Psilocybin-Assisted Group Psychotherapy + Mindfulness Based Stress Reduction (MBSR) for Frontline Healthcare Provider COVID-19 Related Depression and Burnout: A Randomized Clinical Trial

Benjamin R. Lewis MD
Associate Professor of Psychiatry
Huntsman Mental Health Institute
University of Utah

John Hendrick MD
Assistant Professor Department of Internal Medicine, Section of Palliative Medicine
University of Utah, and George E Whalen Veterans Affairs Hospital, Geriatrics Extended Care

Kevin Byrne MD
Assistant Professor of Psychiatry
Huntsman Mental Health Institute
University of Utah

Madeleine Odette MSPH
Research Coordinator
Huntsman Mental Health Institute
University of Utah

Chaorong Wu PhD
Division of Epidemiology, Department of Internal Medicine
University of Utah

Eric L. Garland PhD
Endowed Professor in Health Sciences, Sanford Institute for Empathy and Compassion
Professor, Department of Psychiatry
University of California San Diego

Location of Work and Corresponding Author:
Benjamin R. Lewis MD
Huntsman Mental Health Institute
501 Chipeta Way
Salt Lake City, UT. 84108
ben.lewis@hsc.utah.edu

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Study Drug Supply*:*
Usona Institute

Abstract

Objective

This clinical trial sought to evaluate the safety and preliminary efficacy of psilocybin and MBSR for frontline healthcare providers with symptoms of depression and burnout related to the COVID-19 pandemic.

Methods

This was a randomized controlled trial that enrolled physicians and nurses with frontline clinical work during the COVID-19 pandemic and symptoms of depression and burnout. Participants were randomized in a 1:1 ratio to either an 8-week MBSR curriculum alone or an 8-week MBSR curriculum plus group psilocybin-assisted psychotherapy (PAP) with 25mg psilocybin. Symptoms of depression and burnout were assessed at baseline, and 2-weeks and 6-months post intervention utilizing the Quick Inventory of Depressive Symptoms (QIDS-SR-16) and Maslach Burnout Inventory Human Services Survey for Medical Professionals (MBI-HSS-MP), respectively. Secondary outcome measures included the Demoralization Scale (DS-II) and the Watt's Connectedness Scale (WCS). Adverse events and suicidality were assessed through 6-month follow-up.

Results

25 participants were enrolled and randomized. There were 12 study-related AEs recorded that were Grade 1-2 and no serious AEs. There was larger decrease in QIDS score for the MBSR+PAP arm compared to MBSR-only from baseline to 2-weeks post-intervention and significant between-group differences favoring MBSR+PAP on subscales of the MBI-HSS-MP as well as the DS-II and WCS.

Conclusions

Group psilocybin-assisted therapy plus MBSR was associated with clinically significant improvement in depressive symptoms without serious adverse events and with greater reduction in symptoms than MBSR alone. Study findings suggest that integrating psilocybin with mindfulness training may represent a promising treatment for depression and burnout among physicians and nurses.

INTRODUCTION

Depression and burnout among physicians and nurses have been recognized as worsening crises in the U.S. medical system. These issues have been exacerbated by the SARS-CoV-2 pandemic, where chronic, system-dependent stressors were coupled with dramatic increases in clinical demand, limited resources and resource rationing, assumption of increased personal risk, and increasing difficulties in balancing family life and professional responsibilities.(1–6) Burnout is a recognized psychological syndrome characterized by emotional exhaustion, depersonalization, and reduced personal accomplishment (7) and may lead to a sense of disconnection in the clinician-patient relationship. Mindfulness, a mental training practice involving present-moment, nonjudgmental awareness of thoughts and emotions, may be a promising means of addressing depression and burnout among healthcare providers.

Mindfulness-Based Stress Reduction (MBSR) is a well-established, evidence-based mindfulness training program that has been shown to reduce symptoms of depression, anxiety, and burnout as well as other mental health conditions among patients(8) and healthcare providers.(9–11) Similarly, psychedelics such as psilocybin have demonstrated efficacy in treating depressive symptoms.(12–14) There is increasing scientific interest in the potential synergy between mindfulness training and psychedelics.(15–22) Mindfulness and psychedelics appear to activate overlapping brain circuits(23) and theorists suggest that psychedelic experiences may deepen or help cultivate mindfulness skills.(16) Moreover, administering psychedelic-assisted therapy within the context of mindfulness training may lead to more durable therapeutic effects.

There has been one published randomized controlled trial of individual format psilocybin-assisted therapy for symptoms of depression and burnout in frontline healthcare providers.(24) This study demonstrated a significant reduction in depressive symptoms for the psilocybin treatment group at the 28-day follow up time point and suggested this treatment modality may

be an effective intervention for providers dealing with depressive symptoms in the post-pandemic milieu.

However, this prior study – as with most studies of psilocybin-assisted psychotherapy (PAP) to date – did not involve an active treatment control and also employed an individual PAP format with a 2:1 therapist-to-participant ratio. This delivery format significantly limits scalability and accessibility of this resource-intensive treatment and precludes possible therapeutic aspects of group-based interventions for conditions (like depression and burnout) characterized in part by a sense of isolation and lack of connection. To date, there have been three prior psilocybin trials employing variations on group format interventions.(25–27) There are compelling reasons to hypothesize that group-based psilocybin-assisted psychotherapy (PAP) may offer a uniquely effective way of augmenting the benefits of mindfulness interventions as well as improving symptoms of burnout.

Here we conducted the first randomized controlled trial (RCT) of MBSR vs. MBSR + PAP in a group format for frontline physicians and nurses experiencing burnout and depression related to the COVID-19 pandemic. This study design employing an evidence-based psychotherapeutic intervention with an active control condition responds directly to recent recommendations by Seybert et al. who present a call to the field to clearly specify and examine optimal psychotherapeutic adjuncts to psilocybin treatments.(28)

METHODS

Study Design, Setting, Participants

This parallel randomized controlled trial (NCT05557643) investigated the safety and preliminary efficacy of MBSR+PAP vs. MBSR for health care providers with a DSM-5 depressive disorder and symptoms of burnout as measured by the Maslach Burnout Inventory Human Services Survey for Medical Professionals (MBI-HSS-MP). Patients were recruited from December, 2022

to February, 2024. The University of Utah institutional review board approved the protocol. The study was registered on www.clinicaltrials.gov: ClinicalTrials.gov Identifier: NCT05557643, https://clinicaltrials.gov/study/NCT05557643?term=NCT05557643&rank=1. All study processes were conducted at the University of Utah Huntsman Mental Health Institute.

Eligible participants were physicians (MDs) or nurses (RNs) with at least one month of frontline COVID-19 patient contact, who met DSM-5 criteria for a depressive disorder (PHQ-9 score ≥10) and had MBI-HSS-MP scores of ≥27 on the Emotional Exhaustion subscale and high scores on either the Depersonalization (≥13) or Personal Accomplishment subscales (≤ 21). Exclusion criteria included history of psychosis or mania, family history of first degree relative with a psychotic disorder, recent use of excluded psychiatric medications, active substance use disorder, and suicidal behavior. The Columbia Suicide Severity Rating Scale (C-SSRS) screening version was administered during screening to assess suicidality. Participants randomized to MBSR+PAP were required to taper existing antidepressant medications (n=2). After obtaining informed consent, coordinators collected demographic information.

Masking and Randomization

Before randomization, participants completed a preference/credibility/expectancy assessment, metabolic panel, urine drug screen, and pregnancy test (if applicable). An investigator uninvolved in assessments or analysis generated treatment allocations to MBSR+PAP or MBSR with random assignment (1:1 ratio) in blocks of 3-5 per study arm per cohort. Treatment allocation was assigned to participants with sealed envelopes. Assessments were conducted as self-report measures by participants. To maintain blinding, the study key with allocations was inaccessible to the statistician until study completion. No placebo drug control was used and thus participants were not blinded to psychedelic treatment.

Interventions

Participants enrolled were enrolled in a standard MBSR course, involving eight weekly, two-hour group sessions in which mindfulness meditation training (e.g., mindful breathing, body scan) and psychoeducation were provided.(29) For participants randomized to the MBSR+PAP arm, the psilocybin intervention began after four weeks of MBSR and included three group preparatory sessions over a one week period, a group dosing session (following established group PAP protocols)(25,30) and three group integration sessions over a two week period (**Figure 1)**. See **Supplement 2** for a full, detailed description of the group psilocybin intervention per recommendations by Seybert et al.(28) Each participant in the MBSR+PAP arm was paired with an individual therapist, and preparatory and integration sessions included a 30-minute one-on-one 'break-out' session with their assigned therapist. Group therapy followed a supportive-expressive model. Therapist engagement during the dosing session was supportive and nondirective. During psilocybin dosing, vital signs were monitored every 30 minutes for the first two hours, then hourly. Each participant completed AE assessments, the C-SSRS, and had a clinical evaluation to ensure safety prior to departure from the site. Participants in the MBSR-only arm attended an in-person all-day silent meditation retreat concurrent with the psilocybin dosing day. For the MBSR+PAP arm, three integration sessions were held on days 2, 6, and 13 post-dosing. The Group PAP Protocol can be found in the Supplementary Appendix.

Safety and Feasibility Outcomes

Feasibility was measured by recruitment, retention, and completion rates, with a target of at least 66% attendance at MBSR sessions for both study arms and 75% attendance at preparatory and integration sessions for the MBSR+PAP arm. AEs were evaluated at weeks 1, 3, 5, 6, 7, 8, 9, 11 and 6-months and categorized using Common Terminology Criteria for Adverse Events version 5 (CTCAE v.5). The C-SSRS was administered at screening, weeks 1, 6, 8, 9, 11, and 6-months.

Clinical Outcomes

Outcome measures were collected at baseline, 2-weeks, and 6-months post-intervention. The primary clinical endpoint was reduction in Quick Inventory of Depressive Symptoms (QIDS-SR-16)(31) scores at 2-weeks post-intervention.

Primary Outcome Measure Justification

The Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16) was chosen as the primary outcome measure for this study due to its robust psychometric properties, its wide acceptance in clinical and research settings, and its ease of administration. The QIDS-SR-16 is a 16-item brief, self-administered instrument designed to assess the severity of depressive symptoms along nine DSM-based symptom domains of major depressive disorder. It is translated into multiple languages (including Spanish, French, German, and Chinese). Each symptom domain is represented by 1-4 items, with scores ranging from 0-3 per domain and a total score of 0-27, with higher scores indicating more severe depressive symptoms. The QIDS-SR-16 has excellent reliability and validity across various populations with high internal consistency (Cronbach's alpha typically exceeding 0.85) and correlates highly with other established clinician-administered depression measures such as the HAM-D.(31) There is a precedent for using this tool in previous studies with psilocybin-assisted therapy.(32) A 3.5 point reduction on the QIDS-SR-16 is considered a clinically significant reduction and total score can be interpreted using standard severity ranges (0-5 no depression, 6-10 mild depression, 11-15 moderate depression, 16-20 severe depression, 21-27 very severe depression). This established interpretability facilitates making meaningful conclusions regarding treatment effect. The self-reported format of this tool increases ease of administration, enhances autonomy, and minimizes observer bias. The QIDS-SR-16 is available free of charge for academic institutions with a Master User License Agreement through MAPI Trust (www.mapi-trust.org).

The key secondary clinical outcome was the MBI-HSS-MP, which includes 3 subscales: emotional exhaustion, depersonalization, and personal achievement.(33) Additional secondary outcomes included the Demoralization Scale (DS-II),(34) and the Watts Connectedness Scale, a self-report questionnaire measuring connectedness to self, others, and world that includes a General Connectedness Scale and subscales of Connectedness to Self (CTS), Connectedness to Others (CTO), and Connectedness to World (CTW).(35) Expectancy was assessed using the Credibility/Expectancy Questionnaire(36) prior to randomization and after participants learned of their random assignment. Experiential measures including the Mystical Experience Questionnaire (MEQ-30)(37), Challenging Experience Questionnaire (CEQ)(38), and NADA-state(39) were administered at the end of either the psilocybin dosing day or the MBSR meditation retreat to all participants.

Statistical Analysis

A meta-analysis examining the effects of psilocybin on depressive symptoms reported an effect size of Cohen's d=1.29. (40) Anticipating an 18% drop out rate (consistent with prior PAP studies), with an effect size of 1.0 and alpha=0.05, a sample size of 24 patients would provide 80% power to detect between-groups differences in the primary efficacy outcome.

The intent-to-treat analysis on all efficacy outcomes included all randomized participants (N=25). The per-protocol analysis (N=20) included participants in the MBSR arm who completed two-thirds of the MBSR sessions and, for those in the MBSR+PAR arm, psilocybin dosing and two-thirds of the preparatory and integration sessions. Analyses were conducted with linear mixed models (LMMs) with maximum likelihood estimation. Models specified random intercepts. Time point was treated as a categorical variable and the interaction between treatment arm and time point was included to evaluate between-group changes in outcomes over time. The effect

of post-randomization expectancy on change in QIDS-SR-16 score from baseline to the 2-week endpoint was assessed using correlation analyses on both study arms.

The correlation between experiential scales (MEQ-30, CEQ, and NADA-state) were evaluated using linear regression and summarized with Pearson coefficients.

Statistical analyses were carried out using R 4.4.0 (R Core Team, 2024, with a significance level set at $\alpha = 0.05$.

RESULTS

Participants

We assessed 420 patients for eligibility (**Figure 2**), and enrolled 25. Mean (SD) participant age was 40.4 (SD 8.4) in the MBSR-only arm and 47.4 (SD 10.9) in the MBSR+PAP arm. 72% of participants were women and the majority (96%) were white. Of the enrolled sample, 10 were MDs and 15 were RNs. The mean QIDS-SR-16 score at baseline was 12.3 (SD 3.9), indicating moderate depression(31) with no significant difference between study arms. The majority (88%) of participants had a lifetime history of antidepressant use. One participant dropped out of the MBSR+PAP arm and two participants dropped out of the MBSR-only arm (**Figure 2**) due to inability to adhere to the time commitments. No participants withdrew due to an AE. There was no significant between-groups difference in preference for study arm assignment. Baseline characteristics of the intent-to-treat (ITT) sample are provided in **Table 1.**

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Category	Characteristic	MBSR only (n=12)	MBSR + PAP (n=13)
Demographics	Age– mean (range)	40 (32-49)	47 (36-58)
	Female sex– no. (%)	6 (50%)	12 (92%)
	White race– no. (%)	11 (92%)	13 (100%)
Specialty	MD no. (%)	5 (42%)	5 (38%)
	RN no. (%)	7 (58%)	8 (62%)
	Emergency Medicine	2	4
	Oncology	2	1
	Palliative Care	0	1
	Psychiatry	1	3
	Anesthesiology	3	0
	Critical Care	1	1
	Surgery	1	0
	Urology	1	0
	Pediatrics	0	1
	Neurology	1	0
	Internal Medicine	1	0
	Primary Care	0	1
Psychiatric Diagnoses (1)	Major depressive disorder– no. (%)	11 (92%)	13 (100%)
	Adjustment disorder, with depressed mood– no. (%)	1 (8%)	0
	Adjustment disorder, with mixed anxiety and depressed mood– no. (%)	0	0
Treatment and Substance Use History	Prior Psychotropic Medication– no. (%) (2)	10 (83%)	12 (92%)
	Prior Psychedelic Use– no. (%)	6 (50%)	6 (46%)
	Current Cannabis Use– no. (%)	4 (33%)	5 (38%)
	Current Alcohol Use– no. (%)	8 (67%)	10 (77%
Baseline Depression and Burnout Scores	QIDS-SR-16 – (SD)	12.5 (2.9)	12.1 (4.7)
	MBI(EE), MBI(DP), MBI(PA) -(SD)	42.8(7.4),16(7.1),31.7(7.8)	42.2(8.6), 17.8(6.2), 28.4(8.8)

323 **Table 1. Demographic and Clinical Characteristics of Participants at Baseline.**

324 (1) As determined by chart review and screening visit MD assessment.
325 (2) Two participants randomized to MBSR+PAP arm required tapering of antidepressants. Participants randomized to MBSR-
326 only were not required to taper existing antidepressant treatments.
327 Abbreviations: QIDS-SR-16 = Quick Inventory of Depressive Symptomatology – Self-Report (16-item); MBI (EE),
328 Emotional Exhaustion Subscale of MBI. MBI (DP), Depersonalization Subscale of MBI. MBI (PA), Personal
329 Accomplishment Subscale of MBI.

330 *Safety and Feasibility*

331 All study-related AEs were Grade 1 or 2 per CTCAE v.5.0 categorization, and 12 related AEs

332 were reported (**Table 2**). There were no incidences of emergent suicidality or self-injurious

333 behaviors in either study arm. There were no clinically significant changes in vital signs during

334 psilocybin dosing that required emergent PRN antihypertensive use. The three reported

instances of nausea during the psilocybin session were self-limited and did not require anti-emetic administration. There were no administrations of pro re nata (PRN) lorazepam for acute anxiety.

	MBSR (n=12) No. (%)	**PAP (n=13) No. (%)**
At least one AE	4 (33)	13 (100)
At least one related AE	2 (17)	6 (46)
At least one serious AE	0 (0)	0 (0)
AE severity		
Mild	6	9
Moderate	7	39
Severe	0	0
Study-related AE severity		
Mild	1	11
Moderate	1	3
Severe	0	0
Study-related AEs		
Headache	0	4
Anxiety	2	3
Nausea	0	2
Hot flashes	0	1
Marital conflict	0	1
Dizziness	0	1
Rhinorrea/lacrimation	0	1
Malaise (related to stopping SSRI)	0	1
Drug-related AEs		
Headache	NA	3
Nausea	NA	2
Hot flashes	NA	1
Anxiety	NA	1
Dizziness	NA	1
Rhinorrea/lacrimation	NA	1

Table 2. Study-Related Adverse Events

In the MBSR+PAP arm there was 100% attendance of the three preparatory sessions, 100% attendance of the dosing session, and 97.2% attendance of the three integration sessions. Attendance of scheduled MBSR sessions was 80.9% across both arms; two participants did not attend at least two-thirds of scheduled MBSR sessions and were not included in the per-protocol analysis (**eTable 9**, **Supplement 1**).

Preliminary Efficacy

The MBSR+PAP arm evidenced significantly greater reduction in QIDS-SR-16 scores than the MBSR-only arm from baseline to the primary 2-weeks post-intervention endpoint between-groups effect=4.6, 95% CI=1.51-7.70, p=0.004, d=1.04). A 3.5 point decrease is considered a clinically significant reduction on the QIDS-SR-16(31); MBSR+PAP reduced QIDS-SR-16 scores by 7.26 points (SE=1.04) compared with a 2.66 point (SE=1.14) reduction in the MBSR-only condition at the 2-week endpoint. Mean QIDS-SR-16 score at the 2-week endpoint was 4.75 (SD=2.4) for the MBSR+PAP condition: a score of 5 or lower on this scale is considered evidence of no depression (**Table 3**, **Figure 3**).

Regarding secondary outcomes (**Table 3),** the MBSR+PAP arm demonstrated significantly greater reductions in the depersonalization subscale of the MBI-HSS-MP from baseline to 2-weeks post-intervention (between-groups effect=5.47, 95% CI= 0.3-10.6, p=0.038), and in emotional exhaustion from baseline to 6-months post-intervention (between-groups effect =10.9, 95% CI= 2.1-19.8, p=0.016). There were no significant between group differences on the personal accomplishment subscale due to ceiling effects from high scores at baseline. (**Figure 3**). MBSR+PAP outperformed MBSR-only in reducing demoralization from baseline to the 2-week endpoint (**Figure 4**)**.** There were significant between-group differences on the measure of General Connectedness (a global measure of the 3 WCS subscales) favoring MBSR+PAP from

baseline to 2-weeks (between-groups effect -17.5, 95% CI =-29.6 to -5.5, p=0.005) as well as significant between-group differences on CTS and CTO subscales (**Figures 5 and 6**). There were significant treatment x time interactions across all three time points (baseline, 2-week endpoint, 6-month endpoint) for the QIDS-SR-16, MBI(EE), WCS (General Connectedness) as well as WCS (CTS) and WCS (CTO) subscales (**eTable5 Supplement 1, Figure 6**).

	Mean change from baseline (95% CI)		
Primary Efficacy Endpoint	**MBSR+PAP**	**MBSR-only**	***p* value**
QIDS-SR-16 at 2-weeks	-7.26 +/- 1.04 (-9.3 to -5.2)	-2.66 +/- 1.14 (-4.9 to -0.4)	<0.01
Secondary Efficacy Endpoints			
QIDS-SR-16 at 6 months	-5.93 +/- 1.04 (-8 to -3.9)	-4.56 +/- 1.14 (-6.8 to -2.3)	0.38
MBI (EE) at 2 weeks	-15.94 +/- 2.95 (-21.7 to -10.2)	-8.1 +/- 3.22 (-14.4 to -1.8)	0.08
MBI (EE) at 6 months	-20.05 +/- 3.04 (-26 to -14.1)	-9.1 +/- 3.22 (-15.4 to -2.8)	0.02
MBI (DP) at 2 weeks	-7.66 +/- 1.74 (-11.1 to -4.2)	-2.19 +/- 1.9 (-5.9 to 1.5)	0.04
MBI (DP) at 6 months	-9.28 +/- 1.8 (-12.8 to -5.8)	-4.39 +/- 1.9 (-8.1 to -0.7)	0.07
MBI (PA) at 2 weeks	8.08 +/- 2.08 (4 to 12.2)	3.5 +/- 2.28 (-1 to 8)	0.15
MBI (PA) at 6 months	7.77 +/- 2.15 (3.6 to 12)	4.2 +/- 2.28 (-0.3 to 8.7)	0.26
DS II at 2 weeks	-10.6 +/- 1.76 (-14 to -7.2)	-4.71 +/- 1.93 (-8.5 to -0.9)	0.03
WCS (GC) at 2 weeks	28.06 +/- 4.07 (20.1 to 36)	10.55 +/- 4.45 (1.8 to 19.3)	0.01
WCS (GC) at 6 months	24.92 +/- 4.07 (16.9 to 32.9)	14.64 +/- 4.45 (5.9 to 23.4)	0.1

+/- values are standard errors

Table 3. Primary and Secondary Efficacy End Points (Intention-to-Treat Population).
Abbreviations: QIDS, Quick Inventory of Depressive Symptoms-16 item Self Report. MBI, Maslach Burnout Inventory Human Services Survey for Medical Professionals. MBI (EE), Emotional Exhaustion Subscale of MBI. MBI (DP), Depersonalization Subscale of MBI. MBI (PA), Personal Accomplishment Subscale of MBI. DS-II, Demoralization II Scale. NADA-trait, Nondual Awareness Dimensional Assessment, trait. WCS (GC), Watt's Connectedness Scale General Connectedness measure. *p*-values represent Group x Time interactions from mixed model analyses.

There was a statistically significant difference (p=0.0003) in post-randomization expectancy for the MBSR+PAP arm (65.4, SD=14.7) vs. MBSR-only (37.6, SD=17.9). Expectancy was strongly associated with QIDS-SR-16 depression symptom score reduction in the MBSR-only arm (r=-0.70, p=0.022) but not in the MBSR+PAP arm (r=0.04, p=0.90). (**eTable 7**, **Supplement 1**). There were no significant correlations between expectancy and change in MBI subscales at the 2-week endpoint.

Experiential questionnaires (MEQ-30, CEQ, and NADA-state) were administered to both study arms at either the end of the psilocybin dosing day (hour 7-8) or end of the MBSR retreat day. Mean MEQ score was 112.5 (SD 26.1) for the MBSR+PAP arm and 24.5 (SD 34.5) for the MBSR-only arm. Mean total CEQ score (scale 0-5) was 1.46 (SD 1.15) for the MBSR+PAP arm and 0.39 (SD 0.39) for the MBSR-only arm. Mean NADA-state score was 22 (SD 7.63) for the MBSR+PAP arm and 8.3 (SD 9.25) for the MBSR-only arm. 8/12 participants in the MBSR+PAP arm had a 'complete mystical experience' on the MEQ-30 (≥ 60% on all subscales) compared to 0/10 participants who completed the MEQ-30 in the MBSR-only arm. There was a large overall correlation between magnitude of score on the MEQ-30 and NADA-state and change in QIDS-SR-16 scores from baseline to the 2-week endpoint (r=-0.62, p=0.0019 for MEQ-30, r=-0.65, p=0.0018 for NADA-state) however there were no significant between group differences. Similarly, we found significant correlations between MEQ-30 scores and change in MBI(EE) (r=-0.47, p= 0.0286), MBI(DP) (r=-0.044, p= 0.0421), and WCS (r=0.616, p= 0.0023) scores from baseline to the 2-week endpoint (**eTable 8**, **Supplement 1**). There were no significant correlations found between CEQ outcomes and change in primary or secondary outcome measures from baseline to the 2-week endpoint.

DISCUSSION

This randomized clinical trial demonstrated the safety and preliminary efficacy of 25 mg psilocybin administered in group format in conjunction with an 8-week MBSR curriculum for physicians and nurses experiencing depression and burnout related to COVID-19. There were no serious treatment-emergent AEs through the course of the trial and no emergent suicidality or self-injurious behaviors. Meanwhile, MBSR+PAP was associated with clinically and statistically significant decreases in depressive symptoms and burnout, reduced demoralization, and significant increases in the sense of connectedness.

The observed effect size of MBSR+PAP on depression scores is consistent with previously reported psilocybin effect sizes on depressive symptoms.(40) We observed a large antidepressant effect at the 2-week endpoint. This finding contributes to the growing evidence base that psilocybin is a rapid-acting treatment for depression (13,14) and adds new evidence for efficacy in the unique population of MDs and RNs. This result is consistent with recently reported outcomes by Back et al who have looked at psilocybin-assisted therapy alone in individual format for a similar population.(24) MBSR+PAP also appeared to reduce emotional exhaustion and depersonalization, two key facets of burnout: this suggests the possibility of additional therapeutic aspects of the incorporation of mindfulness training as well as a group format design for this set of symptoms given the lack of statistically significant effects in burnout symptoms in the recent Back et al study.(24) Though current understanding conceptualized burnout and depression as different but overlapping conditions, the two conditions are thought to have reciprocal relationship.(7) While interventions such as MBSR and psilocybin may specifically target individual resilience and psychological flexibility(41,42), they do not necessarily address other possible factors mediating burnout such as adjusting workload demands, time management skills, and conflict resolution skills. It may be the case that these respective interventions address certain internal causal factors but not relevant systemic factors. Notably, the antidepressant effects of PAP were strongest at the 2-week endpoint. By the 6-month endpoint depression scores for participants in MBSR-only approached those of participants in MBSR+PAP, suggesting that psilocybin may accelerate the therapeutic benefits of mindfulness.(43)

Notably, we also observed significant effects of MBSR+PAP on participants' sense of connectedness to self and others. Research on depression and burnout has highlighted the profound effects that social connection and social relationships have on the development as

well as the resolution of these syndromes. Indeed, burnout undermines the clinician-patient relationship by reducing empathy and compassion.(44) The utilization of a group model for the intervention intentionally recognizes these social factors. Prior studies of group format psilocybin-assisted therapy—while small and preliminary—have suggested synergistic effects between group connectedness and therapeutic outcomes.(30) Group models also dramatically increase the scale on which these resource intensive treatments could be delivered.(45)

While there was clear preference for randomization to the MBSR+PAP arm, and higher-rated expectancy in the MBSR+PAP arm than MBSR-only, there was no indication that expectancy effects post-randomization were significantly associated with improvement with the psilocybin condition. Rather, we found a significant association in the MBSR-only condition. This is worth noting, given recent concerns regarding the effects of expectancy, functional unblinding, and confirmation bias in trials of psychedelic-assisted therapies.(46) This also aligns with a recent analysis of expectancy effects in a phase-2 RCT comparing escitalopram to psilocybin for major depressive disorder. (47) These results support prior suggestions(47) that expectancy bias may play a less significant role in the therapeutic effects of psilocybin-assisted therapy than previously suspected.

The MEQ-30, along with the NADA and CEQ were administered to all participants after either at the end of the psilocybin dosing day or MBSR retreat depending on randomization. Magnitude of score on the MEQ-30 was strongly correlated with improved outcomes at 2-weeks on the QIDS-SR-16, MBI(EE), MBI(DP), and WCS scales across the whole study sample. While there were notable between-group differences in mean scores on experiential scales notably the magnitude of mystical experience correlated with outcomes independent of psilocybin and there was no clear effect of study arm on this relationship. Previous studies of psilocybin-assisted therapy have demonstrated a relationship between magnitude of mystical experience on the

MEQ-30 and clinical outcomes. (48) Demonstrating this effect independent of psilocybin administration supports the possibility that self-transcendent states, occasioned by flexible means including mindfulness, have salutary effects.(43)

This clinical trial had several important limitations. The small sample size limited statistical power and generalizability. The homogeneity of our sample, consisting predominantly of white female participants, further restricts the generalizability of our findings to more diverse populations. Our study design, while employing an active behavioral treatment (MBSR) as a control condition, was not blinded, and this may have contributed to the different effects across study arms. The interventions differed between arms, with the PAP group participating in a psilocybin dosing day, while the MBSR-only group attended a silent meditation retreat. This design ensured that both groups received a form of intensive experience, although the nature of these experiences were not equivalent. The study was also limited in that we did not exclude participants based on prior psychedelic experience (six participants in each arm had previously used psychedelics). The effects of PAP may differ between psychedelic-naïve individuals and those with prior experience; the impact of prior psychedelic use on treatment outcomes remains unclear. To more effectively characterize the contributions of PAP vs. MBSR, we recommend that future studies consider a double-blind RCT design with an active placebo or a full factorial study design to disentangle the independent and interactive effects of psilocybin and mindfulness training.

In conclusion, combining MBSR with psilocybin appears to be a safe, feasible, and potentially efficacious approach to addressing depression and burnout among frontline healthcare workers. Larger, more diverse, multi-site studies with placebo controls are needed to further evaluate the efficacy of integrating psychedelics and mindfulness interventions for clinician wellbeing.

References

1. Murthy VH. Confronting Health Worker Burnout and Well-Being. New England Journal of Medicine [Internet]. 2022 Aug 17 [cited 2024 Oct 5];387(7):577–9. Available from: https://www.nejm.org/doi/full/10.1056/NEJMp2207252

2. Apaydin EA, Rose DE, Yano EM, Shekelle PG, McGowan MG, Antonini TL, et al. Burnout Among Primary Care Healthcare Workers During the COVID-19 Pandemic. J Occup Environ Med [Internet]. 2021 Aug [cited 2024 Oct 5];63(8):642–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8327767/

3. De Hert S. Burnout in Healthcare Workers: Prevalence, Impact and Preventative Strategies. Local Reg Anesth [Internet]. 2020 Oct 28 [cited 2024 Oct 5];13:171–83. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7604257/

4. Gambaro E, Gramaglia C, Marangon D, Probo M, Rudoni M, Zeppegno P. Health Workers' Burnout and COVID-19 Pandemic: 1-Year after—Results from a Repeated Cross-Sectional Survey. Int J Environ Res Public Health [Internet]. 2023 Jun 8 [cited 2024 Oct 5];20(12):6087. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10297954/

5. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis. Brain Behav Immun. 2020 Aug;88:901–7.

6. Ghahramani S, Kasraei H, Hayati R, Tabrizi R, Marzaleh MA. Health care workers' mental health in the face of COVID-19: a systematic review and meta-analysis. Int J Psychiatry Clin Pract. 2023 Jun;27(2):208–17.

7. Maslach C, Leiter MP. Understanding the burnout experience: recent research and its implications for psychiatry. World Psychiatry [Internet]. 2016 Jun [cited 2024 Oct 10];15(2):103–11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4911781/

8. Kabat-Zinn J. Mindfulness-based interventions in context: Past, present, and future. Clinical Psychology: Science and Practice. 2003;10(2):144–56.

9. Kriakous SA, Elliott KA, Lamers C, Owen R. The Effectiveness of Mindfulness-Based Stress Reduction on the Psychological Functioning of Healthcare Professionals: a Systematic Review. Mindfulness (N Y) [Internet]. 2021 [cited 2024 Sep 18];12(1):1–28. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7511255/

10. Fendel JC, Bürkle JJ, Göritz AS. Mindfulness-based interventions to reduce burnout and stress in physicians: a study protocol for a systematic review and meta-analysis. BMJ Open [Internet]. 2019 Nov [cited 2022 Jun 12];9(11):e032295. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2019-032295

11. Salvado M, Marques DL, Pires IM, Silva NM. Mindfulness-Based Interventions to Reduce Burnout in Primary Healthcare Professionals: A Systematic Review and Meta-Analysis. Healthcare [Internet]. 2021 Oct 9 [cited 2022 Jun 12];9(10):1342. Available from: https://www.mdpi.com/2227-9032/9/10/1342

12. Raison CL, Sanacora G, Woolley J, Heinzerling K, Dunlop BW, Brown RT, et al. Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial. JAMA [Internet]. 2023 Aug 31 [cited 2023 Aug 31]; Available from: https://doi.org/10.1001/jama.2023.14530

13. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA psychiatry. 2021;78(5):481–9.

14. Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. New England Journal of Medicine [Internet]. 2022 Nov 3 [cited 2023 Aug 4];387(18):1637–48. Available from: https://doi.org/10.1056/NEJMoa2206443

15. Smigielski L, Scheidegger M, Kometer M, Vollenweider FX. Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects. Neuroimage. 2019 Aug 1;196:207–15.

16. Griffiths RR, Johnson MW, Richards WA, Richards BD, Jesse R, MacLean KA, et al. Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. J Psychopharmacol [Internet]. 2018 Jan [cited 2022 Jun 12];32(1):49–69. Available from: http://journals.sagepub.com/doi/10.1177/0269881117731279

17. Berit S, Meling D, Hirsch-Hoffmann M, Michels L, Kometer M, Smigielski L, et al. Psilocybin enhances insightfulness in meditation: a perspective on the global topology of brain imaging during meditation. Sci Rep [Internet]. 2024 Mar 26 [cited 2024 Apr 19];14(1):7211. Available from: https://www.nature.com/articles/s41598-024-55726-x

18. Payne JE, Chambers R, Liknaitzky P. Combining Psychedelic and Mindfulness Interventions: Synergies to Inform Clinical Practice. ACS Pharmacol Transl Sci [Internet]. 2021 Apr 9 [cited 2022 Jun 12];4(2):416–23. Available from: https://pubs.acs.org/doi/10.1021/acsptsci.1c00034

19. Heuschkel K, Kuypers KPC. Depression, Mindfulness, and Psilocybin: Possible Complementary Effects of Mindfulness Meditation and Psilocybin in the Treatment of Depression. A Review. Front Psychiatry. 2020;11:224.

20. Holas P, Kamińska J. Mindfulness meditation and psychedelics: potential synergies and commonalities. Pharmacol Rep. 2023 Dec;75(6):1398–409.

21. Jiwani Z, Goldberg SB, Stroud J, Young J, Curtin J, Dunne JD, et al. Can Psychedelic Use Benefit Meditation Practice? Examining Individual, Psychedelic, and Meditation-Related Factors. medRxiv. 2024 Aug 28;2024.08.27.24312677.

22. Felsch CL, Kuypers KPC. Don't be afraid, try to meditate- potential effects on neural activity and connectivity of psilocybin-assisted mindfulness-based intervention for social anxiety disorder: A systematic review. Neuroscience & Biobehavioral Reviews [Internet]. 2022 Aug 1 [cited 2024 Oct 5];139:104724. Available from: https://www.sciencedirect.com/science/article/pii/S0149763422002135

23. Moujaes FF, Rieser NM, Phillips C, Matos NMP de, Brügger M, Dürler P, et al. Comparing neural correlates of consciousness: from psychedelics to hypnosis and meditation. BPS: CNNI [Internet]. 2023 Jul 15 [cited 2023 Jul 17];0(0). Available from: https://www.biologicalpsychiatrycnni.org/article/S2451-9022(23)00174-X/fulltext

24. Back AL, Freeman-Young TK, Morgan L, Sethi T, Baker KK, Myers S, et al. Psilocybin Therapy for Clinicians With Symptoms of Depression From Frontline Care During the COVID-19 Pandemic: A Randomized Clinical Trial. JAMA Network Open [Internet]. 2024 Dec 5 [cited 2024 Dec 6];7(12):e2449026. Available from: https://doi.org/10.1001/jamanetworkopen.2024.49026

25. Lewis BR, Garland EL, Byrne K, Durns T, Hendrick J, Beck A, et al. HOPE: A Pilot Study of Psilocybin Enhanced Group Psychotherapy in Patients With Cancer. Journal of Pain and Symptom Management [Internet]. 2023 Jun 9 [cited 2023 Jul 25];0(0). Available from: https://www.jpsmjournal.com/article/S0885-3924(23)00530-4/fulltext

26. Agrawal M, Richards W, Beaussant Y, Shnayder S, Ameli R, Roddy K, et al. Psilocybin-assisted group therapy in patients with cancer diagnosed with a major depressive disorder. Cancer [Internet]. [cited 2023 Dec 19];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/cncr.35010

27. Anderson BT, Danforth A, Daroff PR, Stauffer C, Ekman E, Agin-Liebes G, et al. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study. EClinicalMedicine. 2020 Oct;27:100538.

28. Seybert C, Schimmers N, Silva L, Breeksema JJ, Veraart J, Bessa BS, et al. Quality of reporting on psychological interventions in psychedelic treatments: a systematic review. The Lancet Psychiatry [Internet]. 2024 [cited 2024 Dec 13]; Available from:

https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(24)00333-X/abstract

29. Kabat-Zinn J. Full Catastrophe Living. Bantam Dell Publishing Group; 2013.

30. Lewis BR, Byrne K, Hendrick J, Garland EL, Thielking P, Beck A. Group format psychedelic-assisted therapy interventions: Observations and impressions from the HOPE trial. Journal of Psychedelic Studies [Internet]. 2023 Jan 18 [cited 2023 Apr 19];1(aop). Available from: https://akjournals.com/view/journals/2054/aop/article-10.1556-2054.2022.00222/article-10.1556-2054.2022.00222.xml

31. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003 Sep 1;54(5):573–83.

32. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. Trial of psilocybin versus escitalopram for depression. New England Journal of Medicine. 2021;384(15):1402–11.

33. Coker AO, Omoluabi PF. Validation of Maslach Burnout Inventory. IFE PsychologIA : An International Journal [Internet]. 2009 Mar [cited 2024 Aug 28];17(1):231–42. Available from: https://journals.co.za/doi/abs/10.10520/EJC38749

34. Robinson S, Kissane DW, Brooker J, Hempton C, Michael N, Fischer J, et al. Refinement and revalidation of the demoralization scale: The DS-II-external validity. Cancer. 2016 Jul 15;122(14):2260–7.

35. Watts R, Kettner H, Geerts D, Gandy S, Kartner L, Mertens L, et al. The Watts Connectedness Scale: a new scale for measuring a sense of connectedness to self, others, and world. Psychopharmacology [Internet]. 2022 Aug 8 [cited 2022 Aug 8]; Available from: https://doi.org/10.1007/s00213-022-06187-5

36. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. Journal of Behavior Therapy and Experimental Psychiatry [Internet]. 2000 Jun 1 [cited 2024 Jun 27];31(2):73–86. Available from: https://www.sciencedirect.com/science/article/pii/S0005791600000124

37. Barrett FS, Johnson MW, Griffiths RR. Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. Journal of Psychopharmacology. 2015;29(11):1182–90.

38. Barrett FS, Bradstreet MP, Leoutsakos JMS, Johnson MW, Griffiths RR. The Challenging Experience Questionnaire: Characterization of challenging experiences with psilocybin mushrooms. J Psychopharmacol. 2016 Dec;30(12):1279–95.

39. Hanley AW, Nakamura Y, Garland EL. The Nondual Awareness Dimensional Assessment (NADA): New Tools to Assess Nondual Traits and States of

Consciousness Occurring Within and Beyond the Context of Meditation. Psychol Assess [Internet]. 2018 Dec [cited 2022 Jun 13];30(12):1625–39. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6265073/

40. Goldberg SB, Pace BT, Nicholas CR, Raison CL, Hutson PR. The experimental effects of psilocybin on symptoms of anxiety and depression: A meta-analysis. Psychiatry research. 2020;284:112749.

41. Davis AK, Barrett FS, Griffiths RR. Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. Journal of Contextual Behavioral Science [Internet]. 2020 Jan 1 [cited 2023 Aug 5];15:39–45. Available from: https://www.sciencedirect.com/science/article/pii/S2212144719301206

42. Sloshower J, Zeifman RJ, Guss J, Krause R, Safi-Aghdam H, Pathania S, et al. Psychological flexibility as a mechanism of change in psilocybin-assisted therapy for major depression: results from an exploratory placebo-controlled trial. Sci Rep [Internet]. 2024 Apr 17 [cited 2024 Aug 12];14(1):8833. Available from: https://www.nature.com/articles/s41598-024-58318-x

43. Sacchet MD, Fava M, Garland EL. Modulating self-referential processing through meditation and psychedelics: is scientific investigation of self-transcendence clinically relevant? World Psychiatry. 2024 Jun;23(2):298–9.

44. Pavlova A, Wang CXY, Boggiss AL, O'Callaghan A, Consedine NS. Predictors of Physician Compassion, Empathy, and Related Constructs: a Systematic Review. J Gen Intern Med. 2022 Mar;37(4):900–11.

45. Marseille E, Stauffer CS, Agrawal M, Thambi P, Roddy K, Mithoefer M, et al. Group psychedelic therapy: empirical estimates of cost-savings and improved access. Front Psychiatry. 2023;14:1293243.

46. Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert Review of Clinical Pharmacology [Internet]. 2021 Sep 2 [cited 2022 Jun 15];14(9):1133–52. Available from: https://doi.org/10.1080/17512433.2021.1933434

47. Szigeti B, Weiss B, Rosas FE, Erritzoe D, Nutt D, Carhart-Harris R. Assessing expectancy and suggestibility in a trial of escitalopram v. psilocybin for depression. Psychol Med. 2024 Jan 22;1–8.

48. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol [Internet]. 2016 Dec [cited 2022 Jun 12];30(12):1181–97. Available from: http://journals.sagepub.com/doi/10.1177/0269881116675513

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Disclosures:

Benjamin Lewis MD is an investigator on 2 industry sponsored trials that are being conducted at the Huntsman Mental Health Institute:

1. *Title: A Multicenter, Randomized, Double-Blind, Parallel-Group Dose-Controlled Study Evaluating the Safety and Efficacy of RE104 for Injection in the Treatment of Patients with Postpartum Depression (PPD)*

Major Goals: Evaluate the efficacy of RE104, a novel short acting psychedelic agent, for women with postpartum depression.
Status of Support: Active
Project Number: NCT06342310
Name of PD/PI: Benjamin R. Lewis MD
Role: Principal Investigator
Source of Support: Reunion Neuroscience
Primary Place of Performance: University of Utah, multisite trial
Project/Proposal Start and End Date: 06/2024 – 09/2025
Total Award Amount (including Indirect Costs): per enrollment
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months
1. 2024 - 25 1.2
2. 2025 - 26 1.2

2. *Title: A phase III, multicenter, randomized, double blind, controlled study to investigate the efficacy, safety, and tolerability of two initial administrations of COMP360 in participants with treatment resistant depression*

Major Goals: Evaluate the efficacy of psilocybin administration with psychological support for individuals with treatment resistant depression.
Status of Support: Active
Project Number: NCT05711940
Name of PD/PI: Brian Mickey MD PhD
Role: Co-Investigator
Source of Support: COMPASS Pathways
Primary Place of Performance: Huntsman Mental Health Institute, University of Utah, multisite trial
Project/Proposal Start and End Date: 06/2024 – 09/2026
Total Award Amount (including Indirect Costs): per enrollment
Person Months (Calendar/Academic/Summer) per budget period.
1. 2024 - 25 1.8
2. 2025 - 26 1.8

Eric Garland, PhD is the Director of UCSD ONEMIND (Optimized Neuroscience-Enhanced Mindfulness Intervention Design). UCSD ONEMIND provides Mindfulness-Oriented Recovery Enhancement (MORE), mindfulness-based therapy, and cognitive behavioral therapy in the context of research trials for no cost to research participants; however, Dr. Garland has received honoraria and payment for delivering seminars, lectures, and teaching engagements (related to training clinicians in MORE), including those sponsored by institutions of higher education, government agencies, academic teaching hospitals, and medical centers. Dr. Garland also receives royalties from the sale of books related to MORE. Dr. Garland has also been a consultant and licensor to BehaVR, LLC.

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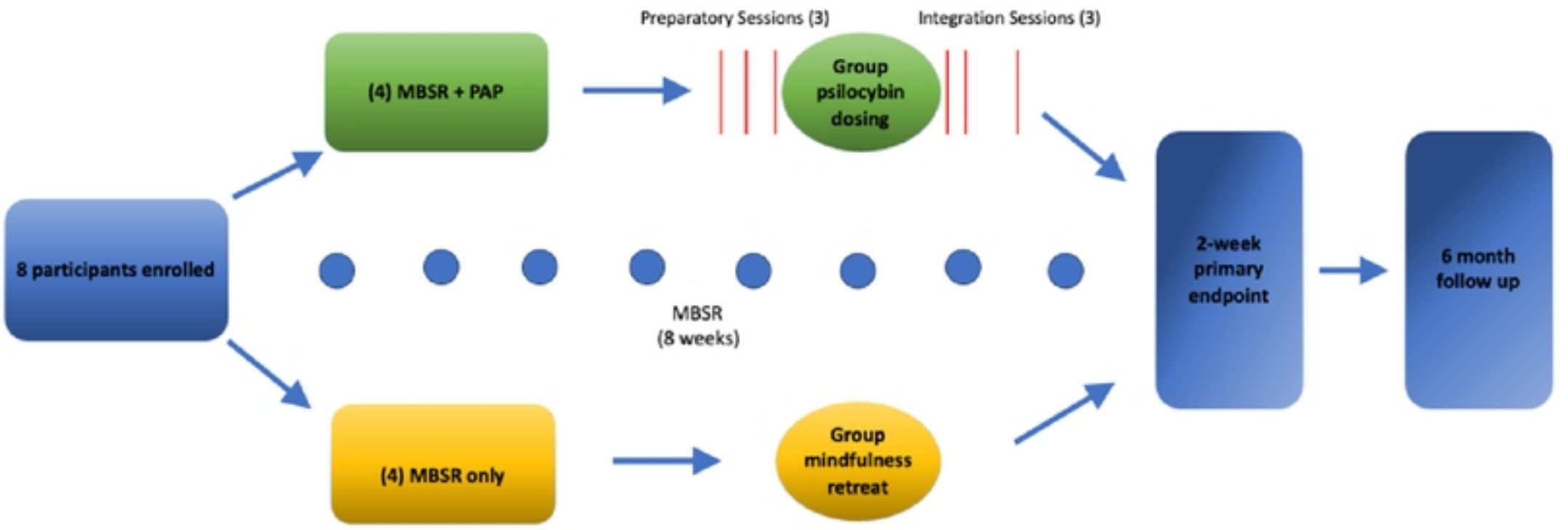


Figure 1. Study Flow Chart

Figure

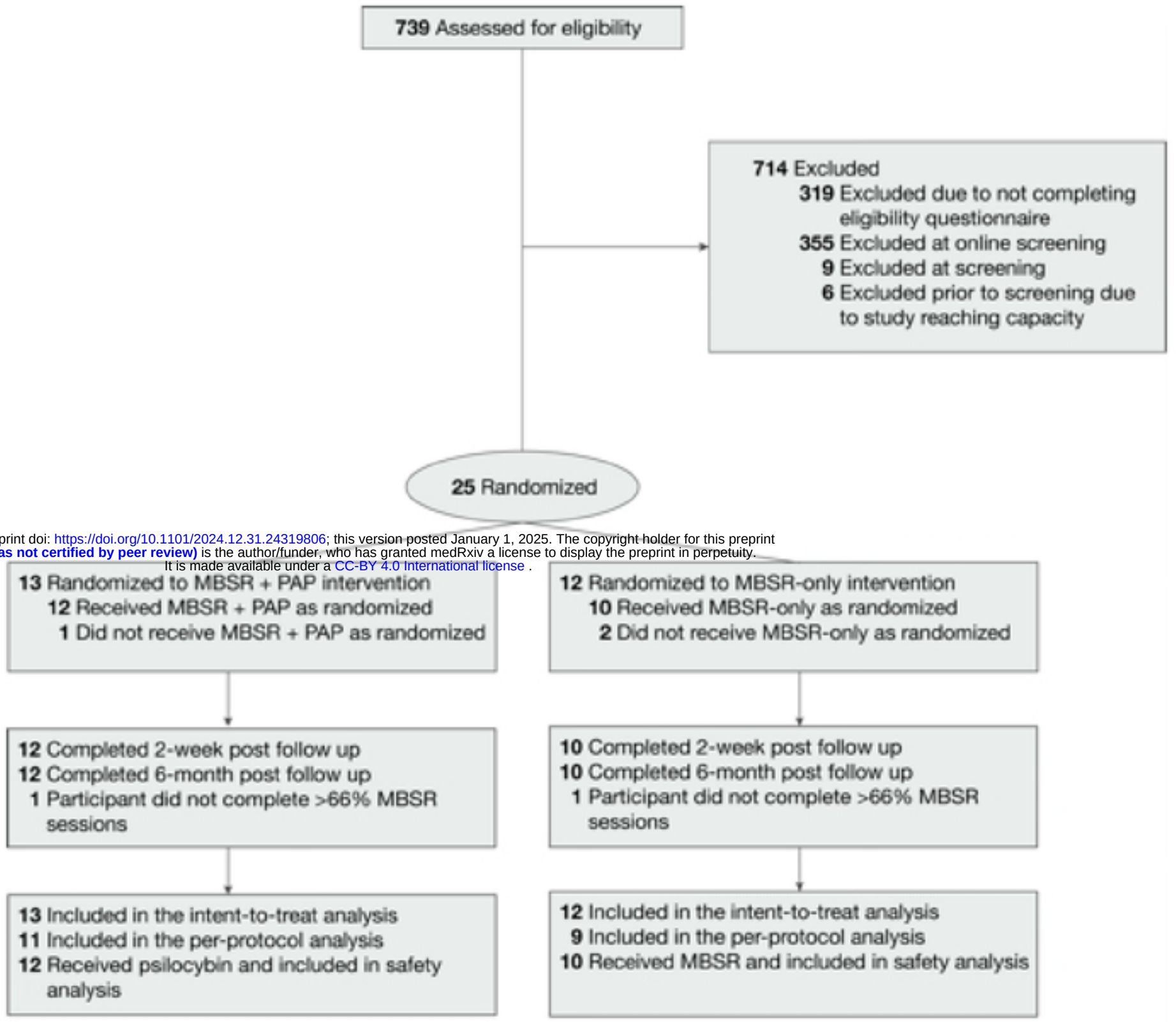
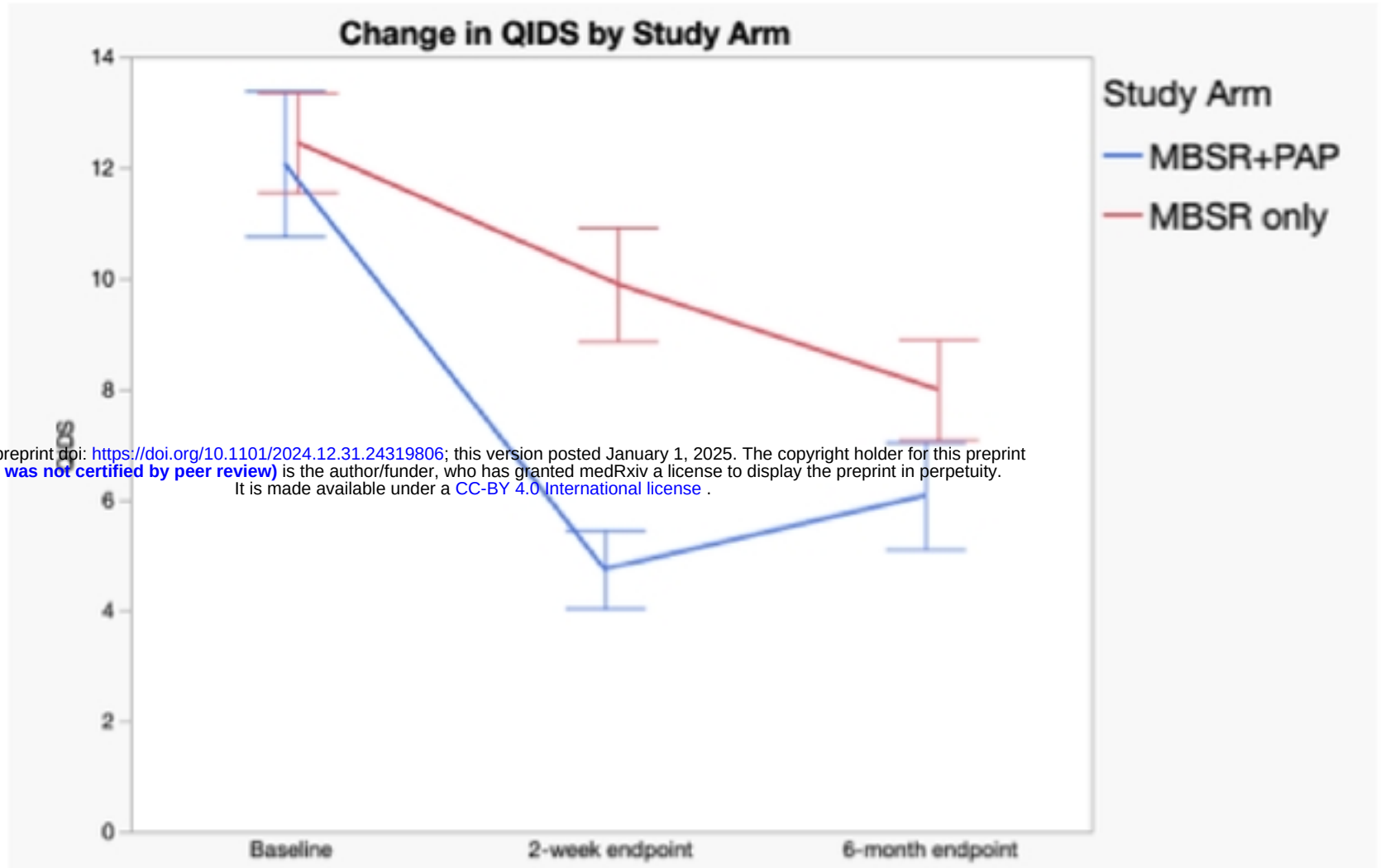
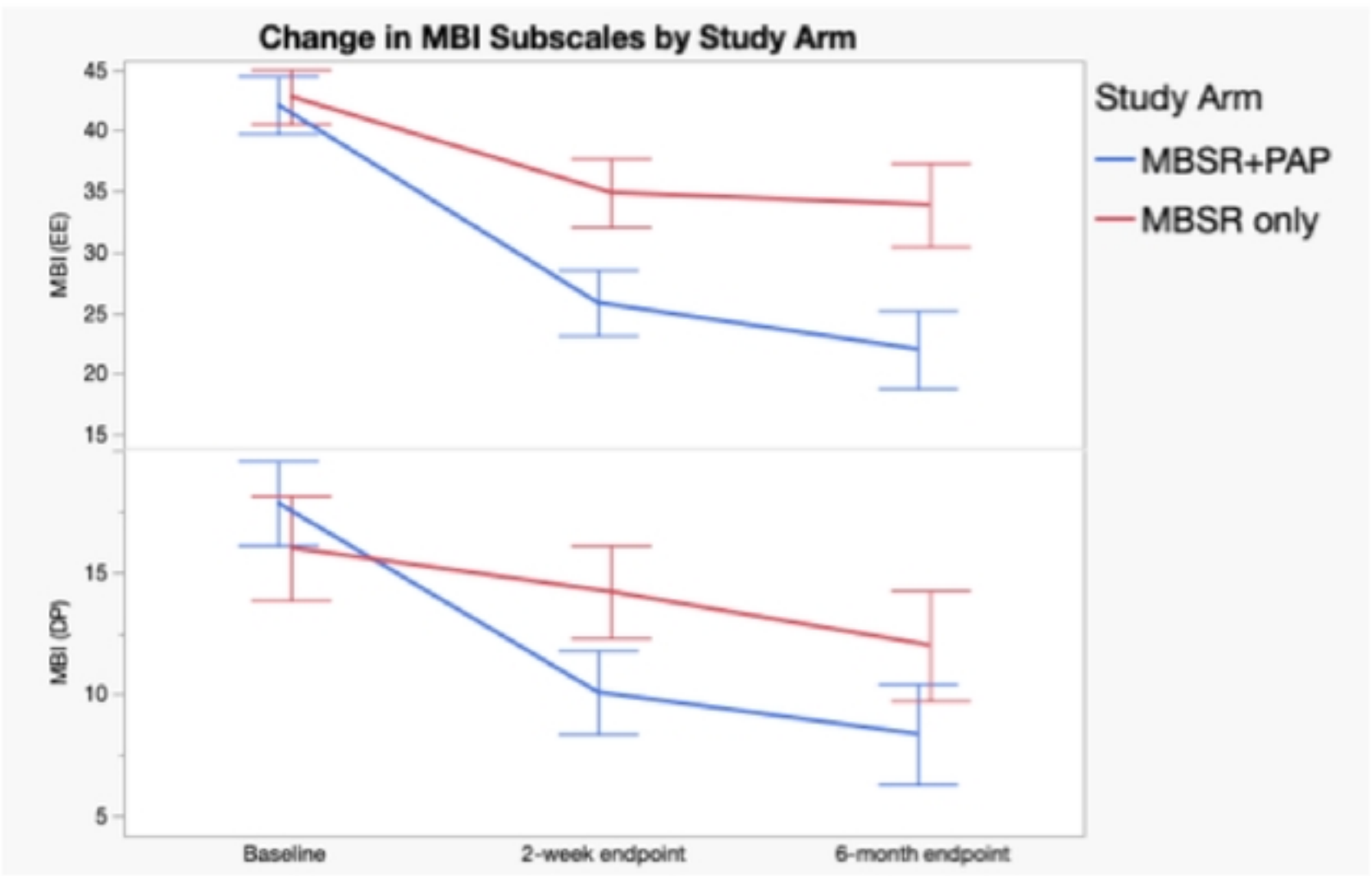


Figure 1. Enrollment, Randomization, and Follow-up of Participants.

Figure

Figure 2: Efficacy Outcomes. Change in Quick Inventory of Depressive Symptoms (QIDS-SR-16) Score and Change in Maslach Burnout Inventory (MBI-HSS-MP) Emotional Exhaustion (EE) and Depersonalization (DP) Subscale Scores by Treatment Group (Intention-to-Treat Analysis). Total scores on the Quick Inventory of Depressive Symptoms range from 0-27 with higher scores indicating greater severity of depression. Bars represent standard errors.





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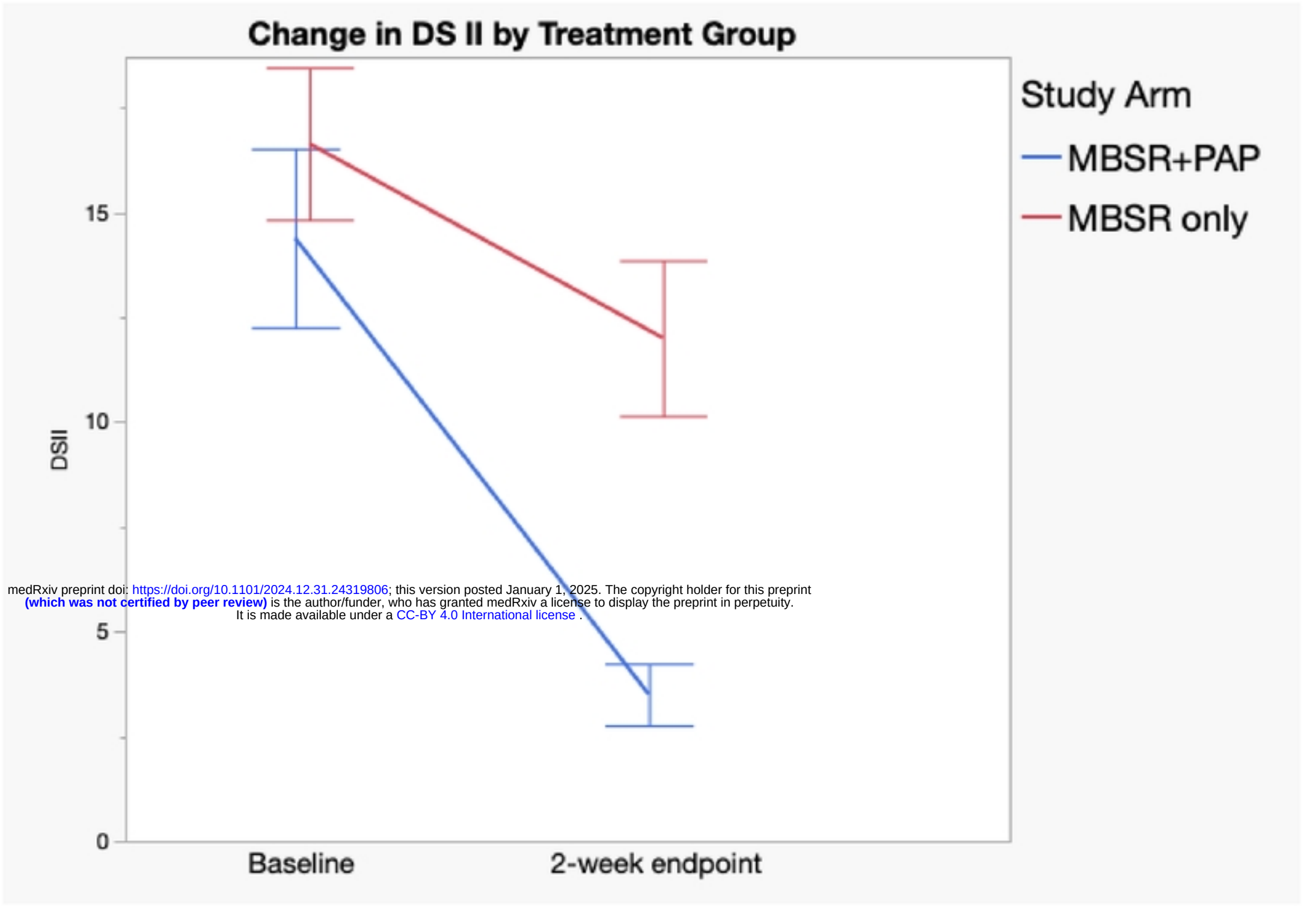

Figure 4. Change in Demoralization Scale (DSII) by Treatment Group. Assessed only at baseline and 2-week Endpoint. Error bars = standard error.

Figure

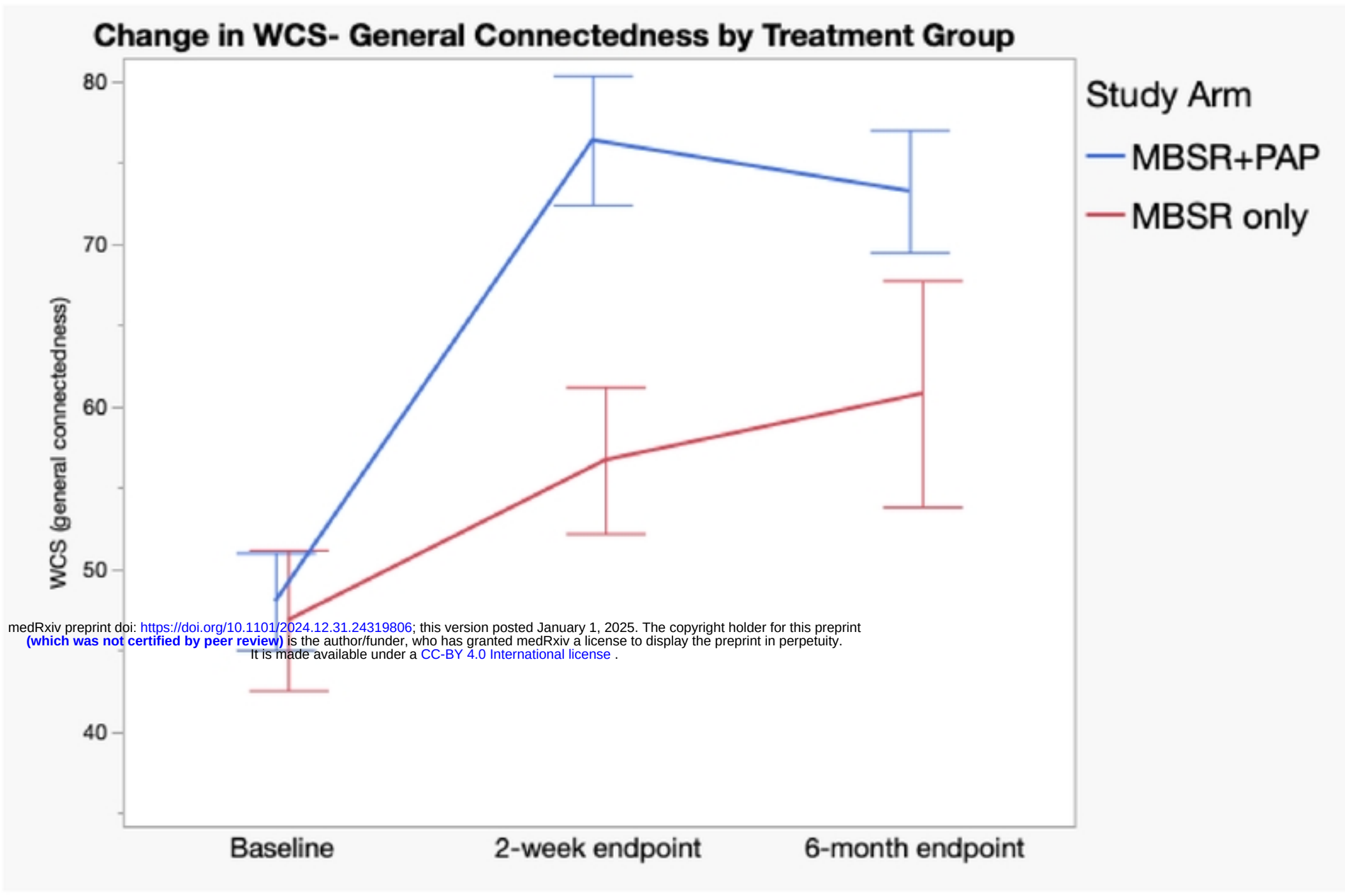

Figure 5: Change in Watt's Connectedness Scale (WCS), General Connectedness by Treatment Group. General Connectedness measure= sum of subscales Connectedness to Self (CTS), Connectedness to Others (CTO), Connectedness to World (CTW). Error bars = standard error.

Figure

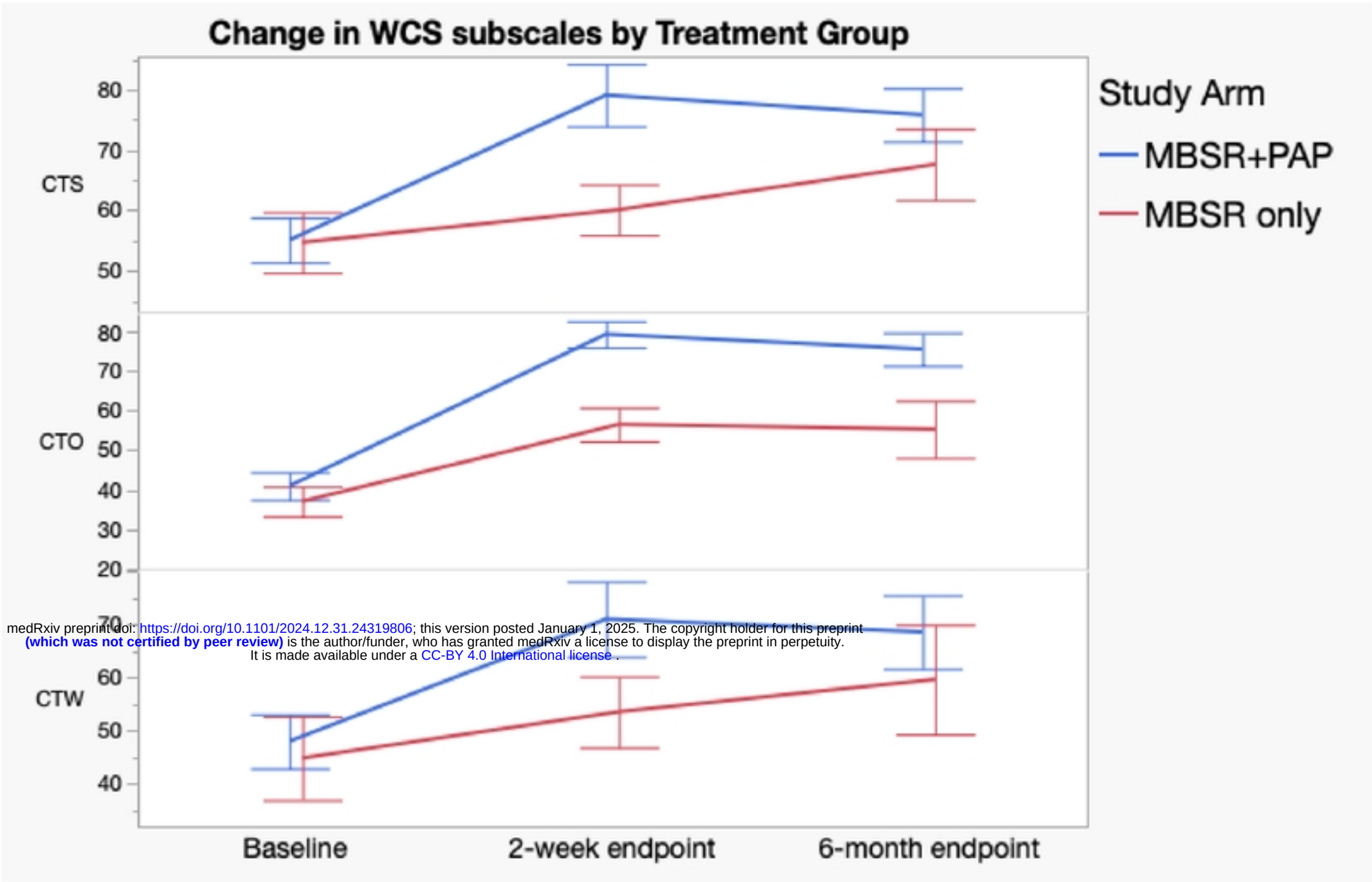

Figure 6. Change in Watt's Connectedness Scale, Subscales by Treatment Group. CTS =Connection to Self, CTO= Connection to Others, CTW= Connection to World. Error bars = standard error.

Figure