Randomized Controlled Trial Comparing Exercise to Health Education for Stimulant Use Disorder:

Results From the CTN-0037 STimulant Reduction Intervention Using Dosed Exercise (STRIDE) Study

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ABSTRACT

Objective: To evaluate exercise as a treatment for stimulant use disorders.

Methods: The STimulant Reduction Intervention using Dosed Exercise (STRIDE) study was a randomized clinical trial conducted in 9 residential addiction treatment programs across the United States from July 2010 to February 2013. Of 497 adults referred to the study, 302 met all eligibility criteria, including *DSM-IV* criteria for stimulant abuse and/or dependence, and were randomized to either a dosed exercise intervention (Exercise) or a health education intervention (Health Education) control, both augmenting treatment as usual and conducted thrice weekly for 12 weeks. The primary outcome of percent stimulant abstinent days during study weeks 4 to 12 was estimated using a novel algorithm adjustment incorporating self-reported Timeline Followback (TLFB) stimulant use and urine drug screen (UDS) data.

Results: Mean percent of abstinent days based on TLFB was 90.8% (SD = 16.4%) for Exercise and 91.6% (SD = 14.7%) for Health Education participants. Percent of abstinent days using the eliminate contradiction (ELCON) algorithm was 75.6% (SD = 27.4%) for Exercise and 77.3% (SD = 25.1%) for Health Education. The primary intent-to-treat analysis, using a mixed model controlling for site and the ELCON algorithm, produced no treatment effect ($P = .60$). In post hoc analyses controlling for treatment adherence and baseline stimulant use, Exercise participants had a 4.8% higher abstinence rate (78.7%) compared to Health Education participants (73.9%) ($P = .03$, number needed to treat = 7.2).

Conclusions: The primary analysis indicated no significant difference between exercise and health education. Adjustment for intervention adherence showed modestly but significantly higher percent of abstinent days in the exercise group, suggesting that exercise may improve outcomes for stimulant users who have better adherence to an exercise dose.

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Suboptimal outcomes in the treatment of stimulant use disorders suggest a need for innovative treatments. Randomized trials of pharmacologic and nonpharmacologic interventions have shown significant variability in abstinence rates, and none of these studies have produced highly effective treatment options for this difficult-to-treat population.[1,2] These findings clearly indicate a need for new treatments for stimulant use disorders.

Previous studies suggest that exercise could be a promising treatment for stimulant use disorders. Animal studies support the use of exercise for stimulant use disorders, as several trials have demonstrated reduced cocaine-seeking behavior following wheel running in rats and mice.[3–6] Previous human studies indicate that exercise is associated with reduced use, increased abstinence, and longer duration of abstinence from alcohol, marijuana, and other substances in both adults and adolescents.[7–10] Exercise has been associated with improvements in smoking outcomes, with greater support for reduced craving and withdrawal, and more limited support for smoking cessation, particularly with respect to long-term outcomes.[11] However, methodological issues, such as insufficient exercise intensity, issues with respect to adherence to exercise and the timing of exercise implementation (eg, post-quit status), and small sample sizes have been major limitations. Exercise has also been shown to improve cognition[12,13] and mood,[14,15,16] both of which may be altered in stimulant-using populations. Finally, several plausible biological mechanisms, including alterations in dopaminergic, serotonergic, glutamatergic, and adrenergic functioning,

as well as epigenetic regulation of the brain-derived neurotrophic factor (BDNF) gene, have been proposed to support the effects of exercise on substance use.[17,18] And yet, there have been few well-controlled trials designed to examine the efficacy of exercise, particularly as augmentation to treatment as usual (TAU), in this population.

This article reports primary outcome results for the CTN-0037 STimulant Reduction Intervention using Dosed Exercise (STRIDE) study. STRIDE was implemented through the National Drug Abuse Treatment Clinical Trials Network (CTN) at 9 residential substance abuse treatment programs across the United States from July 2010 to February 2013. The STRIDE trial aimed to examine the efficacy of an aerobic exercise intervention in reducing stimulant use by recruiting patients in a residential treatment facility but followed in outpatient treatment settings. The hypothesis was that exercise would result in a greater percent of abstinent days compared to a health education control condition, both of which were added to TAU, during the 12-week acute phase of the study.

Clinical Points

- Novel treatment approaches for stimulant use disorders are needed, and preliminary evidence suggests that exercise may be effective in this population, but this intervention has not been sufficiently studied.
- Dosed exercise augmentation was not superior to health education augmentation in reducing stimulant use days, with both groups showing greater than 75% of stimulant abstinent days; however, post hoc analyses that considered the differential adherence rates between groups showed a modest, but significant difference of approximately 5% greater percent of days abstinent with exercise.
- Exercise augmentation to treatment as usual may be considered for individuals with stimulant use disorders, particularly when adherence to exercise is high.

METHODS

The design and methodology of STRIDE have been described elsewhere.[19–23] An overview of the study design relevant to the reported outcomes is presented below. The study was approved by the Institutional Review Boards associated with each of the participating residential treatment programs. Written informed consent was obtained, and the study was registered at ClinicalTrials.gov (identifier: NCT01141608).

Participants

Adult stimulant users, aged 18 to 65 years, in residential substance abuse treatment were recruited and met the following inclusion criteria: (1) ability and willingness to provide informed consent and contact information, (2) agreement to complete residential treatment, (3) self-reported stimulant use (cocaine, methamphetamine, amphetamine, or other stimulant, excluding caffeine and nicotine) in the 30 days prior to treatment admission, (4) met past year *DSM-IV* criteria for stimulant abuse or dependence, (5) cleared to exercise via a protocol-defined stress test (in accordance with American College of Sports Medicine guidelines[24]), (6) body mass index (BMI) ≤ 40 kg/m^2, or BMI > 40 kg/m^2 and medically cleared to exercise, and (7) ability to comprehend and communicate in English. Exclusion criteria included: (1) evidence of a general medical condition or other abnormality contraindicating exercise, (2) past year opioid dependence, (3) considered a high risk for suicide and/or study noncompletion due to the need for psychiatric hospitalization, (4) current psychotic disorder, (5) pregnancy, (6) aerobically exercising more than 3 times per week for 20 minutes or more, consistently for the 3 months prior to study enrollment, (7) prescribed β blockers or any opioid replacement therapies, and (8) anticipated circumstances making study completion unlikely or hazardous.

Screening

Interested persons, identified early in residential treatment as potential participants, were briefly prescreened by study personnel. The study was described as a health intervention to aid in the treatment of stimulant abuse or dependence. Those who provided written informed consent were screened for eligibility. Substance use disorders were diagnosed using the World Health Organization Composite International Diagnostic Interview, version 2.1.[25] Psychiatric disorders were diagnosed using the Mini International Neuropsychiatric Interview.[26] The Timeline Followback (TLFB)[27] was used to assess stimulant use. A study-trained physician provided medical clearance to exercise following a physical evaluation and maximal exercise test.

Treatment Assignment

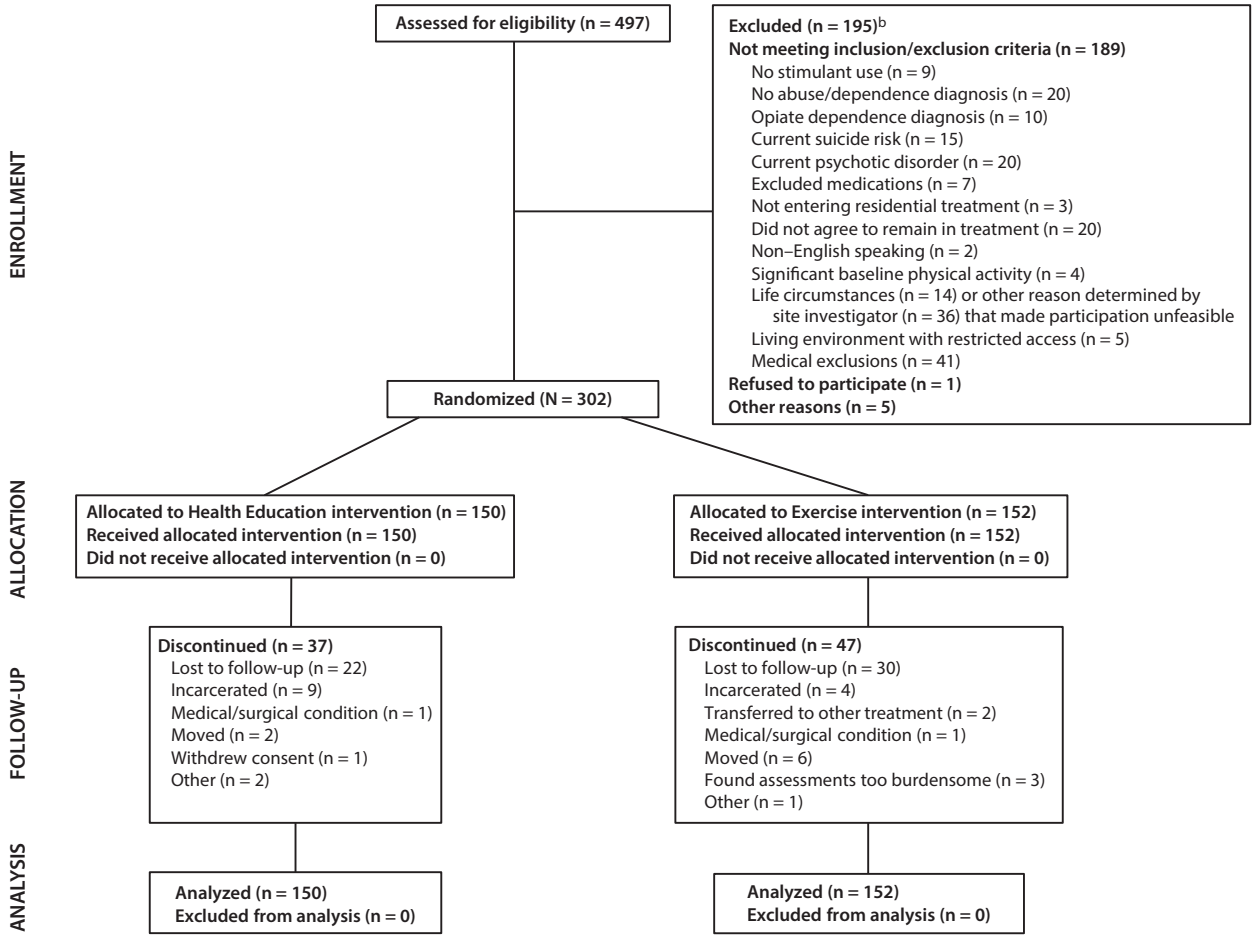
Randomization was stratified by site and within each site by presence of depressive symptoms defined as a score of ≥ 11 on the 16-item Quick Inventory of Depressive Symptomatology (QIDS)–clinician-rated (QIDS-C) format[28] and by severity of stimulant use (≤ 18 days or > 18 days of use prior to admission). A permuted-block randomization procedure was implemented via the electronic data capture system.

Study Interventions

Eligible participants were randomized to 1 of 2 treatment arms that augmented TAU: (1) Exercise or (2) Health Education. Both groups received substance use disorder TAU, first in a residential setting and then typically continued in an outpatient treatment program. Professional attention was controlled for across the 2 groups. Participants received 12 weeks of acute phase intervention followed by an additional 24 weeks of intervention with supervision once per week.

Exercise intervention. Participants randomized to Exercise[20,21] completed supervised exercise sessions 3 times per week during the 12-week acute phase. Exercise was prescribed at a dose of 12 kcal/kg/wk (KKW), with

Figure 1. CONSORT Diagram[a]



[a]In the Allocation row, "received allocated intervention" refers to the fact that all eligible participants were assigned to an intervention; however, this does not account for nonadherence. Because the analyses were intent-to-treat, they were conducted on all participants who were randomized to an intervention, regardless of their adherence to the intervention.
[b]Screened individuals could meet more than 1 exclusion criterion.
Abbreviation: CONSORT = Consolidated Standards of Reporting Trials.

intensity ranging from 70% to 85% of maximal heart rate (HR_{max}). This dose is similar to those doses used in several studies of exercise interventions,[29,30] including in efficacy studies with smokers,[31,32] and is equivalent to ≥ 150 minutes of moderate exercise per week (ie, approximately 30–50 minutes, 3–5 days per week). Exercise dose and intensity were gradually increased during the first 3 weeks (week 1: 4 KKW at 50%–60% HR_{max}; week 2: 8 KKW at 60%–70% HR_{max}; weeks 3–12: 12 KKW at 70%–85% HR_{max}). For most participants, the maximum intensity was equivalent to walking at a moderate speed and incline (3.0 mph at 5% incline) for approximately 150 minutes per week. Additional sessions could be completed for those needing more to achieve the target dose. Supervised sessions were conducted as 1-on-1 sessions.

Health Education intervention. Participants randomized to Health Education[22] also completed 3 visits per week during the 12-week acute phase. Health Education consisted of 1-on-1 sessions in which information on health-related topics (eg, cancer, heart disease, mental health) was distributed via didactics, websites, audio, video, and written materials. Exercise was not an included topic.

Outcome Measures

Stimulant use outcomes were assessed at the assessment visits, which were conducted 3 times per week. Days of self-reported drug use were assessed by the TLFB, a semistructured interview that uses a calendar to retrospectively assess daily drug use since the last assessment. The TLFB was originally developed to assess alcohol use,[33] but has been adapted to acquire information for other substances, including cocaine and other stimulants.[34] The TLFB has high test-retest reliability (intraclass correlation coefficient values from 0.70 to 0.94, with all $P < .001$), good convergent and discriminant validity, and acceptable agreement with urine drug screens (UDS).[35]

Urine drug screens measured stimulant use (cocaine, amphetamine, methamphetamine), as well as opiates, marijuana, benzodiazepines, barbiturates, methadone, methylenedioxymethamphetamine (MDMA, ecstasy), and

Table 1. Baseline Demographic, Drug Use, and Other Clinical Characteristics[a]

Characteristic	Total (N = 302)	Health Education (n = 150)	Exercise (n = 152)
Demographic			
Gender, n (%)			
Male	181 (60)	92 (61)	89 (59)
Female	121 (40)	58 (39)	63 (41)
Age, mean (SD), y	39.0 (11)	39.5 (11)	38.5 (10)
Race, n (%)			
Black/not Hispanic	130 (43)	75 (50)	55 (36)
White/not Hispanic	137 (45)	63 (42)	74 (49)
Other[a]/not Hispanic	12 (4)	6 (4)	6 (4)
Hispanic ethnicity	31 (10)	12 (8)	19 (13)
Education in years, mean (SD)	12.4 (2)	12.3 (2)	12.4 (2)
Marital status, n (%)			
Married	40 (13)	17 (11)	23 (15)
Divorced/separated/widowed	101 (33)	46 (31)	55 (36)
Never married	161 (53)	87 (58)	74 (49)
Employment status, n (%)			
Full time	133 (44)	70 (47)	63 (41)
Part time	53 (18)	30 (20)	23 (15)
Unemployed	92 (30)	37 (25)	55 (36)
Other	24 (8)	13 (9)	11 (7)
Drug Use/Treatment			
Days in residential treatment, mean (SD)	18.1 (10)	17.9 (10)	18.3 (11)
Days of stimulant use in 30 days prior to treatment admission, mean (SD)	13.1 (9)	13.2 (10)	12.9 (9)
Cocaine	9.1 (9)	8.7 (10)	9.5 (9)
Methamphetamine	3.7 (8)	4.1 (8)	3.3 (8)
Other stimulant	0.5 (3)	0.6 (3)	0.4 (3)
Dependence diagnoses, n (%)			
Cocaine	253 (84)	117 (78)	136 (90)
Other stimulant	114 (38)	58 (39)	56 (37)
Alcohol	152 (50)	71 (47)	81 (53)
Marijuana	96 (32)	47 (31)	49 (32)
Other illicit drugs	53 (18)	29 (19)	24 (16)
Fagerström Nicotine Dependence, mean (SD)	3.4 (2)	3.7 (2)	3.2 (2)
Clinical			
QIDS score, mean (SD)	5.4 (3)	4.8 (3)	5.9 (3)
Body mass index, mean (SD)	27.8 (6)	27.6 (6)	28.0 (6)

[a]Designations of American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Other, Multiracial, Unknown, and "Participant chose not to answer" were collapsed into 1 new category of "Other" due to the small numbers of participants in these groups.
Abbreviations: QIDS = Quick Inventory for Depressive Symptomatology, SD = standard deviation.

oxycodone. Urine drug screens were conducted to augment the veracity of TLFB.

Statistical Analyses

The primary outcome measure was the percent of stimulant abstinent days during days 22 to 84 (weeks 4–12) of the acute phase of the study. Outcome measurement began at day 22 because it was anticipated a priori that most individuals would be in residential treatment during the first 21 days of the study and, therefore, would have little opportunity to use illicit substances (ie, the groups would not likely differ during this time period).

Stimulant abstinent days were based on TLFB. In order to estimate the number of days of use when either there were missing UDS data or the thrice weekly UDS showed discrepancy with TLFB, the eliminate contradiction (ELCON) algorithm[36] was used. First, all missing TLFB days and UDS results, including any missing data due to participants discontinuing before the end of the study, were imputed as positive for stimulant use. The ELCON algorithm was then implemented by comparing the TLFB to UDS day by day. For any comparison in which the UDS was positive and the 3 TLFB days prior to the UDS were negative, the TLFB for the last day in the comparison period was changed from negative to positive to eliminate the contradiction between the self-report and objective data. Once the ELCON algorithm was applied, the number of abstinence days was summed and the percent of stimulant abstinent days was calculated; these data were used in all planned and post hoc analyses.

The primary analysis compared the percent of stimulant abstinence days between the 2 treatments taking into account variability in the overall level of abstinence among sites. A linear mixed-effects model was used with site as a random effect and treatment group as a fixed effect. As specified in the analysis plan, this model was used 3 more times with the addition of each of 3 covariates: gender, race, and ethnicity, along with their interactions with treatment group. All participants' data were utilized for the primary analysis and post hoc analyses regardless of their adherence to the interventions in accordance with the intent-to-treat principle.

Because a large between-group difference in adherence (number of intervention sessions attended/number of sessions required) was observed, post hoc analyses were performed in which the treatment effect was evaluated by including adherence as a covariate. Days of stimulant use in the 30 days prior to residential treatment was also included as a covariate. Thus, treatment adherence and prior use were covariates in an adjusted linear mixed-effects model. The interaction of each covariate with treatment group was tested, and any interaction terms that were not significant were removed from the model.

Cohen d[37] was computed as a standardized measure of the unadjusted and adjusted mean difference between treatments. Number needed to treat (NNT)[38] was also computed. For both measures of effect size, positive effect sizes favor Exercise and negative effect sizes favor Health Education. P values less than .05 were considered statistically significant.

RESULTS

Participant Characteristics

Four hundred ninety-seven participants were screened, resulting in 302 randomized (Exercise, n = 152; Health Education, n = 150) participants. A Consolidated Standards of Reporting Trials (CONSORT; consort-statement.org) diagram (Figure 1) presents data on participants who were screened, reasons for exclusion, and reasons enrolled participants discontinued participation during the acute phase. Baseline demographic and clinical information is presented in Table 1. The 2 treatment groups did not differ statistically on any demographic or baseline characteristic. Few participants scored ≥ 11 on the QIDS scale for depression (16 total: 12 in Exercise, 4 in Health Education). Mean days

of stimulant use prior to treatment entry were 12.9 days (SD = 8.8 days) and 13.2 days (SD = 9.5 days) for the Exercise and Health Education groups, respectively, and were not significantly different ($t = 0.3$, $df = 300$, $P = .77$). The mean duration of residential treatment was 18.3 days (SD = 11 days) in the Exercise group and 17.9 days (SD = 10 days) in the Health Education group.

Study Retention and Primary Outcome Availability

Two hundred eighteen participants (72%) completed the week 13 assessment; 105 (69%) in Exercise and 113 (75%) in Health Education. The most frequent reason for not completing the week 13 assessment was being lost to follow-up (n = 52), followed by incarceration (n = 13) and moving from the area (and did not complete phone or off-site assessments; n = 8). Availability of data during the primary outcome period was excellent, with 92% of TLFB data available (92% in Exercise, 93% in Health Education) and 67% of UDS data available (63% in Exercise, 70% in Health Education).

Primary Analysis

Group analyses of self-reported TLFB data produced a nonsignificant difference (Exercise: 90.8%, SD = 16.4%; Health Education: 91.6%, SD = 14.7%; $d = -0.05$, NNT = −34.1, $P = .67$), as did an analysis using only UDS data (Exercise: 80.2%, SD = 29.8%; Health Education: 74.6%, SD = 32.7%; $d = 0.18$, NNT = 10.0, $P = .14$). After imputing missing TLFB days and missing UDS results as positive and applying the ELCON algorithm, the percent of stimulant abstinent days was 76.4% (SD = 26.3%) for all participants, 75.6% (SD = 27.4%) for Exercise participants, and 77.3% (SD = 25.1%) for Health Education participants ($d = -0.06$, NNT = −27.4) (Table 2). After adjustment for random site effects, the difference between groups was not significantly different ($f = 0.3$, $df = 1,292$, $P = .60$). Adjustment for site and site × treatment interactions also indicated no statistically significant difference in percent of days abstinent between the 2 intervention groups. Because the days in residential treatment were less than anticipated, we conducted a secondary analysis using all days of postresidential treatment. This analysis yielded similar results; percent of days abstinent was not significantly different between Exercise (76.2%, SD = 26.4%) and Health Education (77.9%, SD = 24.1%; $d = -0.07$; $P = .59$, NNT = −26.4).

Subgroup Analyses

Tests for interaction of treatment revealed a marginally significant interaction between treatment and ethnicity (Hispanic and non-Hispanic) ($P = .051$), such that Hispanic participants had 83.1% (SD = 16.5%) abstinent days when assigned to Exercise and 66.8% (SD = 30.2%) in Health Education ($d = 0.72$, NNT = 2.6), whereas non-Hispanic participants had 74.5% (SD = 28.5%) abstinent days when assigned to Exercise and 78.2% (SD = 24.5%) in Health Education ($d = -0.14$, NNT = −12.6). Analysis yielded no statistically significant interactions by gender or race.

Adherence and Associated Post Hoc Analysis

Participants in Exercise attended 64.0% (SD = 30.4%) of the 36 (3 visits/wk for 12 weeks) expected intervention visits, compared to 74.7% (SD = 28.7%) in Health Education, and this difference was significant ($t = 3.2$, $df = 300$, $P = .002$). Participants in Exercise completed a median 8.3 KKW per week or 69.2% of the prescribed exercise dose (ie, approximately 79 minutes per week). Table 3 shows estimates and tests for all effects in the full post hoc model. The interactions of treatment group with the covariates were not significant. After removing these interactions, significant effects were found for percent of sessions attended ($P < .001$) and for treatment group (Table 4). The adjusted proportion of abstinent days was 78.7% (SE = 0.02%) for Exercise participants and 73.9% (SE = 0.02%) for Health Education participants ($d = 0.25$, NNT = 7.2, $f = 4.7$, $df = 1,290$, $P = .03$). Figure 2 shows linear regression lines fit for each group independently and illustrates approximately 5% improvement in days abstinent in Exercise over Health Education. Note

Table 2. Percent of Stimulant Abstinent Days Based on Timeline Followback (TLFB) and Eliminate Contradiction (ELCON) Algorithm Adjustment[a]

	All		Exercise		Health Education	
Outcome	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
TLFB	291	91.2 (15.6)	145	90.8 (16.4)	146	91.6 (14.7)
ELCON algorithm	302	76.4 (26.3)	152	75.6 (27.4)	150	77.3 (25.1)

[a]Mean percent of stimulant abstinent days are for days 22 to 84. Eleven participants had no TLFB data: their data are missing when there is no imputation (TLFB row); their data are present when there is imputation and all data are imputed as stimulant use days (ELCON algorithm row).

Table 3. Results for Full Ad Hoc Mixed-Effects Model

Effect	Estimate	SE	Numerator *df*	Denominator *df*	*F*	*P*
Intercept	0.3856					
Treatment group	−0.0439	0.1	1	288	0.4	.510
Days of use for 30 days prior to RTP	−0.0012	0.0	1	288	2.2	.138
Percent sessions attended	0.0060	0.0	1	288	259.3	<.001
Days prior use by treatment group	−0.0013	0.0	1	288	0.3	.581
Percent sessions attended by treatment group	0.0002	0.0	1	288	0.1	.795

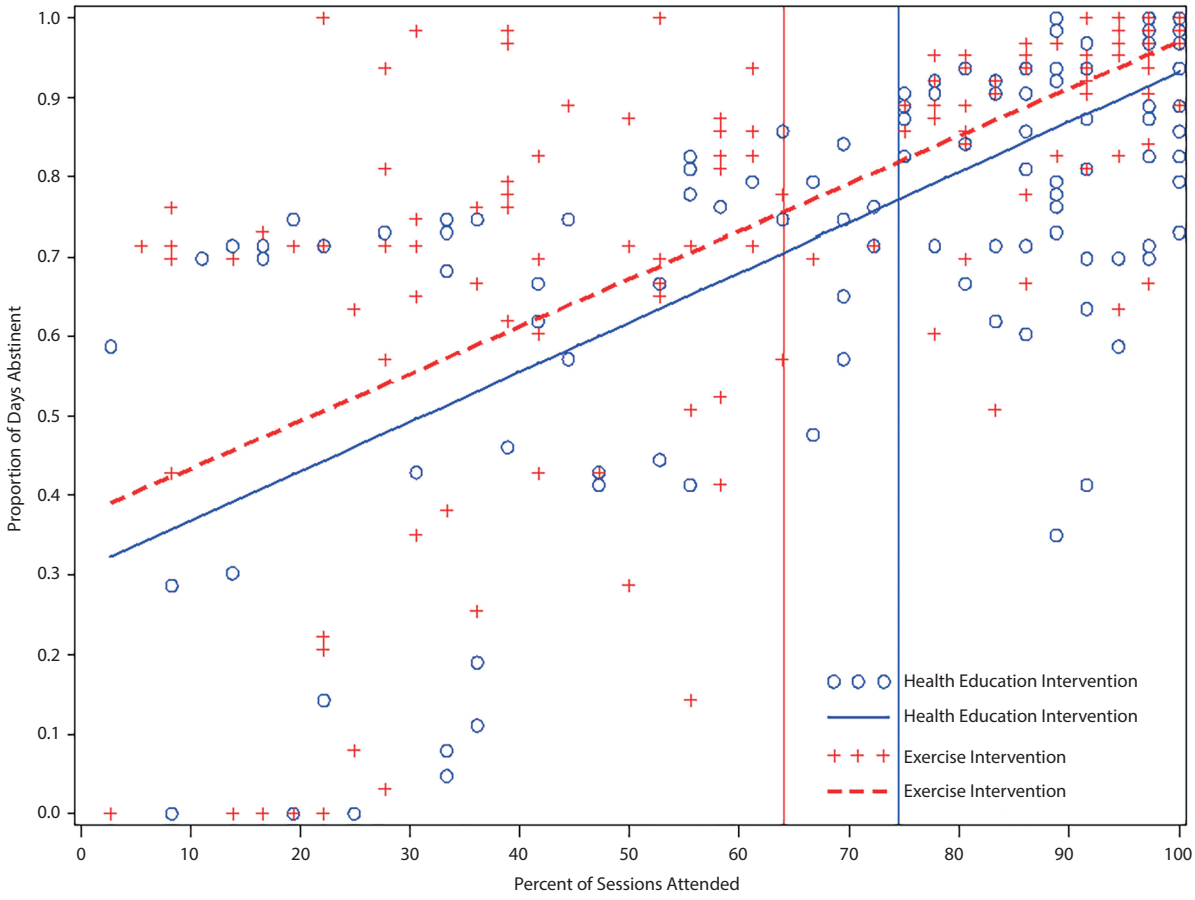
Abbreviations: *df* = degrees of freedom, RTP = residential treatment program, SE = standard error.

Table 4. Results for Ad Hoc Mixed-Effects Model After Removing Nonsignificant Interaction Terms

Effect	Estimate	SE	Numerator *df*	Denominator *df*	*F*	*P*
Intercept	0.3889					
Treatment group	−0.0477	0.0	1	290	4.7	.032
Days of use for 30 days prior to RTP	−0.0019	0.0	1	290	2.3	.127
Percent sessions attended	0.0061	0.0	1	290	261.0	<.001

Abbreviations: *df* = degrees of freedom, RTP = residential treatment program, SE = standard error.

Figure 2. Analysis Adjusted for Adherence and Use Prior to Residential Treatment Program Admission[a]



[a]Independent simple regressions of percent of abstinent days on adherence as defined by percent of intervention sessions attended. Vertical reference lines mark the significantly different means of percent adherence in the 2 treatment groups.

that the pronounced upward slope of the line was a result of assigning missing data as days of use.

Adverse Events

Of the 192 total postrandomization adverse events (AEs) that occurred, 76 were deemed not related to study procedures, while 116 were considered related or possibly related to study procedures. Seventy-nine participants (52%) in the Exercise group had an AE, compared to 28 (19%) in the Health Education group. Sixty-five percent of AEs (125/192) were classified as mild or moderate, with the majority of those occurring in the Exercise group (96%). The most common AEs were classified as musculoskeletal and connective tissue disorders, and they occurred primarily in the Exercise group (32% of Exercise participants reported 49 of the 50 AEs [98%] in that category). Specific AEs in this category that occurred in over 5% of Exercise participants include arthralgia, back pain, muscle spasms, myalgia, and pain in extremity. Dizziness was the only other specific AE that occurred in over 5% of Exercise participants (5.3%) but not in Health Education participants (0%).

Fifty AEs met designated criteria for serious adverse events (SAEs). No SAEs were determined to be related to study procedures. The occurrence of SAEs was comparable across interventions, with 26 in the Exercise group and 24 in the Health Education group. SAEs included 42 inpatient hospital admissions and 1 death.

DISCUSSION

STRIDE is the first large-scale study evaluating the efficacy of exercise training compared to health education, both added to TAU, as potential treatments for stimulant use disorders. STRIDE is also the first clinical trial utilizing the novel ELCON algorithm to reconcile results from TLFB and UDS.

The primary analysis using the ELCON algorithm in this study did not find a statistically significant difference in the percent of abstinent days between the Exercise and the Health Education groups. Overall, the mean days of use for the 30 days prior to entry into the residential treatment program was 13.1 days (SD = 9 days), and the abstinence rates across groups following treatments were extremely high—over 90% via self-report (TLFB), but around 75% by the ELCON algorithm-corrected analyses when missing data were assigned as days of use.

Participants in the Exercise group attended significantly fewer intervention sessions than those in the Health

Education group (64.0% [SD = 30.4%] vs 74.7% [SD = 28.7%], respectively). A post hoc analysis adjusting for intervention adherence and stimulant use prior to treatment entry suggested a positive treatment effect for exercise, albeit modest. This analysis revealed a significant difference between groups, with an approximately 5% greater percent of days abstinent in the Exercise condition versus those in Health Education, suggesting that exercise may improve outcomes for stimulant users who have good adherence to an exercise training program. Subjects in the Exercise group completed approximately 8 KKW of the 12 KKW dose. Previous research suggests that this is likely a suboptimal dose of exercise. In a study of aerobic exercise dose on depression outcomes,[39] a 7 KKW dose was less effective in reducing depression outcomes compared to a 17.5 KKW dose. Similarly, in a study of postmenopausal women,[29] an 8 KKW dose resulted in significantly less improvement in cardiorespiratory fitness compared to a 12 KKW dose.

The abstinence rates observed in our study are significantly higher than those commonly seen in other trials examining combined pharmacologic and behavioral treatments for stimulant use, with 3 recent studies[40–42] reporting percent of abstinent days of approximately 48%–58% among active treatment groups with 1 study[43] yielding a higher range of approximately 60% to 73%. The relatively higher rate of abstinence observed in both groups from the current study may be related to either a modest rate of pretreatment days of drug use in our sample or the continuing effect of the residential treatment prior to randomization. These results could suggest that either both Exercise and Health Education are ineffective in decreasing stimulant use or, given the high abstinence rates observed, it is possible that both interventions were effective in decreasing stimulant use. Participants in both groups received considerable contact with study personnel, which could have impacted stimulant use. Unfortunately, without a study arm of participants receiving only TAU, we are unable to assess the impact of this increased professional contact.

Studies have routinely emphasized the importance of exercise adherence in interpreting the results of studies with exercise interventions. Brown et al[44] noted in their recent pilot study that future research may need to better identify expectations and preferences in drug abusing populations, as well as identify and troubleshoot barriers that prohibit adequate adherence. Similarly, Williams et al[45] commented on the fact that several studies examining exercise for smoking cessation have had poor adherence rates, and they assert that this may be the primary reason that those trials did not yield significant findings, again stressing the importance of adequate and sustained adherence in such interventions. The importance of adherence in exercise trials is not specific to substance abuse outcomes. Adjustment for adherence is often necessary in efficacy studies examining the effects of exercise in patients with other chronic illnesses, such as depression[39] and type 2 diabetes.[30] It is important to note that exercise was generally well-tolerated in this population, with the majority of AEs in the Exercise group being classified as mild or moderate, and expected in association with exercise (eg, muscle spasms). However, further consideration to tolerability in the evaluation of both adherence and efficacy of exercise in this population is warranted.

In addition to better evaluating the role of adherence to exercise on stimulant use outcomes, it is important to evaluate potential mediators and moderators of exercise that may impact its efficacy. It is conceivable that exercise is only effective in a subset of individuals, due either (or both) to certain baseline behavioral characteristics (eg, severity of illness factors, such as years of drug use and past treatment history; poor response inhibition; a particular BDNF polymorphism [eg, rs6265])[46] or to mediators (eg, improved mood, withdrawal, craving, and cognition; changes in BDNF and dopamine). Further investigation will be important to ascertain what behavioral and biological characteristics and/or changes are associated with the efficacy of exercise in individuals with stimulant use disorders.

STRIDE was a hybrid efficacy-effectiveness study with specific eligibility criteria that excluded at-risk individuals with physical or psychiatric conditions that might contraindicate exercise. In addition, the study had fewer participants than expected in the stratum of greater stimulant use at baseline (ie, > 18 days in the 30 days prior to residential treatment entry) or those with significant depressive symptoms (QIDS–self-report > 10), and therefore may have enrolled a less severe group of individuals who use stimulants compared to other individuals in residential treatment. Finally, differential adherence rates in the treatment arms, although not unusual in studies of this sort, are a further limitation.

Despite the above limitations, the study had several notable strengths—the use of geographically diverse sites, adequate intervention adherence rates in a population that had significant attendance and participation barriers (eg, transportation, relapse to drug use), and a well-received comparative condition. Furthermore, this study demonstrated that it is possible to conduct intensive interventions with this population. Because of the unusually high abstinence rates in both intervention groups, as well as the post hoc adjustment for adherence yielding a significant effect of exercise, we believe it is important to continue research in this area to better understand whether exercise may benefit individuals with stimulant use disorders. Additionally, subsequent research should investigate more appealing strategies to encourage exercise (eg, leader-led groups with music, buddy system, use of electronic systems). Future trials should evaluate the influence of adherence on outcomes and aim to improve adherence to exercise interventions.

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owned stock in Bristol-Myers Squibb within the last 5 years. **Dr Nunes** has received medication from Alkermes (Vivitrol) for a NIDA-funded research study on treatment of opioid dependence in recent years and has served as an unpaid consultant to Alkermes at an advisory meeting about planning a study on treatment of opioid dependence. **Drs Rethorst, Carmody, Walker, Shores-Wilson, Stoutenberg, Oden, Silverstein, Hodgkins, Love, Seamans, Stotts, Causey, Reed, Rinaldi, Myrick, Liu, Lindblad, Church, and Blair; Mr Grannemann;** and **Ms Straus** report no disclosures and conflicting interests.

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