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Moment-by-Moment in Women's Recovery: Randomized controlled trial protocol to test the efficacy of a mindfulness-based intervention on treatment retention and relapse prevention among women in residential treatment for substance use disorder

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Abstract

Although therapeutic treatments exist for substance use disorder (SUD), about half of individuals who enter treatment leave early and relapse to substance use. Early dropout from residential treatment places individuals at risk of relapse, and women in SUD residential treatment represent a vulnerable population. Evidence gaps persist for the use of mindfulness-based interventions (MBIs) among racially and ethnically diverse women with SUDs, especially regarding the efficacy of MBIs adapted to prevent residential dropout and relapse. We previously developed and pilot tested an MBI, Moment-by-Moment in Women's Recovery (MMWR), adapted to support women with SUD during residential treatment. The 12-session MMWR program tested in the present study integrates relapse prevention, addresses literacy level and trauma experiences and mental health problems, and is relevant to issues surrounding treatment- and relapse-related stressors among women. The primary objective of the current Phase II randomized controlled trial is to adequately test the efficacy of MMWR on residential treatment retention and substance use relapse and determine psychosocial and neural mechanisms of action underlying MMWR. Participants are women in residential SUD treatment from a community-based residential site that serves mainly women who are low-income and racially and ethnically diverse. A subgroup of participants from each treatment group also completes functional and structural neuroimaging assessments before and after the intervention to explore possible structural and functional brain correlates of change associated with participation in the MMWR program. Findings are expected to inform the utility of adapting MBIs to improve treatment success among vulnerable women in SUD residential treatment.

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Keywords

mindfulness; substance use disorder; relapse; residential treatment; women; race/ethnic minorities

1. Introduction

Although some therapeutic treatments provide promising results for substance use disorder (SUD), 40 to 60 percent of users who enter treatment leave early and relapse to substance use within 1 year [1]. Early dropout from SUD treatment is a significant predictor of relapse, criminal activity, and other negative outcomes [2, 3], making retention of users in SUD treatment paramount to improving long-term recovery [4]. Retention is particularly challenging in residential treatment programs, which typically serve individuals exhibiting greater levels of addiction severity [3, 5].

Of those receiving SUD treatment, women report significantly higher rates of depression (58% vs. 45%, respectively), physical abuse (70% vs. 32%), and sexual abuse (54% vs. 15%) than men [6]. Although gender alone is not consistently associated with treatment retention, women represent a vulnerable population because they often enter SUD treatment with more complex medical comorbidities [7–9]. Further, individuals in women-only residential programs are more likely than individuals in mixed-gender programs to be homeless, on probation, and to have long histories of drug use [10, 11]. Racial and ethnic minorities are also less likely to successfully complete SUD treatment than non-Hispanic Whites [12, 13] and are more likely to have involvement with the criminal justice and child welfare systems [14, 15]. These findings draw attention to the need for specialized programs to address apparent sex, socioeconomic, and racial and ethnic disparities during SUD recovery.

Mindfulness-based interventions (MBIs), defined here as programs founded on the practices of Mindfulness-Based Stress Reduction (MBSR) [16] and include mindfulness as their central therapeutic practice, offer one approach to support SUD recovery [17]. MBIs offer learners a systematic and experiential method to cultivate mindfulness in daily life using the wisdom practice of meditation. Mindfulness refers to a particular conscious form of attention, specifically as the “awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment” [16]. Mindfulness, as a complex process, entails the systematic training and deployment of attention and the awareness and wise action that arises from it. Practitioners learn to at least experiment with attending to, befriending, and accepting their actual experience, inwardly and outwardly, in the present moment. Training in mindfulness is the systematic procedure for honing in on and sensitizing the innate human capacity to inhabit more fully the present moment and welcoming as best one can, the full range of one’s experience, pleasant, unpleasant, and neutral. As such, mindfulness training ultimately reduces suffering by catalyzing a shift or “rotation” in one’s relationship to aversive experience and the reactive mind-states that accompany it. Such mind states include craving—the strong desire for things to be different from how they are, which is usually felt as an urge, desire, or yearning for release or for pleasure. Given that such cravings are a core

feature of SUD and the addiction process, MBIs offer therapeutic potential. MBIs are reportedly part of the third wave of empirically tested psychotherapies, with the first wave being behavioral therapy and second being cognitive behavioral therapy [18]. The first two waves focus on the intentional modification of cognitive, emotional, and behavioral processes, whereas MBIs focus on cultivating a nonjudgmental awareness of the experience of consciousness that encompasses those same cognitive, emotional, and behavioral self-regulation processes.

Reviews of experimental research trials report that MBIs adapted for substance users show some promise for treatment efficacy [19], and theoretical models have been formulated to rationalize their therapeutic integration in SUD recovery [20]. We elaborate on these programs and viewpoints in our Discussion section. However, studies testing the efficacy of MBIs with individuals with substance use disorders remain largely limited to non-Hispanic White or male samples, or a mixture of both. A gap in knowledge persists regarding the efficacy of MBIs among women with SUDs who are low income, members of diverse racial and ethnic groups, or both, especially MBIs integrated during residential treatment to support client retention and prevent relapse.

In 2009 in collaboration with a certified MBSR instructor, Zayda Vallejo, Amaro [23,24] developed Moment-by-Moment in Women's Recovery (MMWR), an MBI focused on SUD treatment retention and relapse prevention for vulnerable women with complex social and clinical histories [21, 22]. MMWR is an adaptation of MBSR and aims to improve intervention acceptability and fit for low-income, racially and ethnically diverse women in SUD treatment. Our adaptation is intended to be integrated during residential treatment and addresses issues pertinent to addiction, relapse prevention, literacy, trauma, and cultural diversity among women and combines elements of stress reduction and relapse prevention [23] skills development rooted in mindfulness and contemplative practice.

We previously tested the acceptability and promise of MMWR using a within-subjects repeated-measures study that enrolled 318 low-income women attending SUD treatment from 5 facilities (4 residential and 1 outpatient) in Boston [21]. Sample race and ethnicity was 45% Hispanic, 35% non-Hispanic Black, and 20% non-Hispanic White or other. Participants reported high satisfaction with the MMWR program (rating of 3.4 of 4, or excellent) and exhibited improved mindfulness skills such as living in the present moment, reduced stress, and increased a sense of well-being. Higher session dosage of the MMWR program significantly predicted reduced alcohol use, drug severity, and perceived stress at 12-month follow-up, after adjusting for baseline sociodemographic, criminal, and treatment exposure variables. This preliminary study did not randomly assign treatment exposures, lacked a control group, and did not assess treatment retention or substance use relapse. The current Phase II experimental trial to address these limitations is the next step to determining the efficacy of the MMWR program.

1.1. Study objectives

Our study aim is to determine if the MMWR program improves SUD recovery among racially and ethnically diverse women by increasing residential treatment retention and reducing substance use relapse post MMWR treatment. To accomplish this aim, we apply a

Phase II randomized controlled trial (RCT) design to test the efficacy of MMWR on these primary outcomes compared to an active psychoeducation control group that accounts for time, attention, group cohesion, expectancy, teacher, and other nonspecific effects. We hypothesize that MMWR relative to the active control group will increase residential treatment retention and decrease relapse (primary outcomes). Our secondary aim is to test if MMWR functions via proposed mechanisms of the intervention, including mindfulness skills, stress reduction, coping skills, self-regulation, craving, and negative affect. We hypothesize that MMWR will increase mindfulness, coping skills, and self regulation and decrease craving and negative affect relative to the control group. Finally, we are aware of no studies providing neural data when applying a MBI with this population; thus, our exploratory aim is to examine possible structural and functional brain correlates of change associated with participation in the MMWR program. We hypothesize against the null hypothesis such that change in brain measures will be non-equivalent across the treatment groups.

2. Methods

2.1. Study design

This Phase II parallel group RCT conducted from 2016 to 2019 is used to contrast two interventions as add-ons integrated during residential SUD treatment: (1) MMWR and (2) Neurobiology of Addiction (NA), with the latter serving as the active control condition. Baseline interviews occur prior to randomization and are administered within the first 6 weeks of starting residential treatment. Postintervention interviews occur within 1–14 days of the last class session and follow-up interviews occur within a 7–9 month postintervention window. A target sample of 200 women who meet study eligibility criteria will be enrolled. A subsample of 30 participants, 15 from each treatment condition, complete brain imaging protocols at baseline and immediate postintervention. All participants receive SUD treatment services as normally provided by the treatment facility. Participation in the study does not reduce the level of usual care received by participants. The study site offers no competing mindfulness-based activities or services. The trial is registered with clinicaltrials.gov (NCT02977988).

2.2. Participants and procedures

Participants are adult women admitted to a residential treatment center in Southern California who are diagnosed with SUD. As part of standard admission protocol at treatment entry for the clinic site, site intake clinicians assess all patients for SUDs, mental health disorders, suicidality, and cognitive impairment using the LR-DSM-IV or DSM-V [24]. Using information from the agency's intake assessment, our on-site study coordinator identifies female patients who meet study eligibility criteria. About 3 weeks after residential treatment admission, our on-site study coordinator confirms eligibility and obtains permission from eligible patients to be contacted by the study interviewer, who makes appointments with prospective participants, conducts the informed consent process, and administers the baseline assessment.

Our trained research interviewers use a computer-assisted interview protocol to collect data from participants in person. Interviewers also administer Breathalyzer tests and urine collection for the assessment of substance use. Baseline interviews are conducted at the study site and subsequent interviews are conducted at the study site for participants who remain in treatment or at convenient community locations for those no longer at the clinic for postintervention and 8-month interviews. Participants who are incarcerated in a county jail within 90 miles one-way from the project study office at either of the last two measurement points are interviewed in jail. Women incarcerated in prisons are not followed due to difficulty in contacting them and human subject concerns regarding collection of drug-related behaviors with prisoners. Breathalyzer tests and urine collection is not completed for participants who are in jail. The postintervention interview occurs up to 2 weeks after the last group session is completed. The 8-month postintervention interview occurs within a 4-week window before and after (months 7–9) of the anniversary of the intervention's end date. Baseline assessment requires approximately 1.5–2 hours and post assessments take 45–60 minutes to complete. Participants receive compensation for their time (baseline and postintervention: \$30 for the interview, \$5 for a urine sample, and \$5 for a Breathalyzer test; 8-month interview: \$50 for the interview, \$5 for a urine sample, and \$5 for a Breathalyzer test; participants no longer in treatment receive \$20 cash for transportation and babysitting costs for travel and babysitting costs). Participants in the imaging substudy receive \$75 for completing a preintervention and \$75 for completing a postintervention imaging session as well as transportation to and from the imaging site located at the USC University Park Campus. Enrollment in the study is rolling until a cohort is defined, and cohorts begin the assigned intervention every 6 weeks, resulting in approximately 10 women per condition to maintain a reasonably small class size. The University of Southern California Institutional Review Board approved this study (UP-14-00391).

2.3. Residential clinic site

The site for the study is a publicly funded, women-only, residential SUD treatment facility located in Southern California that can house up to 110 residents on a 4-acre campus. The site serves racially and ethnically diverse women mainly with low-income status. It includes residential quarters, space for group therapy and classes, a computer lab, a nursery, and a classroom for the preschool program that is provided through the local school district. Women can bring all of their children (ages 0–10 years) to live with them and child care is provided on-site, along with an array of supportive services for pregnant and parenting women. The site integrates and coordinates services for women with multiple vulnerabilities, including those with mental health disorders, history of exposure to traumatic events and PTSD (in their past or present, and health problems such as HIV/AIDS). The program elements include biopsychosocial assessment, chemical dependence education and counseling, individual and group therapy, relapse prevention, random drug testing, specialized women's groups, trauma education and support, family education and counseling, vocational training, educational support, case management, nutritional education and support, health and wellness activities, and 12-step meetings. Referrals to medical, dental, domestic violence, psychiatric care, GED classes, and Early Head Start services are made as needed.

2.4. Eligibility requirements

Inclusion criteria for the main research trial are as follows: client at the study site, female, adult (between 18 and 65 years of age), diagnosed with SUD, fluent in English, and agrees to participate in the study. Exclusion criteria for the main research trial are as follows: inability to comprehend or sign informed consent, cognitive impairment, untreated psychotic disorder or severe chronic mental health condition based on clinical intake LR-DSM-IV or DSM-V or diagnostic assessment, older than 65 years of age, reported suicidality during the prior 30 days based on clinical intake assessment, current prisoner, more than 6 months pregnant, not willing to be audio recorded during interviews and intervention sessions, and not willing to have data used in future studies. Additional exclusion criteria for the neuroimaging substudy are as follows: older than 50 years of age, not in good general health, left handed (mean item score > 1 on the handedness scale), currently or possibly pregnant, currently using medical devices (cardiac pacemaker, implanted cardiac defibrillator, carotid artery vascular clamp, neurostimulator, cochlear implant, metal fragments including shrapnel in the head, eyes, or skin, vascular stent, ocular implant, penile implant, vascular filter for clots) or other nonremovable metal devices including dental braces or retainers, have an intrauterine device, body mass index greater than 36, history of head trauma resulting in loss of consciousness for more than 5 minutes, documented or subjectively reported claustrophobia, hair extensions or a wig connected by wire, and permanent eyeliner. Most of the exclusion criteria for the imaging study pertain to ensuring the safety of participants.

2.5. Randomization

To minimize bias across study groups related to participant characteristics and histories, we apply urn randomization as implemented by the Urn Randomization Program (version 1.01) after a group of 10–30 women are deemed eligible for randomization. Strata variables are current pregnancy (yes or no) and age (18–31 years or 32–65 years). The urn approach is robust against experimental bias in clinical trials because it is a compromise between perfect balance in treatment assignments and complete randomization to eliminate experimental bias [25]. Participants for the neuroimaging substudy were selected by convenience for participation due to the logistical constraints that would have been posed by randomly selecting women from each treatment group.

2.6. Interventions

2.6.1. Moment-by-Moment in Women's Recovery—This intervention is delivered twice weekly for 80 minutes across 12 group sessions during residential treatment. MMWR is guided by an instructional manual with standardized lesson plans [22]. An experienced teacher trained in both MBSR and MMWR facilitates all sessions and an on-site master's-level clinician with experience in SUDs cofacilitates the intervention. Each class session has a central theme that is divided in five segments in the following order: (1) welcome, review of group culture, brief homework practice check-in, objectives, brief mindfulness meditation or practice; (2) didactic psychoeducational presentation and discussion of lesson content; (3) experiential meditation and mindfulness practices related to the session's themes; (4) practice of sitting or walking meditation, body scan, or standing stretching; and (5) selected

reading related to session topic, assignments for the next class, and closing meditation. Trainees are expected to learn skills to approach experiences and stressors using mindfulness principles. Students learn about the role of automatic reactivity to stressors and its relation to addiction and relapse; the connections between stress, triggers, and relapse; and how to use mindfulness practices to respond best to related thoughts, emotions, body sensations including those related to stress in a residential treatment setting, and experiencing triggers while still avoiding relapse. As with MBSR, trainees learn and practice self-regulation strategies using four foundational mindfulness practices: body scan, seated meditation, mindful hatha yoga, and walking meditation. Throughout the course, students are encouraged to bring mindful awareness into daily activities and practice meditation as homework that is supported by practice assignments and guided meditation audio recordings. Those enrolled in the study receive a Participant Workbook at the beginning of the course that is organized by session and for each session contains homework and practice assignments. Study participants are asked to bring this Workbook to each session so that the session's homework practice assignments can be explained by the facilitator and reviewed as women follow along. Some assignments ask participants for specific reflections and written response. Participants receive a MP3 player with meditation audios for each session to guide participants through practices introduced in that class session or previous sessions.

2.6.2. Neurobiology of Addiction—This intervention is delivered twice weekly for 80 minutes across 12 group sessions during residential treatment. NA is guided by an instructional manual with standardized lesson plans [26]. The curriculum was developed over 3 years with input and review from focus groups of women and providers in SUD treatment and was reviewed by three experts in the neurobiology of addiction. A master's-level educator with a background and training in the neurobiology of addiction facilitates all sessions and an on-site master's-level clinician with experience in SUDs cofacilitates the intervention. Students receive didactic education on the structure and function of the brain and neurobiology of addiction. Although educational and focused on knowledge acquisition, the program has no proven efficacy for substance use behavior. Similar to the MMWR intervention, it includes didactic psychoeducational presentation using powerpoint and video recordings, exercises, games and group discussions to reinforce the session content and respond to questions. Sessions do not address behavior change strategies, stress reduction, mindfulness, or relapse-related content. Films, videos, exercises, activities, and discussions are used to keep participants engaged. Topics include: (1) definition of addiction and why it is a brain disease; (2) brain structures and functions and those related to addiction; (3) effects of various types of substances on the brain; (4) rewarding effects of substances and how these effects lead to addiction; (5) definitions and brain functions related to craving and withdrawal; and (6) the roles of recovery and treatment. Participants are expected to gain knowledge pertaining to the effects of drugs on brain structure and function. The intervention is equivalent to MMWR in dosage, frequency, teacher attention, and group structure. Participants receive a Participant Workbook organized by session which includes session specific information covered in each session such as selected powerpoint slides. Participants receive MP3 players with audio clips of key sections of videos introduced in class.

2.6.3. Teacher training and certification—Teachers of the interventions have at least 2 years of experience in their respective topics. MMWR lead teachers hired for this project are experienced mindfulness facilitators; one was in the process of acquiring MBSR instructor certification at project start. The first MMWR facilitator received 5 days of intensive training and the second teacher, hired later in the project, was trained in mindfulness intervention delivery and was trained on MMWR by the first teacher and the MMWR certified senior teacher and codeveloper of MMWR. Both facilitators received training and ongoing supervision from an MBSR-certified senior teacher and codeveloper of MMWR to ensure that the MMWR teachers in the study remain adherent to the foundational principles of mindfulness practice and the MMWR curriculum. The Neurobiology of Addiction condition was led by one teacher. Training and supervision of this group's teacher was conducted by a masters level clinician with specialization in SUD treatment and specialty training in the neurobiology of addiction. After initial training, lead facilitators conducted an audiotaped 12-session cohort of their respective intervention with a pilot group of participants at the study site. Audio recordings of the pilot groups were rated for fidelity by independent raters to ensure high fidelity prior to onset of study cohorts. After the pilot sessions all study intervention group sessions are recorded and a six randomly selected sessions for each cohort are assessed for fidelity.

2.7. Treatment fidelity

Six randomly selected class sessions for each cohort from both study conditions are audio recorded for supervision and fidelity checks to guard against intervention drift. These intervention sessions are reviewed by the PI, senior trainer, and/or trained research assistants and scores are reviewed by the PI in case there is the need to provide immediate feedback to the respective facilitator regarding adherence to the teaching manual. Trained staff members use a published MBI fidelity measure called the Mindfulness-Based Relapse Prevention Adherence and Competence Scale [27] that is slightly modified to fit the intervention content to independently rate the selected sessions for each cohort. The fidelity assessment includes: (1) a session-specific fidelity checklist, (2) a scale measuring adherence to principles of mindfulness, and (3) a scale assessing facilitator competence in delivering intervention components. We established interrater reliability on fidelity ratings at study onset using a pilot cohort and review it every 2 months. Any deviations from intervention protocols are immediately addressed during weekly supervision meetings or at the end of each cohort once high fidelity is consistently observed. A teacher not satisfactorily delivering an aspect of the intervention receives additional training and resumes intervention delivery once required levels of compliance are achieved.

2.8. Assessments and measures

Research staff members capture participant data during in-person interviews using the Research Electronic Data Capture (REDCap) computer-assisted interview process, administer an alcohol Breathalyzer test (Alco-Sensor FST, Intoximeters: St. Louis, MO) to test for recent alcohol use, and then provide instruction for collection of a urine sample (AmediCheck™ Instant Test Cup, Confirm Biosciences: San Diego, CA) to test for recent use of illicit substances.

2.8.1. Primary outcomes—These outcomes, conceptualized as the study endpoints, include: (1) days in residential treatment as confirmed by clinic records from the start of the intervention and (2) relapse to alcohol and illicit drugs obtained from the interviewer-assisted Timeline Followback (TLFB) calendar [28] and cross-verified by the urine drug screen and alcohol Breathalyzer test. The TLFB calendar captures daily use of substances and periods of restricted environments such as residential treatment, incarcerations, and hospitalization every day for a designated period of time. We collected TLFB information for the 8 months prior to residential treatment start, residential treatment start to MMWR program start, MMWR program start to end, and for 8 months post MMWR program. We quantify substance use and relapse as days of abstinence prior to any illicit drug use from the start of the intervention to follow-up points and total days of abstinence during this study period. For alcohol, we quantify the time to first day of heavy drinking and total days of abstinence during this study period. Further, to assess the nuances of relapse, we quantify the following categories according to Gossop et al. [29]: (1) relapse: used substance after intervention and continued to use regularly on more than one third of days from first use to follow-up; (2) lapse: used after intervention but did not revert to regular use on one third or less of days from first use to follow-up; and (3) abstinent: did not use during the time period.

2.8.2. Program mechanisms of action—These mechanisms are measured by participant self-report on validated psychometric scales of applied use of mindfulness in challenging situations (Applied Mindfulness Process Scale [30]), mindfulness disposition (Five Facet Mindfulness Questionnaire [31]), perceived stress (Perceived Stress Scale [32]), psychological distress (Depression, Anxiety and Stress Scale [33]), distress tolerance (Distress Tolerance Scale [34]), self-regulation (Difficulties in Emotional Regulation Scale [35]), craving (Penn Alcohol Craving Scale, inclusive of multiple substances [36]), and negative affect (Positive and Negative Affect Scale [37]). Participants complete mindfulness practice reports and the Applied Mindfulness Process Scale during four class sessions and record of class attendance is obtained via a sign-in sheet.

2.8.3. Covariates—These variables are substantively related to the primary outcome measures and are accounted for in statistical models if deemed influential on intervention effects. Measures include (1) participant satisfaction with treatment as reported during class sessions 2 and 11; (2) treatment days and status obtained from site clinic records (e.g., number of treatment days before treatment departure; final treatment status completion and progress rating, mental health diagnosis); (3) number and types of residential services received at the residential site obtained from weekly clinical service logs collected during the participant's entire stay at the facility; (4) being in a controlled environment from the TLFB (e.g., residential treatment, jail, prison); and (5) intervention program class attendance (number of sessions attended).

2.8.4. Brain imaging—Brain imaging is performed at the USC Dana & David Dornsife Cognitive Neuroimaging Center with a Siemens MAGNETOM Prisma^{fit} MRI scanner with 20-channel head coil. For the experimental task sessions, functional BOLD signals are acquired with a single-shot gradient echo planar imaging sequence. Thirty-two 4 mm thick slices that cover the whole brain are acquired using the following parameters: repetition time

(TR) = 2000 ms, echo time (TE) = 25 ms, bandwidth = 2520 Hz/pixel, flip angle = 85°, field of view = 220×220 mm, and matrix = 64×64.

Enrolled participants complete the neuroimaging protocol once during the 2 weeks prior to the initiation of the intervention and once during the first 2 weeks after intervention completion. Each session lasts approximately two-hours, and include one hour of neuroimaging. During both assessments, brain activity is measured first during a task that requires participants to shift between periods of mindful breathing and periods attention to visual stimuli. This task lasts approximately seven minutes, and is repeated twice, separated by a one-minute break. The task is included to assess neural correlates of internal vs. external attention. Next participants complete a six minute emotional go/no-go task in which participants view expressive faces and respond when a target emotion (which varies between 'happy', 'fear' and 'neutral') is expressed [38]. The task is presented twice, again with an intervening one-minute break. The emotional go/no-go is included to allow assessment of neural activity associated with emotion reactivity and inhibition. Finally, a six minute resting state scan is included at the end of each session, primarily to allow for an analysis of functional brain network activity.

Each BOLD time series is motion-corrected using MCFLIRT, part of the FMRIB Software Library [39]. Data are smoothed with a nonlinear algorithm designed to preserve image structure by only smoothing voxels classified as the same tissue type (5 mm kernel). Permutations testing (FSL "randomise" function) was used to avoid Type 1 error. Correlational analyses are used to identify brain activity at baseline associated with clinically relevant characteristics and changes in brain activity at follow-up associated with participation in the MMWR intervention.

The order of the two fMRI tasks (emotion control and emotion go/no-go, listed as #2 and #5 above) is randomized. A priori regions of interest (ROI) include the 1) insula, parcellated into 3 sub-regions in each hemisphere, 2) amygdala, 3) dorsolateral prefrontal cortex, 4) ventrolateral prefrontal cortex, 5) the anterior cingulate cortex and 6) the frontal pole. These regions are selected because of their role in emotion responsivity, inhibitory control, detection of conflict and goal-directed regulation of attention.

2.8.5. Sample Size Calculation—An a priori power analysis was conducted based on sample size estimation for longitudinal designs with attrition [40]. A total estimated sample size of 206 was needed to detect a between group effect ($d=0.5$) of linear trend at 8 month follow up with 80% power, two-sided $P<.05$, 3 assessment points, assuming the correlation among repeated measures is 0.5 and a 15% total attrition rate at 8 month follow up, making our target enrollment ~100 per group.

3. Statistical analysis

Study data are collected and entered using REDCap [41] electronic data capture tools hosted at the University of Southern California. To ensure data quality control, we apply double data entry to all TLFB calendars and to 10% of randomly selected data that is manually entered to verify accuracy of data entry. Three waves of data collected at baseline,

immediately after intervention completion, and 8 months postintervention completion from participants in the two treatment groups will be used for hypothesis testing using the intent-to-treat principle. We conduct standard statistical diagnosis and transformation of study variables, perform descriptive analysis of background variables, assess variable distributional properties, plot means of the continuous outcome variables at each time point, and assess internal consistency and test-retest reliability of study scales. We will verify the adequacy of randomization on demographic and clinical covariates, and variables found to differ between groups ($p < .05$) will be used as covariates in the subsequent models. We will conduct bivariate analyses to assess attrition by comparing those retained in the sample to those lost to follow-up at each time point on demographic and clinical features. Using an intent-to-treat approach, we will use multiple statistical procedures tied to the analytic objectives of each of our specific aims, including Kaplan-Meier survival analysis, Cox proportional hazards regression, and generalized linear mixed modeling with random effects. Missing data will be handled in mixed-effects models by using all available cases with full information maximum likelihood estimation. Imputation will be considered if substantial missing data is found for key variables. Kaplan-Meier survival analyses will be used to estimate the cumulative incidence of leaving treatment and differences by intervention condition assessed by the log-rank test. Multivariable Cox proportional hazards regression will be used to assess whether group assignment is associated with days in treatment and with treatment status after controlling for covariates. To evaluate group differences in relapse and lapse, a generalized linear mixed model with random effects will be fitted to the outcome variable individually, specified for corresponding distribution (binary for abstinence and Poisson for number of days of substance use). The models will include a variable for group, a covariate for time point, and a time-by-group interaction term, adjusting for covariates. A significant time-by-condition interaction will test this hypothesis with Bonferroni-Holm P test correction. Focus will be placed on effect sizes and their 95% confidence intervals. Completer status (defined as those that attend 9 or more classes out of the 12 offered) will be included as a covariate in the model to determine its influence on primary endpoints. We will also consider including number of classes attended (as a dosage variable) and see how it is related with change in the primary endpoints by group. The primary test of mediation will be the asymmetric distribution of products test, which is based on the distribution of the indirect effect (i.e., product of coefficient tests) of the intervention through each of the hypothesized mediators [42]. The test of mediation will be based on the product of the pathway between treatment and changes in each of the mediators (e.g., Applied Mindfulness Process Scale, Penn Alcohol Craving Scale).

4. Discussion

In this protocol report, we detail the research design and methodology of an ongoing RCT that is testing the efficacy of MMWR in contrast to an active psychoeducation control group. The overarching goal of this effort is to improve SUD treatment outcomes among vulnerable women by improving SUD treatment retention and preventing substance use relapse. Beyond testing the treatment effect of MMWR on these primary outcomes, we will test the impact of the program on theoretically proposed mechanisms of action (i.e., mindfulness skills, stress reduction, coping skills, self-regulation, craving, and negative affect). We also

have the unique opportunity to conduct a substudy to examine brain structural and functional correlates of change associated with participation in the MMWR program using MRI and fMRI methods. This work builds on our previous study that tested the acceptability and promise of MMWR using a within-subjects repeated-measures design among low-income women attending SUD treatment facilities [21]. Our earlier study did not randomly assign treatment exposures, lacked a control group, and did not assess treatment retention or substance use relapse, and the current trial addresses these limitations.

Our MMWR program is thematically similar to, yet is unique from, other MBI treatment programs adapted from MBSR to support SUD recovery. Our adaptation is specifically intended for administration *during* residential treatment to vulnerable women with trauma histories; addresses issues pertinent to SUDs, relapse prevention, literacy, trauma, and cultural diversity among women; and combines elements of stress reduction and relapse prevention skills development rooted in mindfulness and contemplative practice [21, 22]. Our MMWR therapeutic framework proposes that mindfulness training ultimately reduces the subjective urge to use substances and the subjective negative feeling state arising from a stimulus in part by replenishing participants' self-regulation resources that have been depleted from the many challenges inherent in early recovery from SUD.

Mindfulness-Based Relapse Prevention (MBRP) is a MBI adapted for substance users and is intended to be delivered as SUD aftercare to prevent relapse [43]. As with MMWR, MBRP combines mindfulness strategies with relapse prevention to help people with SUDs encounter cravings with less automatic reactivity [44, 45]. A small yet growing body of literature has found that MBRP can reduce alcohol and illicit drug use and craving and increase acceptance and awareness of thoughts and feelings in some populations [46–48]. One study in particular focused on racial and ethnic minority women [47]. Despite the promise of MBIs for individuals with SUDs, empirical knowledge gaps persist. These gaps produce limitations due to studies with small sample sizes, quasi-experimental study designs [19], lack of representation of low-income, racially and ethnically diverse women [49], and nonresidential treatment settings [43]. Only one study to date has evaluated the use of a MBI during residential SUD treatment and used a historical control group. In this study, Marcus et al. [50] conducted a survival analysis of time to treatment dropout and found no significant difference between a MBI and treatment as usual; however, greater participation in the MBI was associated with decreased likelihood of treatment dropout. Although promising, the study did not include random assignment or follow participants after discharge from residential treatment to assess relapse. Considering the gaps in the current state of evidence, there is a continued need for research that carefully evaluates the efficacy of adapted MBIs in reducing residential treatment dropout and longer-term relapse, especially among vulnerable women for reasons discussed in the Introduction.

Our study has several strengths. We administer an RCT design with an active control condition that matches MMWR in terms of time, attention, expectancy, teacher, and social support, and other nonspecific effects. Our selection of racially and ethnically diverse women extends previous research that is mainly representative of Whites, and our requirement of a clinically derived SUD diagnosis allows for direct clinical implications for future treatment. We capture substantively derived measures of intervention mechanisms that

will yield the opportunity for formal tests of mediation using multiple time points. Tracking participants up to 8 months after completion of the intervention allows for an assessment of duration of potential effects or late onset of change. Our use of the TLFB calendar provides comprehensive data on daily substance use behaviors during treatment and follow-up, and our use of biomarkers of alcohol and drug use are useful to cross-verify self-reports of substance use. Our addition of the brain imaging substudy allows us to explore neural changes associated with participation in the MMWR intervention and can inform how MBIs affect the brain during early recovery.

Our study also has some limitations. First, we do not administer an MBI sham control group, which is a promising methodology to support internal validity. Our decision to exclude a sham is to avoid possible negative effects of inaccurate meditation training for this vulnerable population that is sensitive to negative thought patterns and reactive substance use. Second, given the behavioral nature of the intervention, it is likely that participants figure out the treatment intent after the treatment begins. We mask group information until the first day of the intervention class to guard against this threat. Third, cross-contamination is possible because both classes are delivered at the same site, although we separate class location in the facility to guard against this threat. Fourth, the single recruitment site, although large and diverse, limits the generalizability of findings to the broader population of women receiving SUD treatment. Finally, although we have strict tracking protocols in place, given that many of our participants experience poverty, residential disruption, and incarceration, it is likely that some participants will be challenging to follow over time, thus affecting sample retention.

In conclusion, we describe here in detail the significance, rationale, study design, and methodology of a Phase II RCT designed and powered to test the efficacy of MMWR in contrast to an active control group on treatment retention and substance use relapse among racially and ethnically diverse women with SUD. We expect that this trial will contribute valuable scientific evidence to support or refute the utility of integrating MMWR during conventional residential treatment for SUD.

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