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A complier average causal effect analysis of the Stimulant Reduction Intervention using dosed exercise study

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ABSTRACT

Objective: Exercise is a promising treatment for substance use disorders, yet an intention-to-treat analysis of a large, multi-site study found no reduction in stimulant use for exercise versus health education. Exercise adherence was sub-optimal; therefore, secondary post-hoc complier average causal effects (CACE) analysis was conducted to determine the potential effectiveness of adequately dosed exercise.

Method: The STimulant use Reduction Intervention using Dosed Exercise study was a randomized controlled trial comparing a 12 kcal/kg/week (KKW) exercise dose versus a health education control conducted at nine residential substance use treatment settings across the U.S. that are affiliated with the National Drug Abuse Treatment Clinical Trials Network. Participants were sedentary but medically approved for exercise, used stimulants within 30 days prior to study entry, and received a DSM-IV stimulant abuse or dependence diagnosis within the past year. A CACE analysis adjusted to include only participants with a minimum threshold of adherence (at least 8.3 KKW) and using a negative-binomial hurdle model focused on 218 participants who were 36.2% female, mean age 39.4 years (SD = 11.1), and averaged 13.0 (SD = 9.2) stimulant use days in the 30 days before residential treatment. The outcome was days of stimulant use as assessed by the self-reported TimeLine Follow Back and urine drug screen results.

Results: The CACE-adjusted analysis found a significantly lower probability of relapse to stimulant use in the exercise group versus the health education group (41.0% vs. 55.7%, $p < .01$) and significantly lower days of stimulant use among those who relapsed (5.0 days vs. 9.9 days, $p < .01$).

Conclusions: The CACE adjustment revealed significant, positive effects for exercise. Further research is warranted to develop strategies for exercise adherence that can ensure achievement of an exercise dose sufficient to produce a significant treatment effect.

Public health significance

This secondary analysis of the Stimulant use Reduction Intervention using Dosed Exercise study suggests that an exercise level of more than 8.3 kcal/kg/week may reduce relapse to stimulant use and reduce the days of stimulant use for those who relapse. This analysis also demonstrates the importance of ensuring adherence to exercise interventions and accounting for adherence in the interpretation of results, and that statistically rigorous adjustment for post-baseline measures such as exercise dose is possible.

1. Introduction

Currently available treatments for substance use disorders (SUD) are insufficient to achieve abstinence or large reductions in substance use for many treatment-seeking individuals [1,2]. Therefore, the development of new treatments for SUD is an important research goal. Preliminary studies show that exercise has potential as an innovative treatment for SUD [3–6]. Furthermore, exercise acts on a variety of psychological (anxiety [7], depression [8]), and neurobiological mechanisms [9,10] that suggest exercise may be effective as a treatment for SUD [11,12].

The STimulant Reduction Intervention using Dosed Exercise (STRIDE) study evaluated stimulant use outcomes following a dosed

Abbreviations: CACE, Complier Average Causal Effect; ITT, Intention-to-Treat; KKW, kilocalories/kilogram/week; RTP, Residential Treatment Program; STRIDE, STimulant Reduction Intervention using Dosed Exercise; SUD, Substance Use Disorders; TLFB, Timeline Follow Back; UDS, Urine Drug Screens

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exercise intervention versus a health education intervention, both of which were provided as augmentation to treatment as usual. The *a priori* primary analysis [13] was based on the intention-to-treat (ITT) principle in which all participants were analyzed according to the groups to which they were randomly assigned [14]. The primary outcome of percent stimulant abstinent days in the exercise and health education groups was compared after (1) imputing missing data as days of drug use and (2) employing a novel method to reconcile discrepancies between subjective and objective measures of drug use [15]. The ITT analysis revealed no treatment effect as percentage of days abstinent were 75.6% (SD = 27.4) for those in exercise and 77.3% (SD = 25.1) for those in health education (p = 0.60) [13].

However, the ITT analysis is not by itself sufficient to assess the viability of exercise as an augmentation to SUD treatment because many participants did not exercise at the prescribed dose. The median exercise dose of 8.3 kcal/kg/week (KKW) (interquartile range: 4.2 to 10.6 KKW) in this study was approximately two-thirds of the prescribed dose of 12 KKW. This suboptimal adherence to the prescribed dose confounds our ability to interpret the results of the trial because even an effective treatment may produce small treatment effects in people who do not fully participate in the treatment. In order to assess the viability of exercise, we must answer the following question: Is there an exercise dose that will produce a clinically meaningful exercise effect?

For this analysis, an exercise dose greater than or equal to the median exercise dose (8.3 KKW) exhibited by study participants will be subsequently referred to as an "adequate dose." An estimate of the exercise effect among participants who exercised at or above this adequate dose provides two major advantages. First, to determine the most appropriate treatment recommendation for a patient, the clinician must consider the size of the treatment effect for exercise versus other possible treatments. If the clinician believes the patient would be adherent to an assigned exercise dose greater than the median 8.3 KKW observed in STRIDE, the STRIDE *a priori* primary analysis results provide no guidance as to treatment effect size because the effect size is influenced by those who exercised less than the median dose [16]. Second, without understanding the efficacy of exercise, it is unclear how to proceed with future research. If exercise for stimulant users is truly ineffective, additional research as a potential treatment option is unwarranted. If, however, exercise is ineffective due to poor adherence, it may be beneficial to continue pursuing exercise as a treatment option while developing interventions to optimize exercise adherence [16].

Per-protocol and as-treated analyses are sometimes used in an attempt to adjust for an observed dose that is less than the prescribed treatment dose, but these approaches are statistically biased. Per-protocol analysis for STRIDE would compare those in the exercise group who were adherent to exercise versus those in the health education group who were adherent to health education. However, those subgroups could differ substantially in important covariates. As-treated analysis would require exercise participants who did not exercise to be considered as belonging to the health education group for the purpose of analysis, thereby creating non-comparable groups [16]. To address these statistical challenges we employed a complier average causal effect (CACE) analysis. This enabled us to make a statistically rigorous estimate of exercise treatment effects based on the majority of participants' exercise dose (ranged from 8.3 to 11.5 KKW) rather than the dose observed in the intention-to-treat STRIDE sample which included those who did not exercise at all (ranged from 0 to 11.5 KKW). CACE analysis has been used in trials of behavioral interventions [17,18], including substance abuse research [19,20]. If the assumptions of the CACE analysis are fulfilled, we can determine in a statistically rigorous manner that an effective range of exercise dose exists and, hence, that exercise is worthy of further research.

2. Methods

The design and methodology of the STRIDE study have been previously described [21–26]. Below, we briefly describe study procedures relevant to the analysis presented. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards associated with the participating treatment programs. Written informed consent was obtained from all participants prior to beginning study procedures.

2.1. Participants

STRIDE enrolled adult stimulant users, aged 18–65 years, who were admitted to residential substance abuse treatment, had used stimulants within 30 days prior to enrollment, and met DSM-IV criteria for stimulant abuse or dependence within the last 12 months. Participants also had to be medically clear to exercise via a protocol-defined stress test. Exclusion criteria included: opioid dependence within the last 12 months; evidence of a general medical condition, medication, or psychiatric condition that contraindicated study participation; pregnancy; or significant physical activity, defined as aerobic exercise more than 3 times per week for 20 min or more, completed consistently for the three months prior to study enrollment.

2.2. Study procedures and interventions

Randomly assigned participants received either the Dosed Exercise Intervention or the Health Education Intervention. Drug abuse treatment as usual was provided to both groups, beginning with residential treatment (median 17 days, interquartile range 12–22 days) and followed by outpatient treatment. The prescribed exercise dose for the exercise intervention was 12 KKW provided during three one-on-one supervised sessions per week. Twelve KKW is equivalent to 150 min of moderate exercise per week at an exercise intensity of 70–85% of maximal heart rate, and is within public health dose guidelines (http://www.health.gov/paguidelines). Health education was also provided during thrice-weekly one-on-one supervised sessions designed to last as long as the exercise sessions and so ensure equivalent staff contact between groups during the 12-week acute phase. These sessions provided information on health-related topics (e.g., diet, mental health, and sleep) via didactics; Websites; and audio, video, and written materials. To reduce any psychosocial effects of health education, no specific goals were set for participants to achieve during the sessions [26]. Health education has been established as a valid control condition in other exercise studies [27–29] (Marcus et al., 1999; Pahor et al., 2006; Rejeski et al., 2005). Trained facilitators implemented both interventions.

2.3. Measures

2.3.1. Drug use

Self-reported drug use was assessed using the TimeLine Follow Back (TLFB), a semi-structured interview that uses calendar prompts to retrospectively recall daily drug use over a specified period of time [30]. Qualitative urine drug screens (UDS) were collected 3 times per week and assessed stimulants (cocaine, amphetamine, methamphetamine) as well as opiates, marijuana, benzodiazepines, barbiturates, methadone, methylenedioxymethamphetamine (ecstasy), and oxycodone. The daily TLFB was compared with the 3 times per week UDS, and contradictions between the two were resolved using the Eliminate Contradiction algorithm [15] as follows: when the UDS was positive but the prior 3 days were all negative according to the TLFB, then the TLFB for the last day in the window was changed from negative to positive. Drug use was assessed during the post-residential treatment program (RTP) period from the day after discharge to 84 days after randomization.

2.3.2. Adequate exercise dose

Participant exercise dose was defined as energy expended per week computed in KKW averaged over the entire acute phase from