Published in final edited form as:

Contemp Clin Trials. 2014 January ; 37(1): 139–147. doi:10.1016/j.cct.2013.11.010.

Exercise for Methamphetamine Dependence: Rationale, Design, and Methodology

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Abstract

Background—Effective pharmacotherapies to treat methamphetamine (MA) dependence have not been identified, and behavioral therapies are marginally effective. Based on behavioral studies demonstrating the potential efficacy of aerobic exercise for improving depressive symptoms, anxiety, cognitive deficits, and substance use outcomes, the study described here is examining exercise as a potential treatment for MA-dependent individuals.

Methods—This study is randomizing 150 participants with MA dependence at a residential treatment facility for addictive disorders to receive either a thrice-weekly structured aerobic and resistance exercise intervention or a health education condition. Recruitment commenced in March, 2010. Enrollment and follow-up phases are ongoing, and recruitment is exceeding targeted enrollment rates.

Conclusions—Seeking evidence for a possibly effective adjunct to traditional behavioral approaches for treatment of MA dependence, this study is assessing the ability of an 8-week aerobic and resistance exercise protocol to reduce relapse to MA use during a 12-week follow-up period after discharge from residential-based treatment. The study also is evaluating

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ClinicalTrials.gov identifier: NCT01103531

Disclosure statement

Dr. Christopher Cooper has consulted for the company CareFusion which produces the exercise testing equipment used for study assessments.

improvements in health and functional outcomes during and after the protocol. This paper describes the design and methods of the study.

Keywords

methamphetamine dependence; exercise; aerobic; treatment intervention; outcomes

INTRODUCTION

Worldwide, between 14.3 million and 52.5 million adults engage in nonmedical use of methamphetamine (MA) and other amphetamine-type stimulants (ATS), second in number only to marijuana users and more than the numbers of heroin and cocaine users combined [1], with over 400,000 MA users in the United States [2]. In the United States, admissions to publicly funded drug treatment programs due to ATS-related problems peaked at 9% in 2005 and decreased to 6% in 2010 [3]. To date, there are no medications approved for the treatment of MA dependence. Behavioral approaches, such as cognitive behavioral therapy and contingency management, have proven modestly effective and remain the standard treatment.

Despite the paucity of literature on exercise-based interventions for substance use disorders, studies to date provide preliminary evidence in support of this approach. The majority of research has focused on aerobic exercise as a potential intervention to aid smoking cessation and has shown inconsistent effects of exercise on smoking abstinence. Some studies have demonstrated positive effects of exercise on cigarette cravings, withdrawal symptoms, and smoking-related behaviors after exercise sessions [4,5]. Observational studies have suggested benefit of exercise in reducing drug use in substance users within treatment settings [6,7] as well as in non-treatment-seeking cannabis users [8]. A prospective investigation of more than 4,000 twins revealed lower rates of illicit drug use among physically active adolescents compared to those who were less active [9].

Seeking evidence for a possibly effective adjunct to traditional behavioral approaches, the aim of this study is to assess the ability of an 8-week aerobic and resistance exercise training protocol to reduce relapse to MA use after treatment. The study is also evaluating the effects of exercise in terms of improved health and fitness measures during and after the protocol.

STUDY DESIGN AND APPROACH

Rationale for the Study

The contribution of emotional stress and aversive mood states to drug use and relapse has been well documented (e.g., [10–12]), and considerable evidence is accumulating to suggest that substance users exhibit deficits in their ability to regulate such stress. MA dependence is associated with elevated rates of comorbid depression and anxiety (e.g., [13]), and severity of psychiatric symptoms has been associated with poorer treatment outcomes in multiple prior studies (e.g., [14–16]. Upon cessation of MA use, an abstinence syndrome comprising prominent psychiatric features may emerge (e.g. [17]), characterized by drug cravings coupled with anhedonia, dysphoria, irritability, poor concentration, hypersomnia, low energy, and even suicidality [18].

Randomized controlled trials (RCTs) have demonstrated that exercise interventions ameliorate negative mood states, including depression and anxiety [19]. Prior studies have demonstrated efficacy of exercise in reducing symptoms of depression in humans (e.g., [20,21]). Exercise has been shown to be as effective as cognitive behavioral therapy (CBT) [22] and to psychotropic medications [23] for depression. State anxiety has been shown to acutely diminish after individual episodes of exercise [24], and aerobic exercise may confer significant benefit in the treatment of adults with anxiety problems including anxiety sensitivity [25], panic disorder [26,27] and obsessive compulsive disorder [28].

Positive relationships between physical exercise and cognition have been documented in meta-analyses of RCTs, confirming that normal and cognitively impaired adults derive cognitive benefits from physical exercise (e.g., [29,30]). Improvements are the greatest for executive functions, for participants in combined aerobic and strength training regimens, and when exercise duration is greater than 30 minutes [31]. While considerable cognitive impairment remains in post-treatment MA users, exercise may improve recovery by contributing effects on underlying neurobiological processes, such as dopamine activity [32]. Exercise has been associated with structural integrity of white matter in the brain [33] and with volume changes in the frontal cortex, which may be related to cognitive performance in domains including memory and executive function [34]. Thus, this study was designed to assess cognitive performance at several points in order to determine, as hypothesized, whether cognitive performance is improved in the exercise group compared to the control group.

This study was also designed to examine the effects of exercise on striatal D2/D3 dopamine (DA) receptors in a subset of MA-dependent participants (via positron emission tomography; PET) and on related structural brain changes in the striatum (via magnetic resonance imaging; MRI). Compared with healthy control (HC) participants, individuals who abuse MA have deficits in striatal D2/D3 receptors [35], which have a role in modulating addictive behavior and reward sensitivity. Individuals who have used MA chronically show deficits in striatal DA system markers (e.g., [36,37]), and partial recovery of striatal dopamine transporter activity (DAT) may occur after prolonged abstinence from MA [38].

Study Objectives

The primary objective of the study is to determine whether MA-dependent individuals who participate in an 8-week aerobic and resistance exercise intervention (“EX”) have fewer days of MA use compared to participants in health education (“ED”) condition after discharge from a residential treatment program. The primary outcome measure for the study is evidence of MA use by self-report and by urine test during the 12-week post-discharge period. Secondary objectives are to: 1) characterize effects of EX on MA craving and negative affect states, including anxiety, depression, and anhedonia; 2) characterize effects of EX on neurocognitive functioning; 3) characterize variations in health-related outcomes among participants in the two groups; 4) examine changes in dopamine D2/D3 receptor availability among a subset of participants assigned to both conditions; 5) assess structural changes in brain regions using MRI; 6) examine differences in addiction-related behaviors

and consequences as per Addiction Severity Index (ASI) domains (e.g., employment, legal, medical, interpersonal, psychiatric)..

Study Setting

The protocol is being conducted in a residential, community-based rehabilitation facility in Los Angeles, California. All participants are provided at least 12 weeks of residential treatment services as usual in this program. The program incorporates a combination of individual and group counseling employing cognitive behavioral therapy, 12-step facilitation, motivational interviewing, and family therapy. Brain imaging takes place at the UCLA Semel Institute's Center for Cognitive Neuroscience and the Positron Emission Tomography Center of the Veteran's Administration of Greater Los Angeles Health System.

Participants

A total of 150 MA-dependent participants age 18 and older are being randomized to one of two study conditions, Exercise (EX) or Education (ED). MA-dependent individuals in the residential program are informed about the study within 72 hours of their admission to the treatment facility, and individuals interested in the study are asked a series of pre-screening questions to determine initial eligibility. Participants who remain interested and potentially eligible are consented and screened for inclusion criteria (e.g., vital sign stability, age 18–45 for men and 18–55 for women as per American College of Sports Medicine [ACSM] guidelines for supervision of exercise with non-physicians [39]) and exclusion criteria (e.g., acute or unstable medical conditions precluding safe participation in the exercise program, clinically significant ECG abnormality, acute neuropsychiatric condition) to determine eligibility (see Table 1). A subset of 30 participants who complete a second consent procedure (15 from each condition) also receive PET and MRI scans immediately following randomization and again after completion of the 8-week protocol. This study was approved by the UCLA Institutional Review Board.

METHODS

Study Procedures

The study schema is presented in Figure 1. Individuals in the residential program who express interest about study recruitment materials are invited to participate in informed consent procedures, and those who voluntarily consent to participate then enter a 2-week screening phase. During screening, participants obtain a physician-administered medical history and physical examination, clinical laboratory testing, and 12-lead ECG and other assessments to determine whether participants meet eligibility criteria (see Table 1) and to collect baseline measures of drug use and other life domains (e.g., HIV risk, family/social problems, legal problems, etc.). After collecting baseline data, participants who meet eligibility criteria are randomly assigned in a 1:1 ratio to one of two study conditions, EX or ED. Randomization is stratified by two variables, sex and severity of prior MA use (as defined by less than or greater than 18 days/month by self-report).

Maximal Exercise Performance Test—All study participants complete a maximal incremental exercise test (XT) on a treadmill ergometer using a symptom-limited

incremental protocol with linear increases in the work rate with respect to time [40]. This test is conducted by an experienced exercise physiologist from the UCLA Exercise Physiology Research Laboratory at baseline, study week 5, and immediately following the intervention phase. During the baseline maximal incremental XT, the ECG is continuously monitored throughout the test and recorded every 2 minutes during warm-up, exercise, and up to 10 minutes of recovery. Aerobic capacity ($\dot{V}O_2\text{max}$), and the metabolic or lactate threshold ($\dot{V}O_2\theta$), which is the level of oxygen uptake that defines one's ability to perform prolonged work, is measured using indirect calorimetry with a portable automated metabolic measurement system (OxyCon Mobile®). The $\dot{V}O_2\text{max}$ and $\dot{V}O_2\theta$ are used as baseline markers of aerobic fitness as well as objective indices for developing each subject's individualized aerobic exercise intervention. Both heart rate and oxygen uptake are used to quantitate exercise intensity for each participant with a goal of maintaining heart rate between 60–85% of maximum for 30 minutes, which corresponds to 60–85% of maximum exercise intensity (% $\dot{V}O_2\text{max}$).

Muscle Strength, Endurance and Body Composition—All randomized participants undergo further fitness assessments by the exercise physiologist to determine baseline anthropometrics, muscle strength by 1-repetition maximum (1-RM) for leg press and chest press, and muscle endurance (repetitions to failure using 85% of their leg press and chest press 1-RM values). The 1-RM represents the maximum weight that can be lifted only once through a complete range of motion. The 1-RM and muscle endurance test data are used to establish baseline values of muscle strength and endurance in the study population and to help guide the development of the individualized resistance training exercise program [41]. This test is administered at baseline, during week 5, and upon intervention termination.

Body weight is measured using a calibrated digital scale, and height is assessed using a precision stadiometer. Body composition is determined using a 3-site skinfold method using standard techniques [42] while body density is estimated from skinfold thickness using sex-specific equations [43; 44]. Equations specific for sex, age, and ethnicity are used to calculate relative body fat from estimates of body density [43; 45]. Data obtained from the body composition analysis will be used to track changes in the fat-free mass and skeletal muscle mass using MRI-validated equations, [46].

Exercise Intervention (EX)—Participants randomized to the exercise intervention participate in supervised progressive endurance and resistance training three times per week for 8 weeks (24 sessions) consistent with current guidelines for comprehensive exercise programs [39]. Participants are supervised individually or in pairs by a trained research staff member. Each session consists of a 5-minute warm-up, 30 minutes of aerobic activity on a treadmill, 15 minutes of resistance training, and a 5-minute cool-down with stretching and light calisthenics. The goal of the aerobic training is to accumulate at least 30 minutes of continuous aerobic exercise at a moderate target intensity set by data derived from maximal incremental exercise testing as described above. Heart rate is monitored continuously for each subject throughout their training session using a heart rate monitor (Polar RS400™) and transferred into a database. Treadmill speed and grade are adjusted at the trainer's discretion to maintain the prescribed intensity and the 30-minute target duration. Maximum effort is

encouraged using an algorithm tool; if necessary, rest periods are given until the subject is able to accumulate a total of 30-minutes at the chosen intensity.

The goal of the resistance training is to develop progressive adaptations in muscle strength and body composition to complement the aerobic training program. A total of nine exercises are performed for major muscle groups (e.g., chest, quadriceps, triceps, hamstrings, biceps) following aerobic training sessions 3 times weekly. The exercise trainer instructs all subjects in proper exercise technique for all lifts and continuously monitors each training session. For the first three weeks, subjects perform a warm-up set with very light weight then complete one set of 8–12 repetitions for each exercise using resistance that results in “substantial fatigue” [47]. During the final five weeks of the training protocol, subjects perform a low resistance warm-up set and then add a second set of each exercise and increase the resistance to a level equal to 8–12-RM. A 1-minute rest interval is provided between sets. Subjects progress by adding resistance at the trainer’s discretion once the subject is able to complete 12 repetitions for both sets in three consecutive exercise sessions. The target range of two sets of 8–12 RM is maintained through the end of the study. Alternative exercises are substituted in instances where subjects are unable to perform a particular movement.

Education Condition (ED)—Participants randomized to the control condition participate in a health and wellness education session three times a week for 50 minutes. A research staff counselor is present to provide informational materials, facilitate discussion of educational content, and monitor attendance. Sessions consist of an integrated multimedia educational program addressing a variety of health, wellness, and lifestyle topics adapted from a previously implemented wellness manual used by Kinnunen et al. [48] (modules available upon request). Daily educational topics include: stress relief, nutrition, acupressure, sleep hygiene, time management, health screening, movement therapy, meditation, home emergencies, healthy relationships, and self-defense.

Brain Imaging Procedures—A subset of consenting participants (N=30) undergo two PET sessions and two MRI sessions, one of each before commencement of the experimental condition and again after the eight weeks of intervention. The first 15 participants in each group who meet additional inclusion criteria (see Table 1) are invited to participate in imaging procedures. Participants are driven to imaging appointments by research staff and accompanied throughout the procedures. Brain region volumes will be determined for subcortical regions including the caudate, putamen and nucleus accumbens. Dopamine D₂/D₃ receptor availability will be calculated from PET data as binding potential (BP_{ND}) using the D₂/D₃ ligand [(18F)]fallypride; calculations will be determined from the distribution volume ratio using a graphical analysis (Logan Plot, PMOD2.9). The MRI scans are used to confirm the absence of structural brain lesions and to aid in localization of volumes of interest.

Study Assessments

The schedule of assessments is presented in Table 2. In addition to data collection at baseline and during the active 8-week intervention phase, all participants are followed for 12 weeks after discharge, with data collection at 4, 8 and 12 weeks post-discharge and again at

a 26-week follow-up point. The Mini Neurodiagnostic Interview (MINI) [49] is administered at baseline to characterize psychiatric disorders in the sample including DSM-IV substance dependence diagnoses. To assess the primary outcome of MA use days over the 12-week post-discharge period, the Substance Use Inventory (SUI) [50] is used to collect self-report data, in addition to urine drug screens collected at each time point. The SUI is administered at baseline to document the participant's self-reported use of substances for the 30 days prior to screening, and at each follow-up time point to document use for each day since the previous SUI assessment. Urine specimens are collected using FDA-approved one-step temperature-controlled urine drug test cups and screen for the presence of MA, amphetamine, cocaine, opiates, and marijuana.

Secondary outcome measures include: 1) safety of the study conditions as measured by adverse events (AEs); 2) other drug use during the follow up phase using the SUI and urine drug screen 3) severity of MA craving, assessed weekly using a visual analog scale (VAS) ranging from 0 (no craving) to 100 (most intense craving); 5) reduction in drug-related problems as indicated on the ASI [51]; 6) severity of depression symptoms, assessed weekly using the Beck Depression Inventory (BDI) [52] and Profile of Mood States (POMS) [53]; 7) severity of anxiety symptoms, assessed weekly using the Beck Anxiety Inventory (BAI) [54] and POMS; 9) severity of anhedonia as measured by the Snaith Hamilton Pleasure Scale (SHAPS) [55]; 10) retention in treatment across the duration of the active treatment phase; 11) changes in physiological outcomes as measured by: maximum oxygen uptake, muscle strength, endurance, weight, percent body fat, blood pressure, lipid profile, and health outcomes captured on the Short Form 36 (SF-36) [56] administered at baseline, monthly during active treatment, upon discharge and at follow-up points; 12) changes in cognitive performance tests of memory, attention, motor speed, and executive function as measured by Choice Reaction Time, Stroop Color Naming Task [57], Stop Signal Task, Memory Search Test, Logical Relations Test, and Matching to Sample Test administered at baseline, end of active treatment phase, 12 and 26 week-follow up time points.

Information about demographic characteristics of the participant, including sex, date of birth, ethnicity/race, education, employment pattern, and marital status is collected at screening. The MINI is administered at baseline to establish MA dependence diagnosis required for eligibility as well as other psychiatric diagnoses. The Client Evaluation of Self and Treatment (CEST) [58] is completed during screening to assess treatment motivation, psychological functioning, and social functioning; a follow-up version of the CEST is then administered at week 5 of the study intervention and at treatment-end.

The HIV Risk Behavior Scale (HRBS) [59] is self-administered at screening, discharge, and follow-up to assess past-month and lifetime intravenous drug use and sexual risk behaviors. The Addiction Severity Index (ASI)-Lite [52] is used to assess severity of substance use and areas of functioning impacted by addiction (e.g., employment, legal status, medical and psychiatric issues) at screening, and treatment-end. The Drug Avoidance Activity (DAA) Survey [60] is administered to document engagement in healthy non-drug activities at baseline, program discharge, and follow-up time points. Effects of treatment on four domains including health, lifestyle, community involvement, and substance use are captured in the Treatment Effectiveness Assessment (TEA) [61]. The Client Perception of Care [62]

is administered at program discharge to assess consumer perceptions of treatment experience at the residential treatment facility.

The extent of participation in regular physical activity over and above activities of daily living is documented at screening, termination from intervention, and follow-up using the International Physical Activity Questionnaire (IPAQ) [63]. Subjective ratings of perceived exertion ratings are collected once during each training session after 20 minutes of aerobic activity using the Borg Rating of Perceived Exertion (RPE) scale [64]. Participants are asked to record the number of cigarettes smoked weekly.

Safety assessments include a medical and psychiatric history and physical examination at baseline to determine eligibility and ensure that there are no medical issues that might preclude safe participation in the study. An ECG and laboratory studies, including chemistry panel, liver function tests (i.e., AST, ALT, GGT, ALP, and bilirubin), hematology panel, and a standard urinalysis are performed at baseline to help determine eligibility and are repeated at treatment-end. Pregnancy and use of birth control is assessed at screening, monthly during the active intervention phase, and at the termination of intervention visit. Vital signs are recorded at screening, once weekly throughout the active intervention phase, and at termination of intervention (last visit of Week 8 or sooner if stopped early). AEs are recorded at each study visit after consent. The study physician evaluates all AEs for relatedness to study intervention. SAEs are reviewed, reported, and tracked in accordance with applicable regulatory requirements. Participants who indicate possible suicidal ideation on the BDI are assessed by a qualified site clinician.

DATA ANALYSIS

The sample size (N=150) was based on expectation of at least 80% of the participants being located and interviewed at each assessment point. Thus, a baseline sample of 150 participants with 75 per group will yield a final sample of approximately 120 participants in the data matrix at all assessment points, which will allow us to determine a medium effect size difference between the groups, with 80% power and at 95% level of significance. The intention-to-treat (ITT) population is defined as participants who were randomized and received at least one session of the 8-week protocol interventions. The evaluable population is defined as the participants who are eligible to participate in the study in accordance with the inclusion and exclusion criteria and who received at least 4 weeks of the intervention (at least one session per week). Each of the primary and secondary efficacy outcome measures will be analyzed for the ITT and for the evaluable population. Statistical tests will be two-sided at a 5% Type I error rate. Confidence intervals will be two-sided with a 95% confidence coefficient.

The primary efficacy measure will be self-reported days of any MA use over the 12-week post-discharge period. The percentage of non-MA use days over the 84 days (as collected using the SUI at each follow-up time point) will be calculated for each participant. Percentages of non-MA-use days will be compared between groups using a t-test. For participants with missing interviews, the percentage will be calculated on the data from interviews that do occur. No assumptions about missing data will be made. Urinalysis data

will be used to confirm self-report. In cases of non-concordance between the urinalysis result and the self-report, the data for the entire 28-day period in the non-concordant interval will not be included in the analysis. In addition, we will define a “Successful” participant as one who participates in all of the interviews at 4, 8, 12, and 26 weeks, reports zero MA use, and provides four MA-free urine samples. The proportion of participants achieving a successful outcome will be compared between groups using a Chi-square test or Fisher exact test, as appropriate based on the estimated expectation of the contingency table’s cell sizes computed from the table’s row and column totals. As a secondary analysis, the individual effects, if any, of age, race, gender, severity of depression, and usual route of methamphetamine use (oral/nasal inhalation versus intravenous/smoked) on the primary study group effects will be determined.

The effect of the interventions will be compared between the Exercise and Education groups using generalized regression for repeated measures on each of the secondary outcome test results (e.g., psychiatric symptoms, neurocognitive testing, physical health measures) from baseline to discharge to 12 and 26 weeks post-discharge [65]. This approach allows the optimal inclusion of cases even if subjects are missing some observations across time, as opposed to using simple ANOVA on repeated measures, where cases are dropped if they have any observations missing. The approach will also allow inclusion of covariates if randomization does not produce groups that are equivalent on basic demographics and drug use history characteristics. To examine pre- to post-intervention differences in D₂/D₃ receptor availability a repeated-measures ANOVA will be performed using the binding potential for [¹⁸F]fallypride in subcortical regions of interest.

CURRENT STATUS OF THE STUDY

The study commenced recruitment in March of 2010, and at the time of writing this manuscript, enrollment, active EX and ED participation, and follow-up phases are ongoing. Recruitment is exceeding targeted enrollment rates. Out of 125 subjects randomized to date, 40 have completed the exercise intervention and 41 have completed the education intervention. Preliminary findings related to physical outcomes demonstrate a significant benefit of exercise compared to health education in improving maximum oxygen uptake, muscle strength and endurance, body mass index (BMI), percent body fat [66], and heart rate variability [67]. Additional results related to primary and secondary outcomes will be reported in future publications.

DISCUSSION

The lack of FDA-approved pharmacotherapy for MA dependence underscores the need for further treatment intervention development. This exercise study will yield valuable information on a number of levels. First, as the initial study of its kind to test such an approach, this trial will provide unique findings on the feasibility and utility of engaging MA-dependent adults in a highly structured exercise regimen within a residential treatment setting. Second, this study will examine whether a combination of aerobic exercise and resistance training can facilitate relapse prevention and maintenance of abstinence from MA after discharge from residential treatment. The addition of exercise to standard residential

treatment may provide a reinforcing behavior that offers an alternative to drug use as a means of enhancing positive mood states. Exercise has been shown to improve anxiety and depression, symptoms commonly associated with active MA use and early abstinence from MA [68], via effects on the endogenous opioid system and potentiation of dopaminergic transmission [69]. Exercise also improves sleep [70] and performance on cognitive tasks, which may be impaired in MA users and in long-term MA users in early phases of abstinence.

Whether or not definitive exercise-related benefits on drug use are demonstrated, this study will provide valuable data on the effects of exercise compared to effects of health education on craving, negative affect states, and cognition, factors that may be associated with relapse risk in MA users and that impact treatment outcomes. General health and wellness outcomes, such as aerobic performance, muscle strength and endurance, blood pressure, lipid profile, and serum glucose will also be examined pre- and post-study intervention. Neuroimaging procedures will determine if exercise has an impact on D2/D3 receptor availability in a subset of abstinent MA-dependent participants.

There are some limitations to this study. First, given that aerobic and resistance training are combined in the study intervention, effects specific to aerobic exercise or resistance training cannot be determined. Second, given that subjects are enrolled in an abstinence-based residential treatment program while engaged in the 8-week study interventions, differential effects on drug use can only be measured after discharge from the treatment program and thus reflect potential effects sustained after the interventions have been completed. Effects on substance use during the active intervention phase cannot be determined. Third, though the design of this study enhances compliance with the study interventions (i.e. supervised sessions within a residential facility), results may not generalize to MA-dependent individuals in outpatient treatment settings or who are engaged in personal exercise programs. Results may also not generalize to less frequent or less intense exercise engagement, and findings will not determine the optimal length of time or frequency of an exercise intervention. Lastly, data on self-initiated physical activity that occurs outside of supervised exercise sessions is limited to self-report; objective measures of total daily activity (e.g. with fitness monitors or pedometers) are not obtained in this study.

In addition to examining effects of exercise compared to health education on substance use and psychiatric symptoms, this study will examine health effects of exercise including the potential to reduce cardiovascular risk factors such as hypertension and dyslipidemia that can be prevalent in the study population. A further benefit of exercise may occur if individuals who are introduced to exercise as part of treatment continue exercise when they complete treatment. Follow-up assessments will gather data on self-reported exercise activity among the participants.

In light of the documented associations between stress, negative affect, and substance relapse in addicted populations [71, 72], together with evidence demonstrating stress regulation deficits in substance users, the development of interventions to ameliorate symptoms of depression and anxiety and improve affect regulation may help to reduce relapse risk in this population. By reducing psychological symptoms and attendant distress,

exercise may serve to complement other therapy and medication approaches for MA users, particularly if users are able to more readily utilize relapse prevention skills and incorporate positive behavioral changes consistent with treatment goals. If findings from this study suggest benefit of a supervised aerobic and resistance exercise program in sustaining abstinence from MA after discharge from residential treatment, future research is warranted to explore other applications of exercise, including its potential to reduce substance use during the active intervention applied in an outpatient context. Additional research efforts are warranted to explore the utility of exercise in outpatient treatment settings and to examine additional biological mechanisms of action.

Acknowledgments

The study described in this paper was funded by NIH/NIDA grant R01 DA027633. We thank the staff and participants at Cri Help, Inc., for their work on this project.

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Figure 1.
Study Schema
* Length of time client remains in treatment after study participation varies. Follow-up period begins after discharge from treatment center.

Table 1**Study Eligibility Criteria****Inclusion criteria**

- 1 Age of 18 years or older, and 45 or younger for males, 55 or younger for females;
- 2 Seeking treatment for MA dependence;
- 3 Meet DSM-IV criteria for MA dependence;
- 4 Vital signs that are within clinically acceptable normal range, e.g., resting pulse between 50 and 99/min, blood pressures between 85–150mm Hg systolic and 45–90mm Hg diastolic;
- 5 Medical history and physical examination that, in the judgment of the study physician or Principal Investigator, show no clinically significant contraindications for study participation;
- 6 For females, negative pregnancy test before randomization (and for the imaging sub-sample, another negative test before each PET scan at the beginning and end of intervention).

Exclusion criteria

- 1 Clinically significant heart disease or hypertension; unstable pulmonary or cardiovascular disease that would interfere with participation in exercise regimen
- 2 Neurological or psychiatric disorder as assessed by MINI or clinical interview, such as psychosis, bipolar illness, Tourette's syndrome, major depression, organic brain disease, dementia, that would require ongoing treatment make study compliance difficult
- 3 Musculoskeletal disease that would prevent participation in exercise regimen;
- 4 Baseline ECG showing evidence of clinically significant abnormalities;
- 5 Untreated or unstable medical illness including: neuroendocrine, autoimmune, renal, hepatic, or active infectious disease (other than HIV) that requires immediate medical attention;
- 6 Clinically significant abnormalities in hematology and chemistry laboratory tests that may make participation hazardous;
- 7 HIV positive and unable to obtain a clearance for participation from medical care provider;
- 8 Currently pregnant;
- 9 Any other illness, condition, or use of medications that, in the opinion of the PI and/or the study physician, would preclude safe participation or completion of the study.

Additional exclusion criteria for imaging sub-sample

- 10 Central nervous system, cerebrovascular, and/or infectious disease that may make participation hazardous, or history of head trauma
- 11 Claustrophobia
- 12 Participation in another study involving exposure to ionizing radiation in the past year if the total cumulative exposure from the past research studies and the current research study would exceed the limits described by the FDA in 21 CFR 361.1. (i.e., total cumulated dose to the whole body, active blood-forming organs, lens of the eye, and gonads below 5 rems and the cumulated dose to all other organs below 15 rems).
- 13 Presence of a metal device (e.g., pacemaker, infusion pump, aneurysm clip, metal prosthesis or plate) that could either interfere with the acquisition of the MRI scan of the brain or for whom the MRI scan would pose a potential risk.
- 14 Current dependence on substances other than MA, alcohol and/or cannabis as per DSM-IV
- 15 Use of a medication that is known to interact with dopamine (DA) receptors (e.g., neuroleptics, aripiprazole).

Table 2

Schedule of Assessments

ASSESSMENT	FREQUENCY
Informed Consent	Baseline
General Measures	
Locator Form	Baseline, Discharge, Each post-discharge visit *
Demographics Form	Baseline
Client Perception of Care	Week 9 **
CEST	Baseline, Week 5, Week 9 **
Safety and Medical Measures	
Physical Exam	Baseline, Week 9 **
Medical History	Baseline
Pregnancy Test	Baseline, Twice during active intervention, Week 9 **
Maximal Exercise Performance Test	Baseline, Week 5, Week 9 **
Lab Tests (CBC, LFT, chemistry)	Baseline, Week 9 **
Vital Signs	Baseline, Weekly during active intervention, Week 9 **
ECG	Baseline, Week 9 **
Exercise Data Collection	3 Xs/week during active intervention
BORG	3 Xs/week during active intervention
Adverse Events	As needed during active intervention and follow-up
Physical Activity Logs	At each study visit Baseline, Weekly during active intervention, Week 9 **, At FU visits
IPAQ	Baseline, Week 9 **, At FU visits
Drug Use, Psychological and Cognitive Measures	
MINI	Baseline
Urine Drug Screen	Baseline, At FU visits
VAS	At each study visit Baseline, Weekly during active intervention, Week 9 **, At FU visits
ASI-Lite	Baseline, Post-discharge Week 12 *
BDI and BAI	At each study visit Baseline, Weekly during active intervention, Week 9 **, At FU visits
POMS	Baseline, Weekly during active intervention, Week 9 ** At FU visits
SHAPS, Smoking Questionnaire	At each study visit
SUI	Baseline, Week 9 **, At FU visits
SF-36	Baseline, Twice during active intervention, Week 9 **, At FU visits
DAA and TEA	Baseline, Week 9 ** At FU visits
HRBS	Baseline, Week 9 **, At FU visits
Neurocognitive Tests ***	Baseline, Week 9 **, Post-discharge week 12 *, Week 26
Brain Imaging	

ASSESSMENT	FREQUENCY
PET & MRI	Baseline, Week 9 [*]

^{*} Post-Discharge Window begins 4, 8, 12 weeks after discharge from residential treatment facility

^{**} Also done at termination if earlier than week 9

^{***} Including Choice Reaction Time, Logical Relations, Matching to Sample, Memory Search, Stroop, Stop Signal