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

1. 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.

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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 4000 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.

2. Study design and approach

2.1. 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 min [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 D_2/D_3 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 D_2/D_3 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].

2.2. 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 D_2/D_3 receptor availability among a subset of participants assigned to both conditions; 5) assess structural changes in brain regions using MRI; and 6) examine differences in addiction-related behaviors and consequences as per Addiction Severity Index (ASI) domains (e.g., employment, legal, medical, interpersonal, psychiatric).

2.3. 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.

2.4. Participants

A total of 150 MA-dependent participants age 18 and older are being randomized to one of two study conditions,