**Effects of a Dosed Exercise Intervention in Craving and Anhedonia:
A Secondary Analysis from the STRIDE-CTN 0037 Clinical Trial**

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Introduction

According to the Research Domain Criteria (RDoC) framework, addictive disorders can be explained as the result of a Positive Valence Systems abnormality, more specifically, in reward processing (Nusslock & Alloy, 2017). In one side, individuals with low sensitivity to reward, are prone to use substances to cope with negative emotions. On the other side, such individuals, after a continuous use of substances, develop an impairment in the dopamine signaling related, becoming hypersensitive to cues related to drugs.

Much of the research has used experimental paradigms, such as neuroimaging, to measure these impairments (Clark, Boileau, & Zack, 2018), however, both can be assessed in the clinical practice using subjective accounts. Low reward sensitivity is closed represented by anhedonia which is defined as the inability or difficulty to experience pleasure (Rizvi, Pizzagalli, Sproule, & Kennedy, 2016). Hypersensitivity to cues can be expressed as cravings, which are subjective motivational states consisting in an intense desire to engage in drug use (James, Davies, & Willner, 2004).

Individuals with chronic substance use commonly experience anhedonia, which tend to decrease as the abstinence time increases (Garfield, Lubman, & Yücel, 2013). Additionally, anhedonia has been linked to higher dropout rates and treatment non-response (Kiluk, Yip, DeVito, Carroll, & Sofuoglu, 2019). Cravings are also highly correlated to treatment drop-out, relapse and inability to achieve substance use reduction (Li, Caprioli, & Marchant, 2015). Stimulant drug cravings are common in individuals receiving treatment for substance use disorders, and they can even occur a year after abstinence (G. Wang et al., 2013). Previous evidence has shown that behavioral and pharmacological treatment for stimulant drugs could benefit the management of craving, however their effect sizes have been mild to moderate (Duailibi et al., 2017; Kiluk et al.,

2019). These results suggest that more treatment alternatives for drug cravings and anhedonia are needed, such as systematic physical exercise programs

Current evidence suggest that structured physical exercise programs are a promising option to treat drug cravings and anhedonia in stimulant abusers (Colledge, Gerber, Pühse, & Ludyga, 2018; Toups et al., 2017; D. Wang, Zhou, & Chang, 2015). Previous studies have shown mixed results regarding to the effects of structured physical exercise programs for different types of user of drugs. For instance, previous studies have found positive results in craving reduction, when using 30-minutes of treadmill exercise in marijuana (Buchowski et al., 2011) or using 20-min of acute stationary cycle exercise in heroin (D. Wang et al., 2020). However some other studies have failed to attain positive results using treadmill exercise in cocaine users (De La Garza et al., 2016). The main limitation of this studies is the use of small sample sizes. These results have motivated to develop more studies in polysubstance users, however such studies are currently in conduction (Ellingsen, Johannesen, Martinsen, Dahl, & Hallgren, 2020). In addition to these studies, preclinical evidence suggest that participant characteristics such as age and gender could be associated with the positive results of exercise in craving (Lynch, Abel, Robinson, & Smith, 2017).

The current study

This is a secondary analysis from the project “CTN-0037-Stimulant Reduction Intervention Using Dosed Exercise (STRIDE)”. We aimed to test the effects of a Vigorous Intensity High Dose Exercise Augmentation (VIHD) when compared to a health education intervention (HEI) in stimulant drug-cravings and anhedonia. Published STRIDE results is focused only on the effects of the intervention in percentage of days of stimulants abstinence, obtaining no significant differences (Trivedi et al., 2017).

In this study we will analyze the differences between VIHD and HEI in the self-report measures of cravings and anhedonia. Additionally, we will test for potential differences related to gender and age in the intervention effects.

Method

Design and Participants

STRIDE was designed to test the efficacy of exercise or health education augmentation for the treatment of stimulant abuse. The STRIDE study was a multi-site investigation (9 study sites) designed to investigate the efficacy of supplementing TAU with either a dosed exercise intervention (DEI) or a health education intervention (HEI) in individuals diagnosed with stimulant abuse and/or dependence.

This study evaluated individuals diagnosed with stimulant abuse or dependence (cocaine, methamphetamine, amphetamine, or other stimulant, except caffeine or nicotine, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [DSM-IV-TR]) who were receiving treatment in a residential setting.

Participants who provide informed consent were randomized to one of two treatment arms: Vigorous Intensity High Dose Exercise Augmentation (DEI) or Health Education Intervention Augmentation (HEI). In both arms, participants began with supervised sessions 3 times per week during the 12-week acute phase of the study. Supervised sessions were conducted as one-on-one (i.e., individual) sessions. Following the 12-week acute phase, participants began a 6-month continuation phase during which time they will attend one weekly supervised DEI or HEI session. After randomization participants were monitored for 36 weeks. More detailed information regarding the study aims see Trivedi et al. (Trivedi et al., 2011).

Eligibility Criteria

Participants were ambulatory males or females, ages 18 to 65, who had been admitted to substance use treatment in a participating residential setting. Participants had self-reported stimulant drug use (cocaine, methamphetamine, amphetamine, or other stimulant, excluding caffeine and nicotine) within the 30 days prior to admission for residential treatment and met DSM IV-TR criteria for substance abuse or dependence for stimulants within the last 12 months. They received medical clearance through a protocol-defined maximal exercise test in accordance with American College of Sports Medicine (ACSM) guidelines (Pescatello, Riebe & Thompson, 2014) and a careful history and physical examination from protocol-approved medical personnel. Participants had the ability to understand and willingness to provide written informed consent. Persons that met the following criteria were excluded from participation: general medical condition(s) that contraindicate exercise, opiate dependence, psychosis, or other psychiatric issue(s) that poses a safety risk, pregnancy, or concomitant treatment with beta blockers or opioid replacement therapy (e.g., methadone or buprenorphine).

Measures

Craving. In addition to the baseline, participants provided responses for the Stimulant Craving Questionnaire (SCQ) at each week. SCQ is a self-report instrument adapted from the 10-item version of the Cocaine Craving Questionnaire. Participants were asked to indicate if they agree or disagree at the current moment using a response scale ranging from 0 (“Strongly Disagree”) to 6 (“Strongly Agree”). Psychometric properties of the SQC can found elsewhere (Northrup, Green, Walker, Greer, & Trivedi, 2015).

Anhedonia. To assess anhedonia the study used the Snaith-Hamilton Pleasure Scale (SHAPS). The SHAPS is composed by 14 items that ask about the experience of pleasure in several activities (e. g. a television or radio program, a cup of coffee, reading a book, etc.). The response is provided through four option (Strongly disagree/Disagree/Agree/Strongly agree) (Snaith et al., 1995). Its psychometric properties are described elsewhere (Franken, Rassin, & Muris, 2007; Nakonezny, Carmody, Morris, Kurian, & Trivedi, 2010).

Statistical Analysis

To test the effects of VIHD compared to HEI we used linear mixed models (LMM). Here we display the specification of the models

$$\begin{aligned}
 CAS/ECQ_{tij} = & \beta_0 + \beta_1 \times TIME_t + \beta_2 \times TREATMENT_{ij} + \beta_3 \times GENDER_{ij} + \beta_4 \times AGE_{ij} \\
 & + \beta_5 \times TIME_t \times TREATMENT_{ij} + \beta_6 \times TIME_t \times GENDER_{ij} \\
 & + \beta_7 \times TIME_t \times AGE_{ij} + \beta_8 \times TIME_t \times TREATMENT_{ij} \times GENDER_{ij} \\
 & + \beta_9 \times TIME_t \times TREATMENT_{ij} \times AGE_{ij} + u_{0i} + u_{1i} \times TIME_t + u_{0i|j} + \varepsilon_{tij}
 \end{aligned}$$

Where CAS/ECQ_{tij} denotes CAS or ECQ score at time t in patient i nested within a site j . Parameters $\beta_0 - \beta_9$ represent the fixed effects associated with the intercept, time, treatment (using HEI as reference), participant gender (using female as reference) and age, in addition to the time by treatment, time by gender, time by age, time by treatment by age and time by treatment by gender interactions (Taking into account that gender and treatment have two values, then two coefficients are produced to assess the interaction by each gender). Where u_{0i} denotes patient level random intercept, u_{1i} is the random coefficient for patient level slope, $u_{0i|j}$ is a random intercept in the j site and ε_{tij} is the residual at time t in patient i nested within a site j .

For this analysis, a “top-to-down” approach will be used with the package nlme and the function lme in R ver. 4.0.2 using the following steps:

(1): Fit a model with a “loaded” mean structure (Model 1). This model includes every intended fixed and random effects using Restricted Maximum Likelihood estimation (REML). (2). Selection of the random effects structure (Model 2). Compared model 1 with similar model that includes only site intercept as random effect. For this comparison we used Likelihood Ratio Test (LRT) for random effects. (3): Selection of a covariance structure for the residuals (Model 3). We tested whether a between-treatment heterogeneous residual variance specification improves our model. For this comparison we used use LRT for random effects. (4): Model reduction. Resultant model was compared to a reduced model with only significant terms (Model 4), using LRT for fixed effects. (5) Re-estimate the final model using REML (Model 5). A significance of $p < .05$ was set. To determine that VIHD was superior to HEI a significant Time x Treatment interaction was needed.

Results

Participant characteristics

Three-hundred and two participants were randomized (VIHD = 152, DEI = 150). Table 1 present relevant baseline characteristics. Additional baseline characteristics were published elsewhere (Trivedi et al., 2017).

Effects of VIHD for anhedonia and craving

No significant Time x Treatment interaction was found neither for craving nor anhedonia. For craving scores, a positive Time and negative Age effects were found. The results suggest that craving increases over time, and that younger individuals had higher craving scores across the trial.

In the case of anhedonia scores, Gender had a positive direct effect, and the interaction Time x Gender had a negative effect. This could be interpreted in the following manner: higher scores for women in anhedonia scores across the whole trials, however with a significant reduction overtime (men scores were lower, but they did not change). The results can be seen in Tables 2 and 3.

Discussion

The current analysis used data from the study CTN-0037-Stimulant Reduction Intervention Using Dosed Exercise (STRIDE) to assess the effects of a systematic exercise program (VIHD) compared to an active control (HEI) in stimulant drug cravings and anhedonia. We found no evidence of superiority of VIHD compared to HEI, as shown by non-significant time x treatment interactions for both craving and anhedonia outcomes. We also aimed to analyze the possible gender/age differential effects, with non-significant results too.

Our results are in line with the primary outcomes of the study, which did not find a significant difference in percentage of days of abstinence (Trivedi et al., 2017). Considering that the correlations between anhedonia, craving and substance use have been widely documented, it is possible to expect the same results in other clinical outcomes. The evidence regarding the efficacy of exercise-based programs for substance use disorders is mixed, however, the study of moderators suggests that individual with high adherence and certain clinical characteristics are those who benefit from those interventions. Such is the case of a recently published study using the CTN-0037 data, which found that individuals with higher level of impairment and addiction severity are those who benefited more from VIHD (Rethorst et al., 2021). Taking into account that this sample was composed mostly by individuals with low depression level and days of substance use (Trivedi et al., 2017), our results suggest that more impaired individuals, could respond to exercise in

craving and anhedonia. However more research about the moderators of response to exercise using other clinical outcomes is still needed.

The main strengths for this study are: for both anhedonia and craving, individual and site random effects were modeled as recommended by previous literature (Barr, Levy, Scheepers, & Tily, 2013; Feaster, Mikulich-Gilbertson, & Brincks, 2011), accounting for to potential variability for each level. Additionally, the inclusion of participants in diverse site increases the external validity of the findings (Nunes et al., 2010). Two types of limitations regarding this study are worth noting: the first is related to the lack of control in the engagement of exercise. In the final weeks of the study, engagement in physical exercise was non-supervised, so it is possible the minimal dosing of exercise to be effective was not achieve (Carmody, Greer, Walker, Rethorst, & Trivedi, 2018). A second limitation is that the data didn't include characteristics at the site level. As result, we are unable to understand if there were any site-related variables that could predict the efficacy of exercise-based interventions.

In conclusion, according to results VIHHD was no superior to HEI for anhedonia and craving in individuals with stimulant use disorder. Weighting the current evidence about exercise interventions for substance use, is possible that a particular patient profile and high adherence are required to be successful. Future research should focus on the identification of variables to identify who could benefit from systematic exercise programs.

Disclosures

Declaration of conflicting interests

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