC**	**Guess PBO**	**Don't Know**
Research Staff	THC (n=11)	4	2	5
	PBO (n=12)	3	1	8

Note. Participant drug-assignment guesses were based on the End-of-Session Questionnaire completed following the final medication-paired session (Visit9/PE Session 6). Participants indicated whether they believed they had received THC or placebo. Research staff completed a blinding integrity questionnaire at study completion (Visit 17). Staff response options included "strongly believe THC," "somewhat believe THC," "somewhat believe placebo," "strongly believe placebo," and "don't know." For descriptive analyses, THC-related and placebo-related responses were collapsed into THC and placebo categories, respectively, while "don't know" responses were retained as a separate category. THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Table S6. Summary of Adverse Events by Drug Condition

Category	PBO (n=12)	THC (n=11)
Participants with ≥1 adverse event, n (%)	12 (100%)	7 (63.6%)
Total number of adverse events	31	12
Serious adverse events	0	0
Adverse events possibly related to study participation	13	4
Most common adverse events	Nausea, headache, illness	Nausea, headache

Note. Values summarize the number of participants experiencing at least one adverse event and the total number of reported events within each drug condition. “Possibly related” reflects events judged by study clinicians to have a potential relationship to study participation. All adverse events were mild and transient. No serious adverse events were reported. THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Table S7. Estimated marginal means and between-group contrasts for CAPS-5 total severity across assessment visits.

Visit	Drug	EMM (SE)	95% CI	THC − PBO	Contrast SE	Contrast 95% CI	df
Baseline	PBO	40.25 (3.35)	[33.52, 46.98]	−2.43	4.85	[−12.17, 7.30]	51.7
	THC	37.82 (3.50)	[30.79, 44.85]				
Mid-treatment	PBO	26.25 (3.35)	[19.52, 32.98]	−6.25	4.85	[−15.98, 3.48]	51.7
	THC	20.00 (3.50)	[12.97, 27.03]				
Post-treatment	PBO	15.50 (3.35)	[8.77, 22.23]	−2.68	4.85	[−12.42, 7.05]	51.7
	THC	12.82 (3.50)	[5.79, 19.85]				
3-month Follow-up	PBO	15.25 (3.35)	[8.52, 21.98]	−5.98	4.85	[−15.71, 3.76]	51.7
	THC	9.27 (3.50)	[2.24, 16.30]				

Note. Estimated marginal means (EMMs) and 95% confidence intervals were derived from a linear mixed-effects model with fixed effects of drug, visit, and their interaction, and a random intercept for participant. Degrees of freedom were estimated using the Kenward–Roger method. THC–PBO contrasts represent between-group differences in clinician-rated PTSD symptom severity (CAPS-5 total score) at each visit; negative values indicate lower symptom severity in the THC condition relative to placebo. Contrasts are reported for descriptive purposes given the pilot sample size. THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Table S8. Estimated marginal means and THC–PBO contrasts for self-reported PTSD severity (PCL-5 total)

Visit	Drug	EMM (SE)	95% CI	THC − PBO	Contrast SE	Contrast 95% CI	df
Baseline	PBO	44.83 (3.48)	[37.87, 51.79]	0.17	5.03	[−9.90, 10.24]	57.9
	THC	45.00 (3.63)	[37.73, 52.27]				
PE Session 1	PBO	41.75 (3.48)	[34.79, 48.71]	2.34	5.03	[−7.72, 12.40]	57.9
	THC	44.09 (3.63)	[36.82, 51.36]				
PE Session 3 (1st drug administration)	PBO	37.08 (3.48)	[30.12, 44.04]	1.73	5.03	[−8.33, 11.79]	57.9
	THC	38.82 (3.63)	[31.55, 46.09]				
PE Session 5	PBO	33.42 (3.48)	[26.46, 40.38]	−1.87	5.03	[−11.94, 8.20]	57.9
	THC	31.55 (3.63)	[24.27, 38.82]				
PE Session 6 (mid-treatment)	PBO	24.58 (3.48)	[17.62, 31.54]	−0.77	5.03	[−10.83, 9.29]	57.9
	THC	23.82 (3.63)	[16.55, 31.09]				
PE Session 9	PBO	22.08 (3.48)	[15.12, 29.04]	−1.76	5.10	[−11.95, 8.43]	57.9

Visit	Drug	EMM (SE)	95% CI	THC − PBO	Contrast SE	Contrast 95% CI	df
	THC	20.32 (3.73)	[12.88, 27.77]				
PE Session 10 (post-treatment)	PBO	17.83 (3.48)	[10.87, 24.79]	1.80	5.03	[−8.26, 11.86]	57.9
	THC	19.64 (3.63)	[12.37, 26.91]				
1-month Follow-up	PBO	16.58 (3.48)	[9.62, 23.54]	1.05	5.03	[−9.01, 11.11]	57.9
	THC	17.64 (3.63)	[10.37, 24.91]				
3-month Follow-up	PBO	15.58 (3.48)	[8.62, 22.54]	−5.22	5.03	[−15.29, 4.85]	57.9
	THC	10.36 (3.63)	[3.09, 17.63]				

Note. Estimated marginal means (EMMs) and 95% confidence intervals were derived from a linear mixed-effects model with fixed effects of drug, visit, and their interaction, and a random intercept for participant. Degrees of freedom were estimated using the Kenward–Roger method. THC–PBO contrasts represent between-group differences in self-reported PTSD symptom severity (PCL-5 total score) at each visit; negative values indicate lower symptom severity in the THC condition relative to placebo. Contrasts are reported for descriptive purposes given the pilot sample size. THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Table S9. Exploratory outcomes among participants with baseline dissociative symptoms

Outcome	PBO (n=8)	THC (n=7)
Persistent dissociation, post-treatment	4 (50.0%)	1 (14.3%)
Persistent dissociation, 3-month follow-up	4 (50.0%)	0 (0%)
Mean CAPS-5 Total change, baseline to post-treatment	23.25	25.43
Cohen's *d* (THC − PBO)		0.17

Note. Values reflect descriptive change scores computed to align with the conceptual direction of improvement for each outcome. Improvement corresponds to lower scores, and change values are expressed such that positive values indicate symptom reduction. Effect sizes are reported as Cohen's d for between-group differences in change scores (ΔTHC − ΔPBO); positive values indicate greater improvement in the THC condition relative to placebo. All analyses are descriptive and exploratory, given the pilot sample size. Dissociation subgroup analyses include only participants endorsing dissociative symptoms at baseline. CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Table S10. Descriptive change scores and between-group effect sizes for secondary clinical and exploratory psychosocial outcomes

Measure	Domain	Assessment window	n (PBO)	n (THC)	Mean change (PBO)	Mean change (THC)	*d* (THC − PBO)
HAM-D	Depression	Baseline to Post-treatment	12	11	3.25	3.36	0.01
HAM-A	Anxiety	Baseline to Post-treatment	12	11	7.00	8.64	0.21
PSQI	Sleep quality	Baseline to Post-treatment	12	11	2.10	3.50	0.46
PTCI	Trauma-related cognitions	Baseline to Post-treatment	12	11	41.18	31.20	−0.27
CAQ Total	Cognitive avoidance	Baseline to Post-treatment	12	11	32.45	28.00	−0.20
CD-RISC	Resilience	Baseline to 3-month follow-up	12	11	3.00	2.64	−0.04
PTGI	Posttraumatic growth	Baseline to 3-month follow-up	12	11	9.30	6.36	−0.15

Note. Values reflect descriptive change scores computed to align with the conceptual direction of improvement for each outcome. For clinical symptom measures (CAPS-5 Total, CAPS-5 Total [baseline dissociation subgroup], HAM-D, HAM-A, PSQI, PTCI, CAQ Total), improvement corresponds to lower scores, and change values are expressed such that positive values indicate symptom reduction. For resilience and posttraumatic growth measures (CD-RISC and PTGI), improvement corresponds to higher scores, and change values are expressed such that positive values indicate increased resilience or growth over time. Effect sizes are reported as Cohen's d for between-group differences in change scores (ΔTHC − ΔPBO); positive values indicate greater improvement in the THC condition relative to placebo. All analyses are descriptive and exploratory, given the pilot sample size. Dissociation subgroup analyses include only participants endorsing dissociative symptoms at baseline. CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; PSQI = Pittsburgh Sleep Quality Index; PTCI = Posttraumatic Cognitions Inventory; CAQ = Cognitive Avoidance Questionnaire; CD-RISC = Connor–Davidson Resilience Scale; PTGI = Posttraumatic Growth Inventory; THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Table S11. Distribution of US expectancy responses during post-treatment early extinction recall

Drug Condition	Stimulus	"No" n (%)	"I Don't Know" n (%)	"Yes" n (%)
PBO	CS+E	94 (76.4)	16 (13.0)	13 (10.6)
	CS+U	98 (79.7)	13 (10.6)	12 (9.8)
THC	CS+E	86 (75.4)	17 (14.9)	11 (9.7)
	CS+U	86 (76.1)	18 (15.9)	9 (8.0)

Note: Distribution of individual US expectancy responses ("No," "I don't know," and "Yes") during post-treatment early extinction recall. Percentages are calculated within each drug condition and stimulus type. Response distributions were highly similar across drug conditions and conditioned stimuli, consistent with the absence of significant drug condition, stimulus, or drug condition-by-stimulus effects in the ordinal logistic regression analysis. THC = delta-9-tetrahydrocannabinol; PBO = placebo.

Table S12. Descriptive statistics and effect sizes for significant hippocampal clusters identified in small-volume correction analyses.

MNI Coordinate	PBO Mean (SD)	THC Mean (SD)	Cohen's *d*
-28, -4, -18	-0.07 (0.15)	0.23 (0.22)	1.58
-22, -20, -8	-0.19 (0.29)	0.15 (0.15)	1.46

Note. THC = delta-9-tetrahydrocannabinol; PBO = placebo; MNI = Montreal Neurological Institute.

Supplemental Figure Captions

Figure S1. CAPS-5 symptom cluster trajectories across treatment and follow-up. Trajectories of clinician-rated PTSD symptom clusters assessed using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) across Prolonged Exposure (PE) therapy with adjunctive delta-9-tetrahydrocannabinol (THC; green) or placebo (PBO; purple). Panels depict CAPS-5 intrusion, avoidance, negative alterations in cognition and mood, hyperarousal, and dissociation subscales. Thin lines represent individual participants; thick lines and points represent estimated marginal means with 95% confidence intervals. Assessments were conducted at baseline, mid-treatment (following completion of medication-paired exposure sessions), post-treatment (following PE Session 10; dashed vertical line), and at the three-month follow-up. Across both drug conditions, symptom severity decreased substantially over time across all clusters. No statistically significant drug condition × time interactions were observed in this pilot sample; exploratory inspection of trajectories suggested descriptively lower symptom severity in the THC condition at post-treatment and follow-up for several clusters.

Figure S2. Secondary clinical outcomes across treatment and follow-up. Trajectories of sleep quality assessed using the Pittsburgh Sleep Quality Index (PSQI), clinician-rated anxiety assessed using the Hamilton Anxiety Rating Scale (HAM-A), and clinician-rated depression assessed using the Hamilton Depression Rating Scale (HAM-D) across baseline, post-treatment, and three-month follow-up. Thin semi-transparent lines represent individual participant trajectories, and thick lines represent drug condition means for placebo (PBO; purple) and THC (green). Error bars indicate ±1 standard error of the mean. Across all outcomes, symptom severity improved over time in both drug conditions. Between-group differences were small and variable across timepoints and are interpreted as exploratory in this pilot sample.

Figure S1.

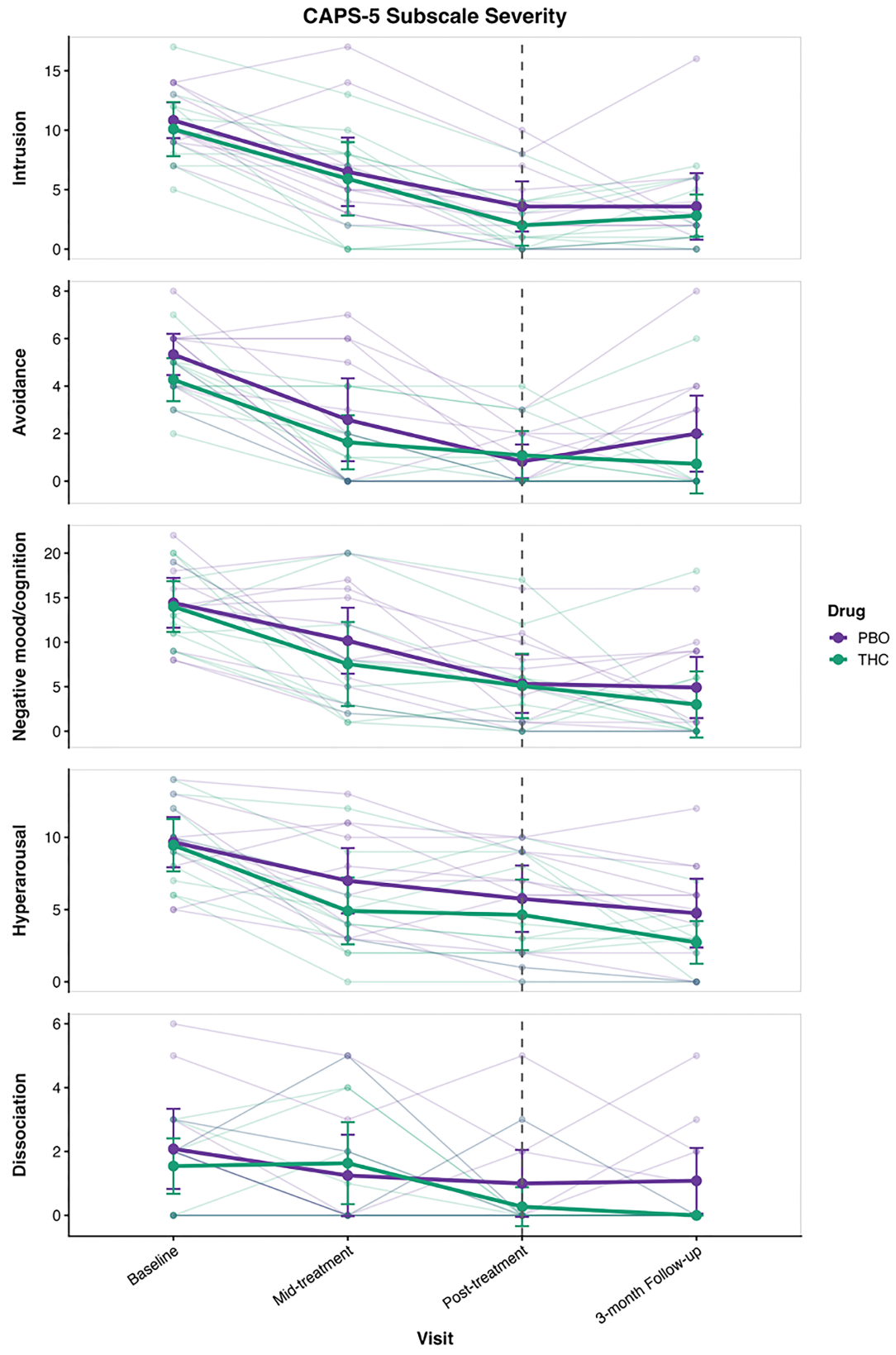
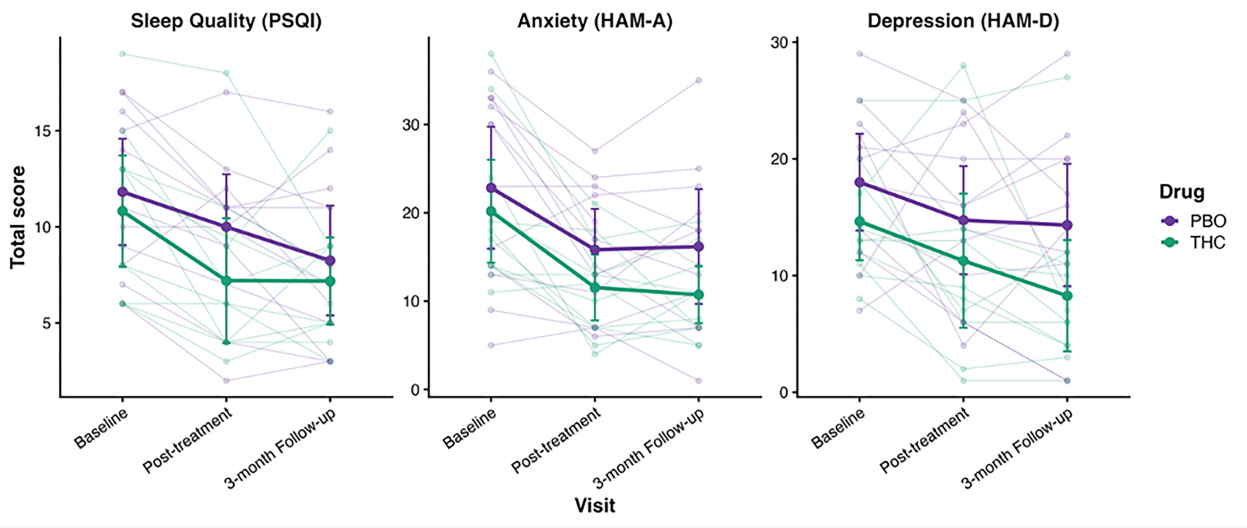

CAPS-5 Subscale Severity
Intrusion
Avoidance
Negative mood/cognition
Hyperarousal
Dissociation
Drug
PBO
THC
Baseline
Mid-treatment
Post-treatment
3-month Follow-up
Visit

Figure S2.


Sleep Quality (PSQI)
Anxiety (HAM-A)
Depression (HAM-D)
Total score
Visit
Baseline
Post-treatment
3-month Follow-up
Drug
PBO
THC