Exercise for the Treatment of Addiction

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Objectives

- Discuss the use of exercise as a novel treatment for substance abuse
- Discuss the STRIDE Study Rationale and Design
- Discuss the vigorous dose high intensity exercise intervention being tested in STRIDE

Why Examine Exercise as a Treatment for SUD?

- Need for novel treatments for substance use disorders
- Exercise is showing promise as a treatment for other disorders: depression, anxiety, nicotine, alcohol
- Neurobiological plausibility
- Additional health benefits and reductions in comorbidities

Exercise may yield both direct and indirect benefits in SUD

- Exercise may have direct effects on withdrawal symptoms, cravings
- Exercise may have indirect effects on other critical issues in substance users: e.g., quality of life, cognitive function, comorbid health conditions (both general medical and mental)

Need for Novel Treatments for Stimulant Abuse

Need for Novel Treatments:
Cocaine and Methamphetamine Abuse

- Current unmet needs with existing treatments
- Relapse is always a consideration in substance users:
  - Stress is a potent trigger of relapse; exercise is a potent regulator of stress

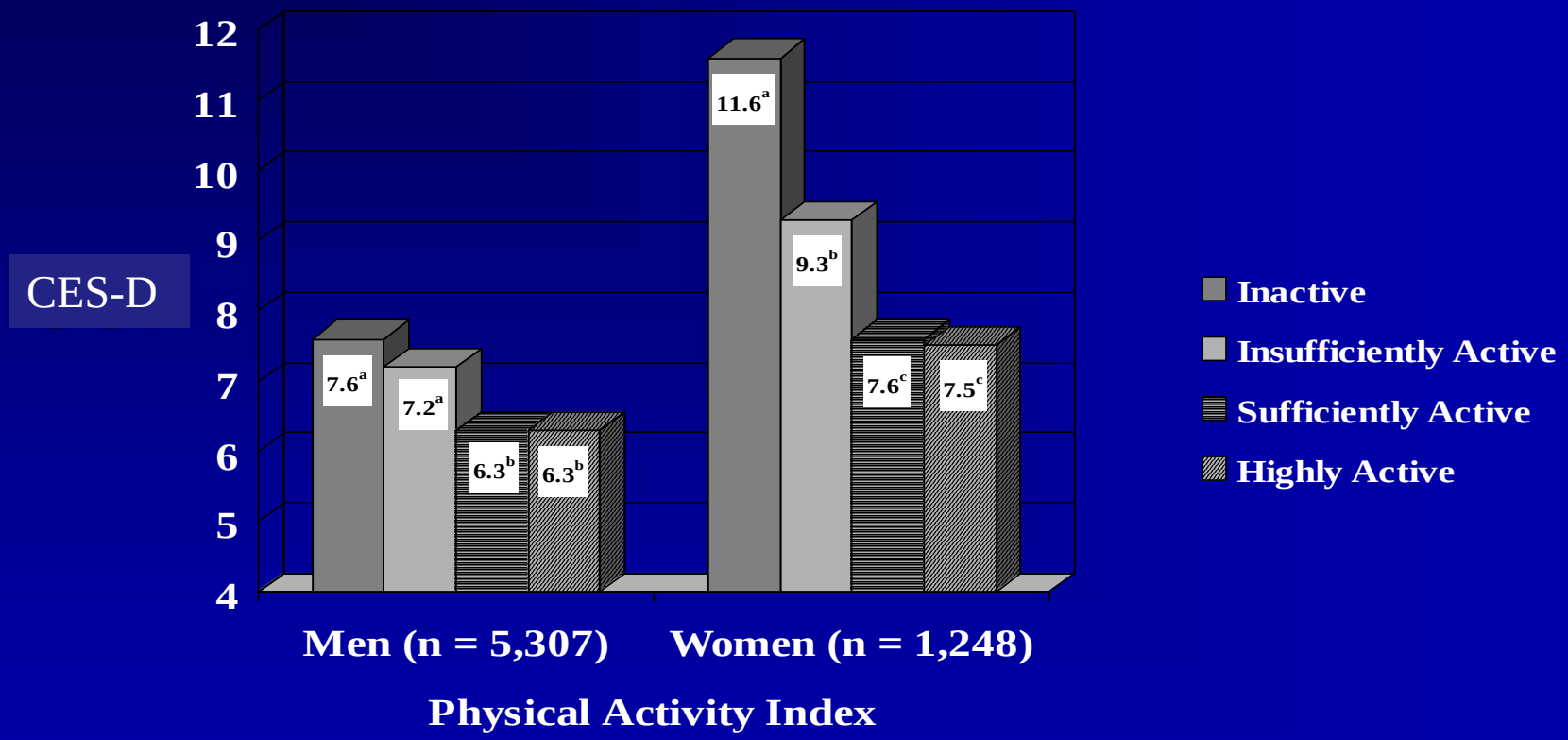
Exercise is appropriate based on many of the principles of effective treatments for drug addiction:

- No single treatment is appropriate for all individuals – exercise would be a novel option
- Treatment needs to be readily available – after training, exercise can be implemented with minimal supervision and is easily accessible
- Effective treatment should meet multiple needs of the individual – exercise offers a variety of health benefits
- Behavioral therapies are critical – exercise is a rewarding nondrug-using activity that could replace drug-using activity
- Co-existing disorders should be treated – exercise also benefits depression and anxiety, which are often comorbid in SUD
- Recovery is a long-term process requiring multiple episodes of treatment – maintenance of exercise may reduce relapse

NIDA. Principles of Drug Addiction Treatment: A Research Based Guide. http//www.nida.nih.gov/PODAT/PODAT1.html

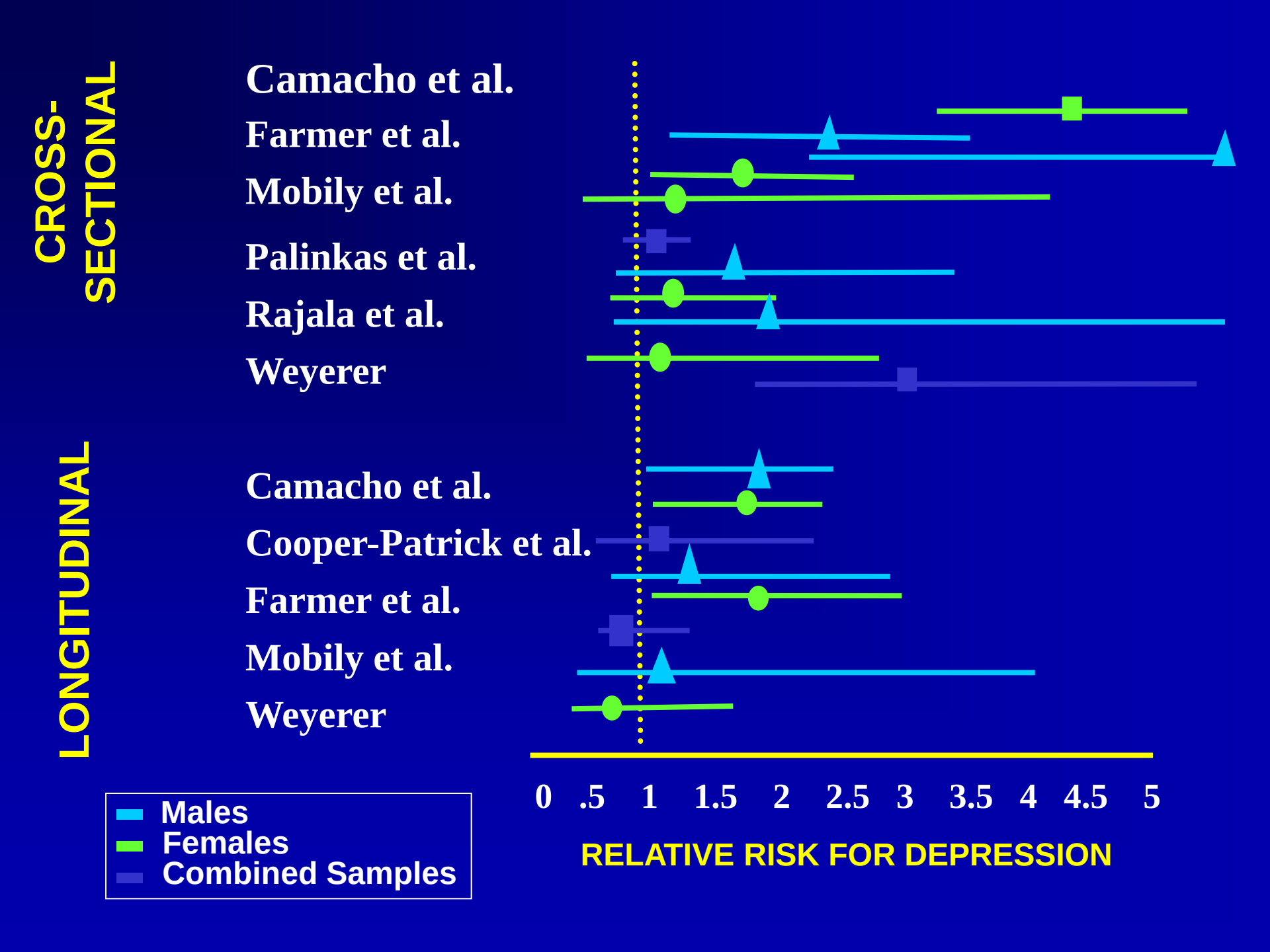
Exercise in the Treatment of Other Psychiatric Disorders

Epidemiological Studies



Galper, Trivedi et al. (2006). Inverse association between physical inactivity and mental health in men and women. *Medicine & Science in Sports & Exercise, 38,* 173-178

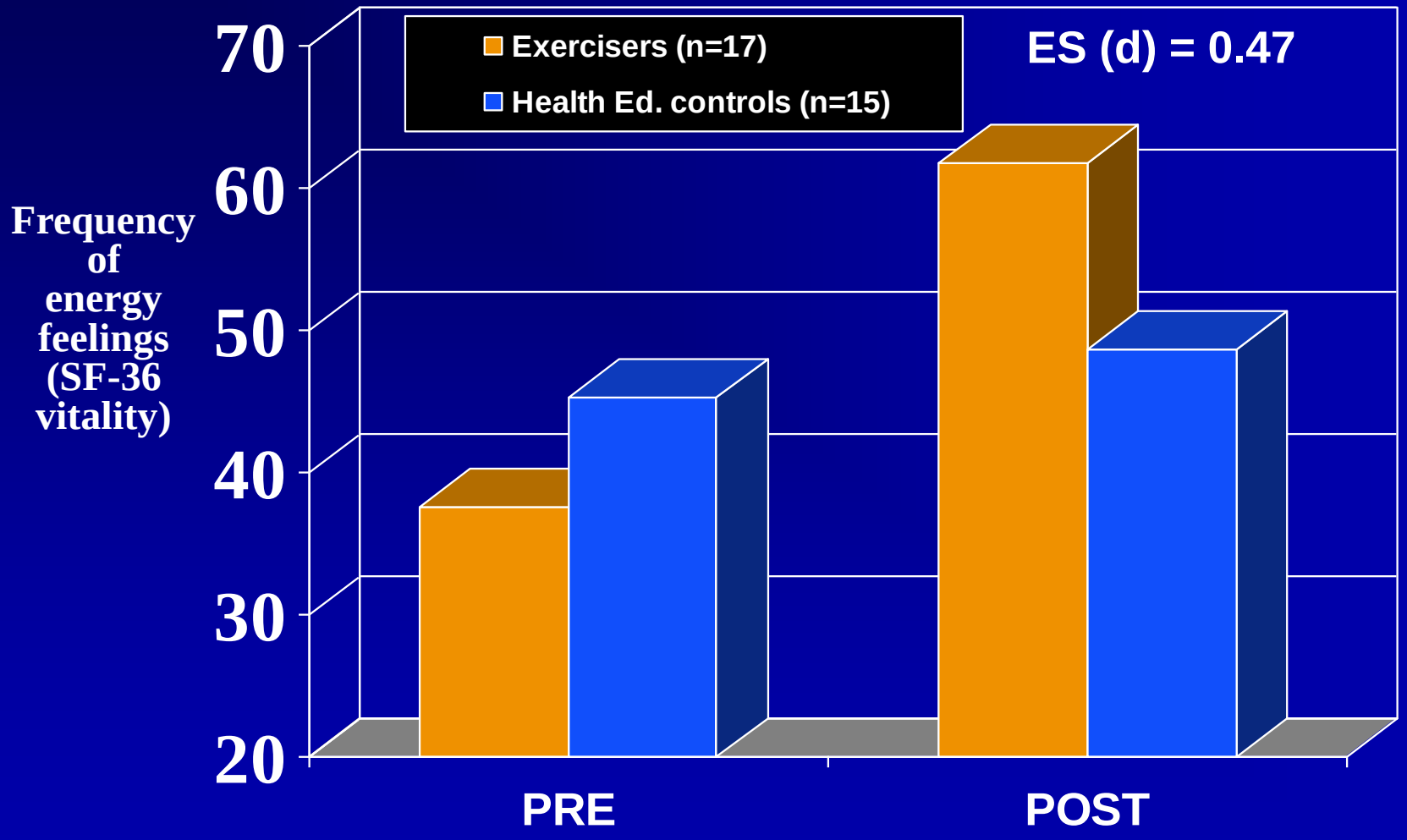
Inactive = less than 1 mile/wk of walking, running or jogging; Insufficiently Active = 1 - 10 miles/wk; Sufficiently Active = 11-19 miles/wk; Highly Active = 20+ miles/wk.


CROSS-SECTIONAL
LONGITUDINAL
Camacho et al.
Farmer et al.
Mobily et al.
Palinkas et al.
Rajala et al.
Weyerer
Camacho et al.
Cooper-Patrick et al.
Farmer et al.
Mobily et al.
Weyerer
Males
Females
Combined Samples
0 .5 1 1.5 2 2.5 3 3.5 4 4.5 5
RELATIVE RISK FOR DEPRESSION

Blumenthal et al. (1999)

- **N=156 older adults (55+) w/ MDD**
- **walk/jog 3x/wk, 30 min @ 70-85% HRR**
- **All groups exhibited significant symptom reduction at 16 wk**
- **10 month follow-up: Exercise < relapse (Babyak et al, 2000)**

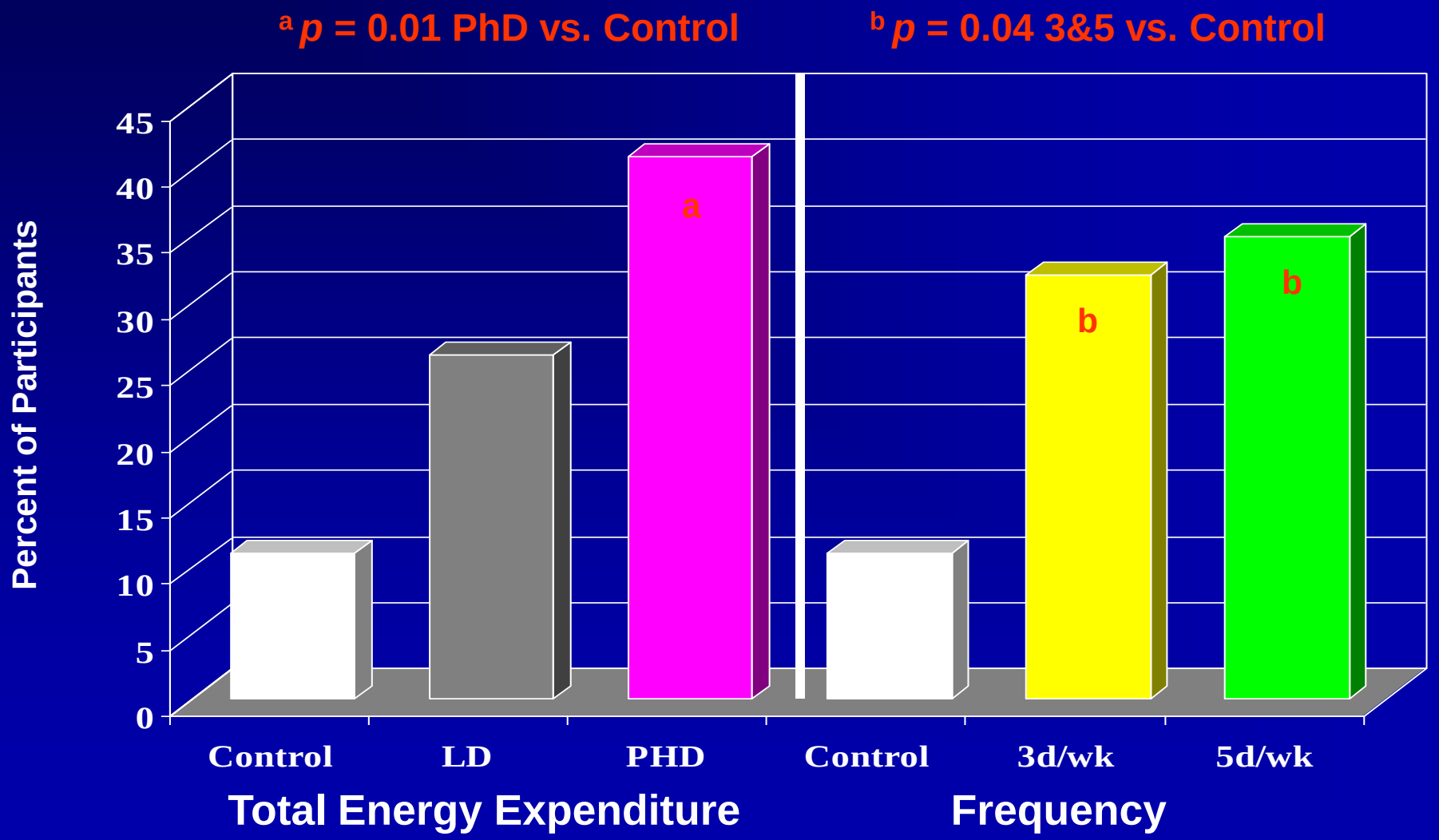
RCT of Weight Lifting exercise in older adults with mild depressive symptoms (>12 on BDI)



45 min, 3/wk, 5 lifts @ 80%1 RM, 10 weeks

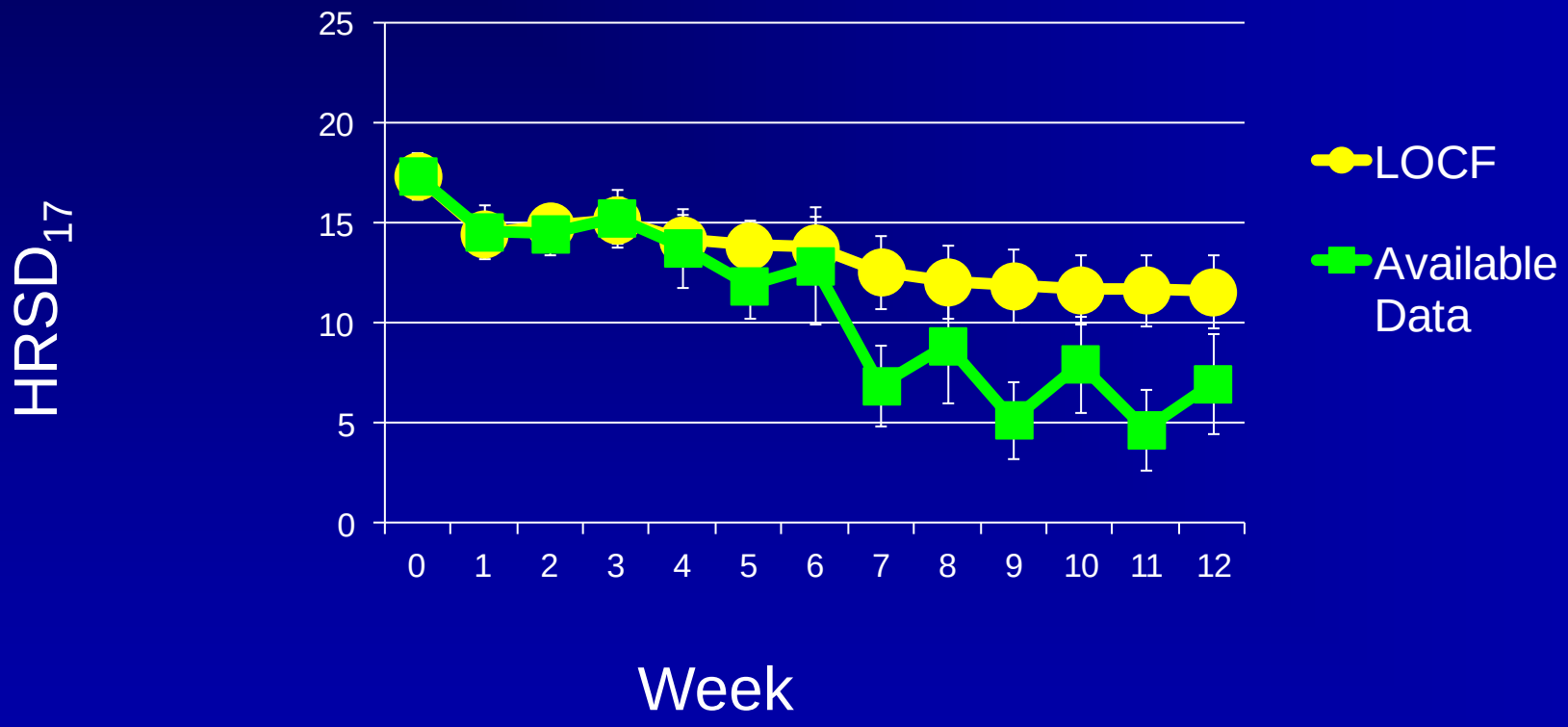
Adapted from: Singh et al., 1997, *J. Gerontology*., 52 (1): M27-35.

Remission Rates - DOSE



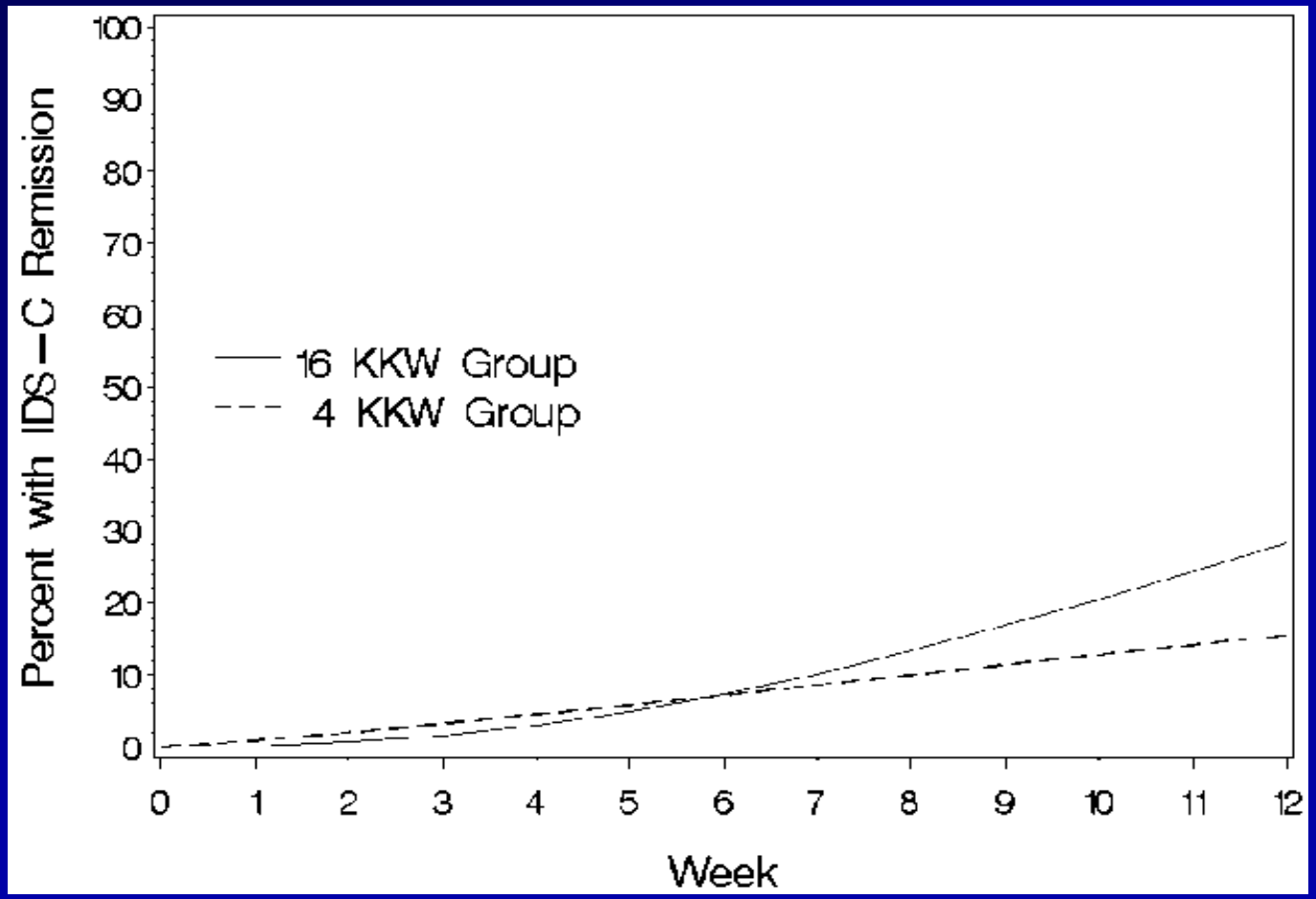
Dunn, Trivedi et al. (2005). Exercise treatment for depression: Efficacy & dose response. *American Journal of Preventive Medicine, 28,* 1-8.

Exercise Augmentation Pilot



Trivedi MH, Greer TL, Grannemann BD, Chambliss HO, Jordan AN. Exercise as an Augmentation Strategy for Treatment of Major Depression. J Psychiatr Pract, 12, 205-213.

TREAD: Adjusted Remission Rates



4 KKW: 15.5%
16 KKW: 28.3%
P = .07

NNT = 7.8

Trivedi MH, Greer TL, Church TS, Carmody TJ, Grannemann BD, Galper DI, Dunn AL, Earnest CP, Sunderajan P, Henley SS, and Blair SN. Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. Journal of Clinical Psychiatry, 2011 May;72(5):677-84.

Nicotine and Alcohol

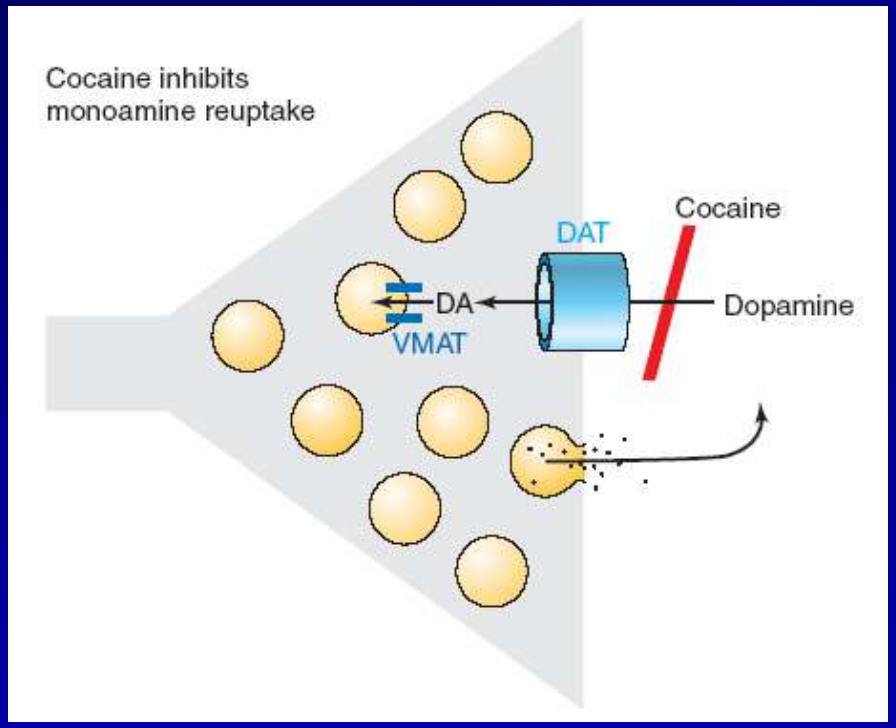
- Review by Taylor et al. (2007) on exercise and smoking:
  - 9 of 10 studies comparing active and passive conditions reported significantly reduced cravings both during and following exercise

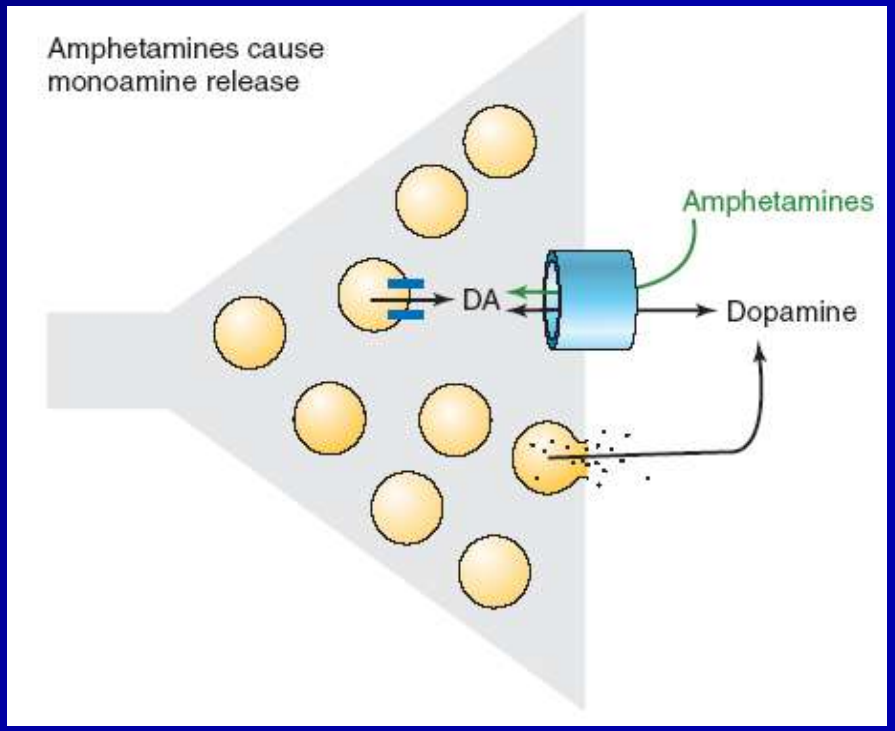
Neurobiological Plausibility

Neurobiological Effects of Exercise and SUD

	Exercise	Substance Use
Neurogenesis	increases	decreases
Gliogenesis	enhances	reduces
Cognitive function (e.g., prefrontal BDNF)	improves	impairs
Dopaminergic function	enhances	enhances

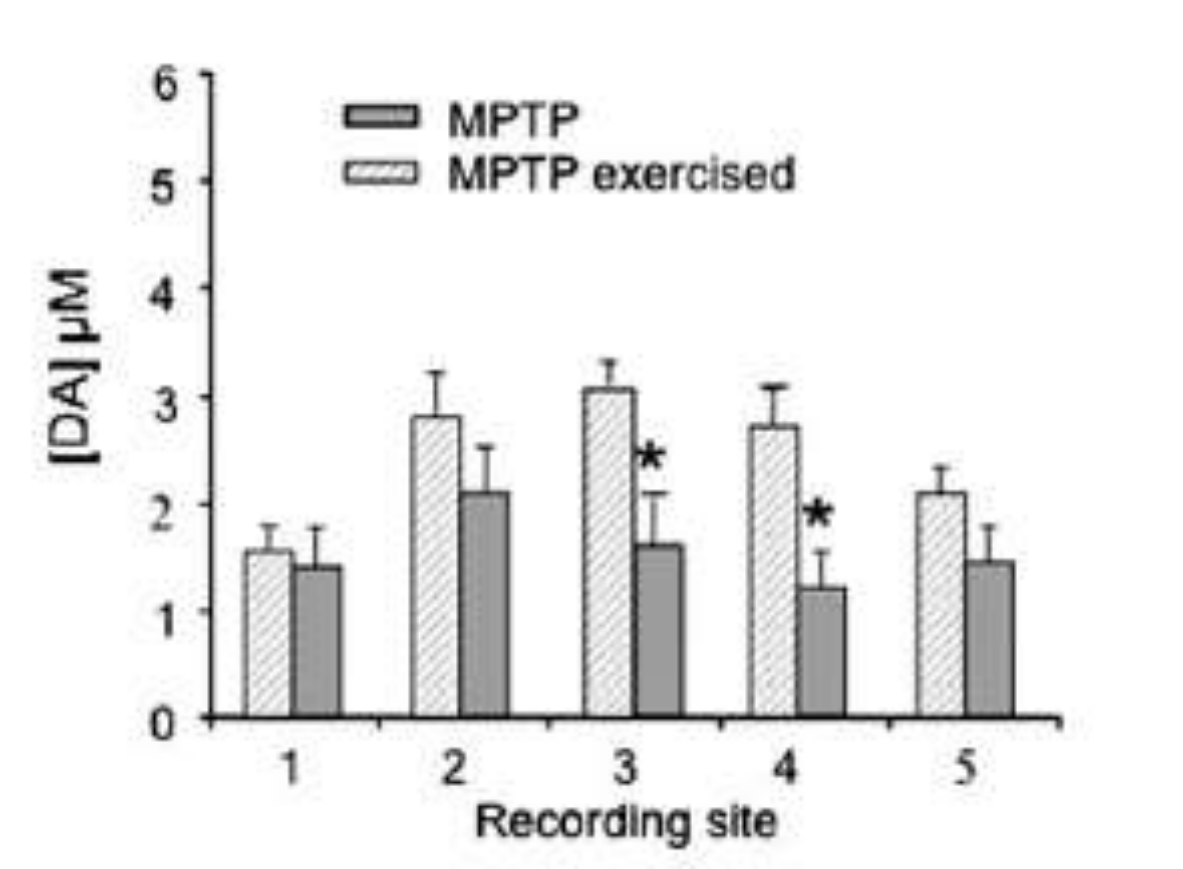
Cocaine and amphetamine increase synaptic dopamine





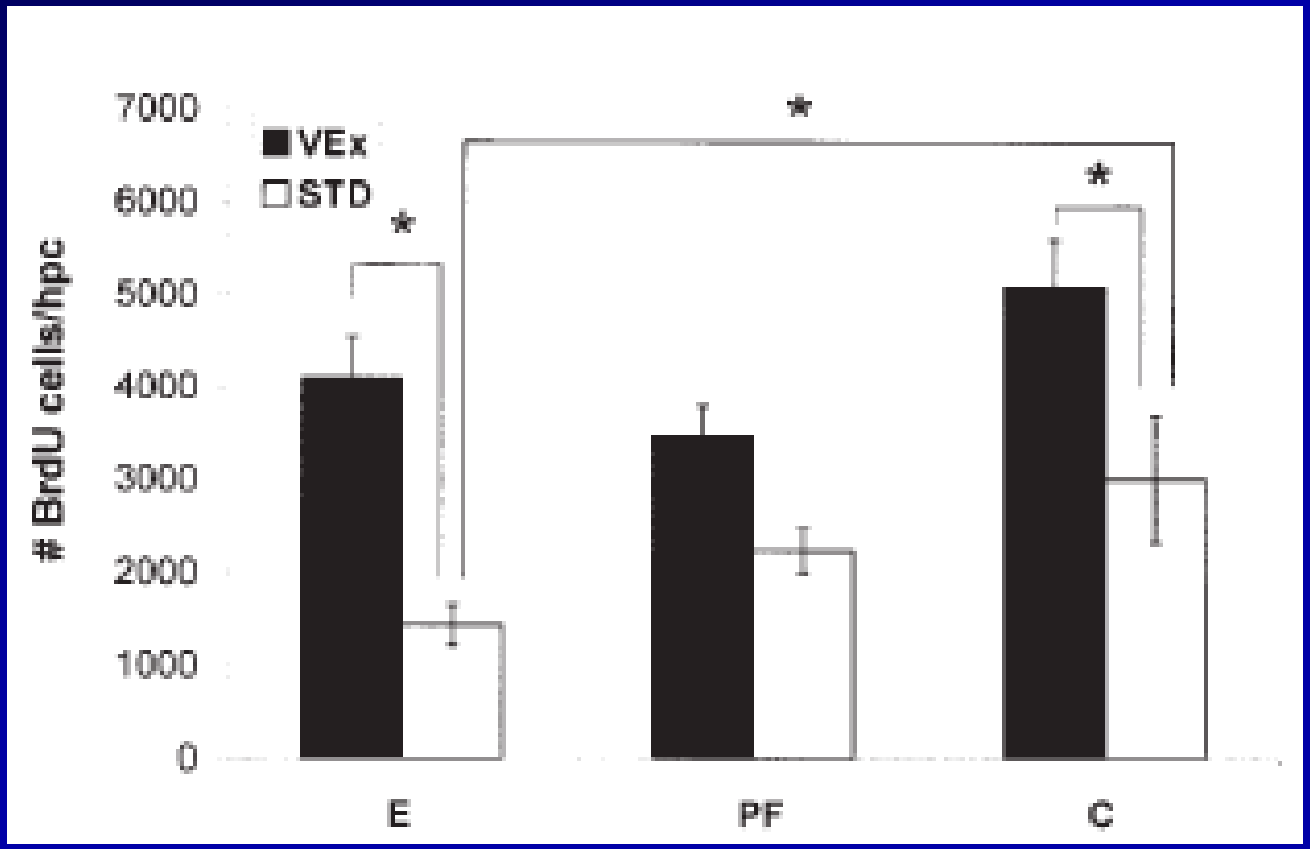
Adapted from Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci. 2006;29:565-98.

Exercise increases synaptic dopamine



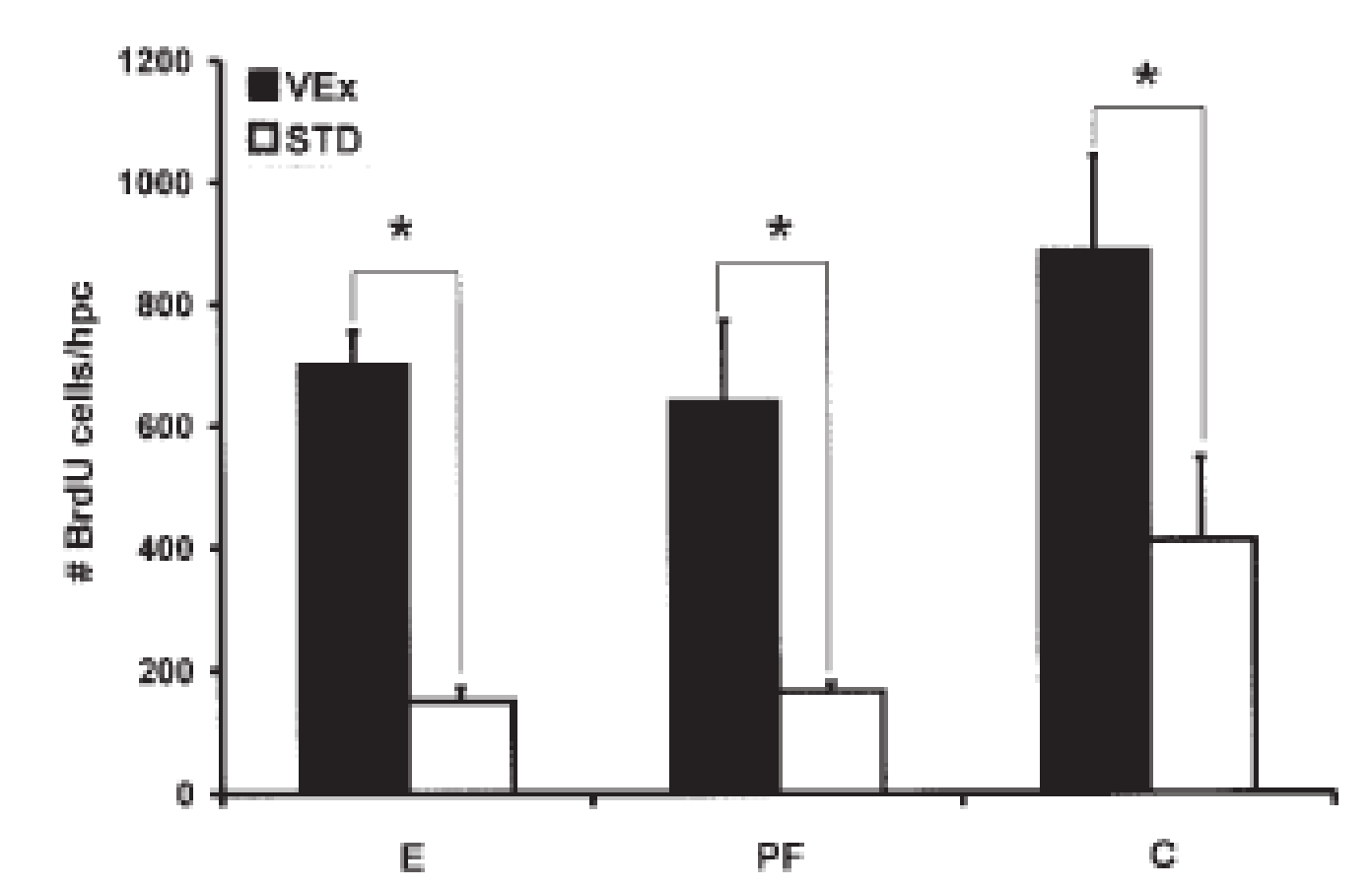
Adapted from Petzinger GM, Walsh JP, Akopian G, Hogg E, Abernathy A, Arevalo P, Turnquist P, Vucković M, Fisher BE, Togasaki DM, Jakowec MW. Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. J Neurosci. 2007 May 16;27(20):5291-300.

Exercise can reverse decreased hippocampal cell proliferation following prenatal ethanol exposure…



Adapted from Redila VA, Olson AK, Swann SE, Mohades G, Webber AJ, Weinberg J, Christie BR. Hippocampal cell proliferation is reduced following prenatal ethanol exposure but can be rescued with voluntary exercise. Hippocampus. 2006;16(3):305-11.

as well as increase neurogenesis…



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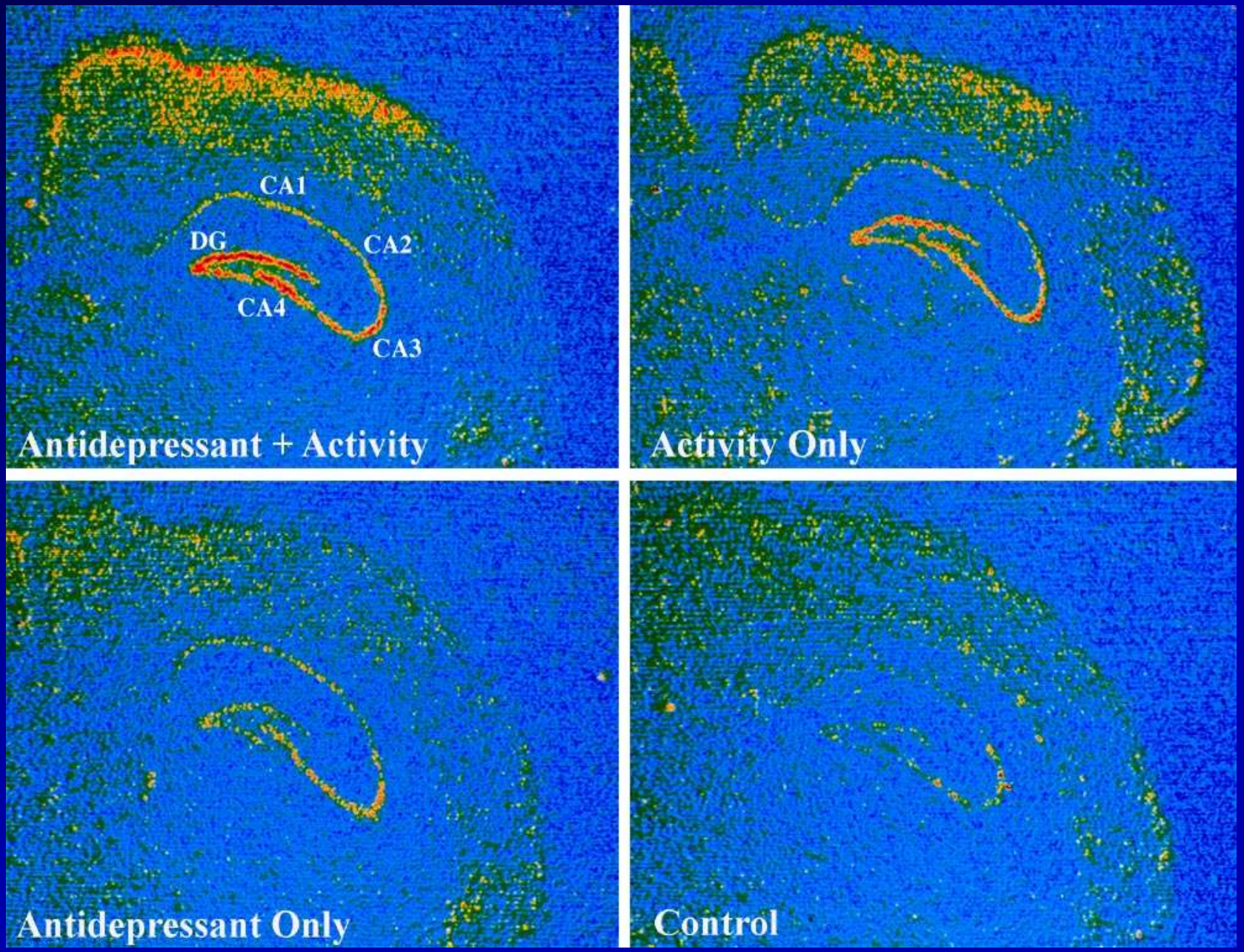
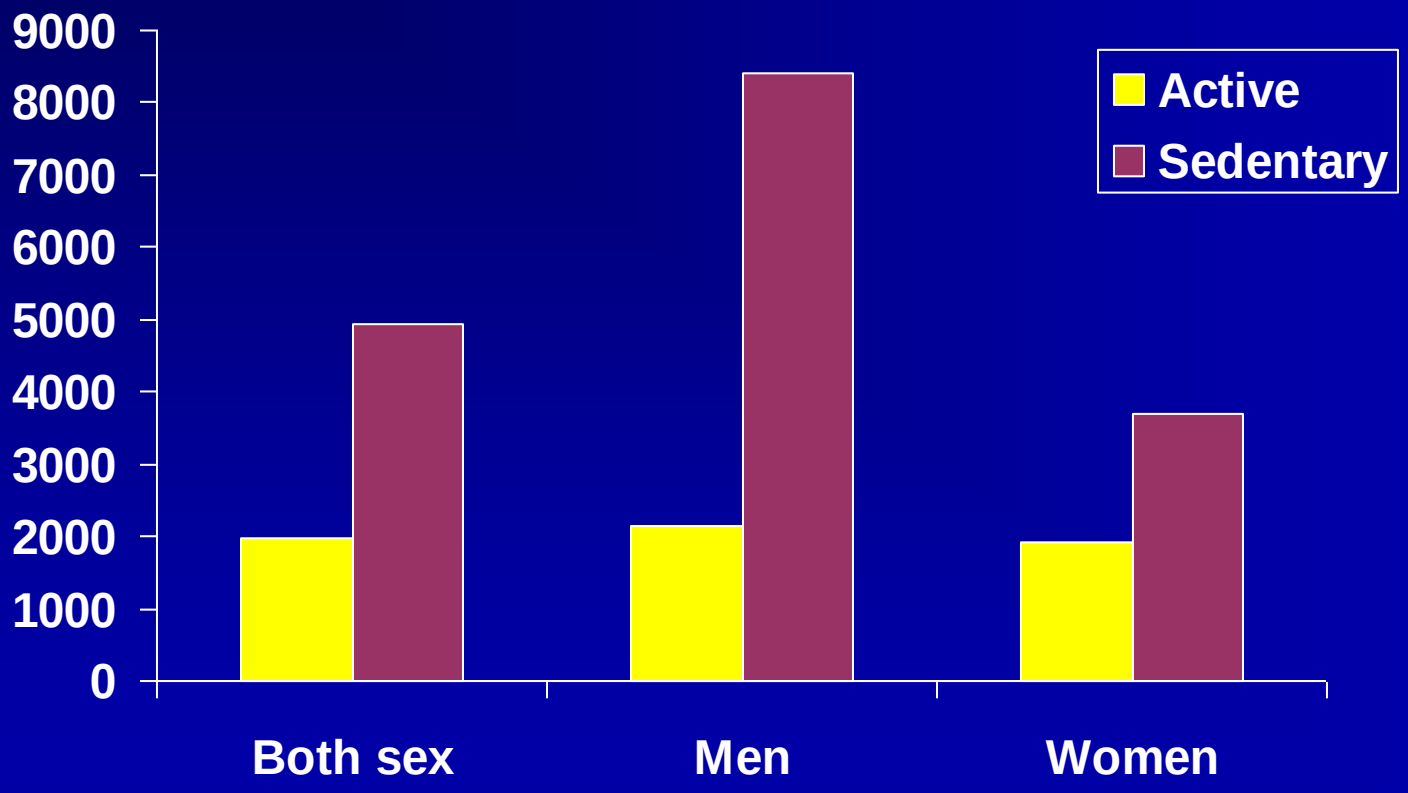


Russo-Neustadt A, Beard RC, Cotman CW. (1999). Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. Neuropsychopharmacol., 21, 679-682.

Overall Health Benefits

Annual medical expenditure ($) of active and sedentary persons with any mental disorder



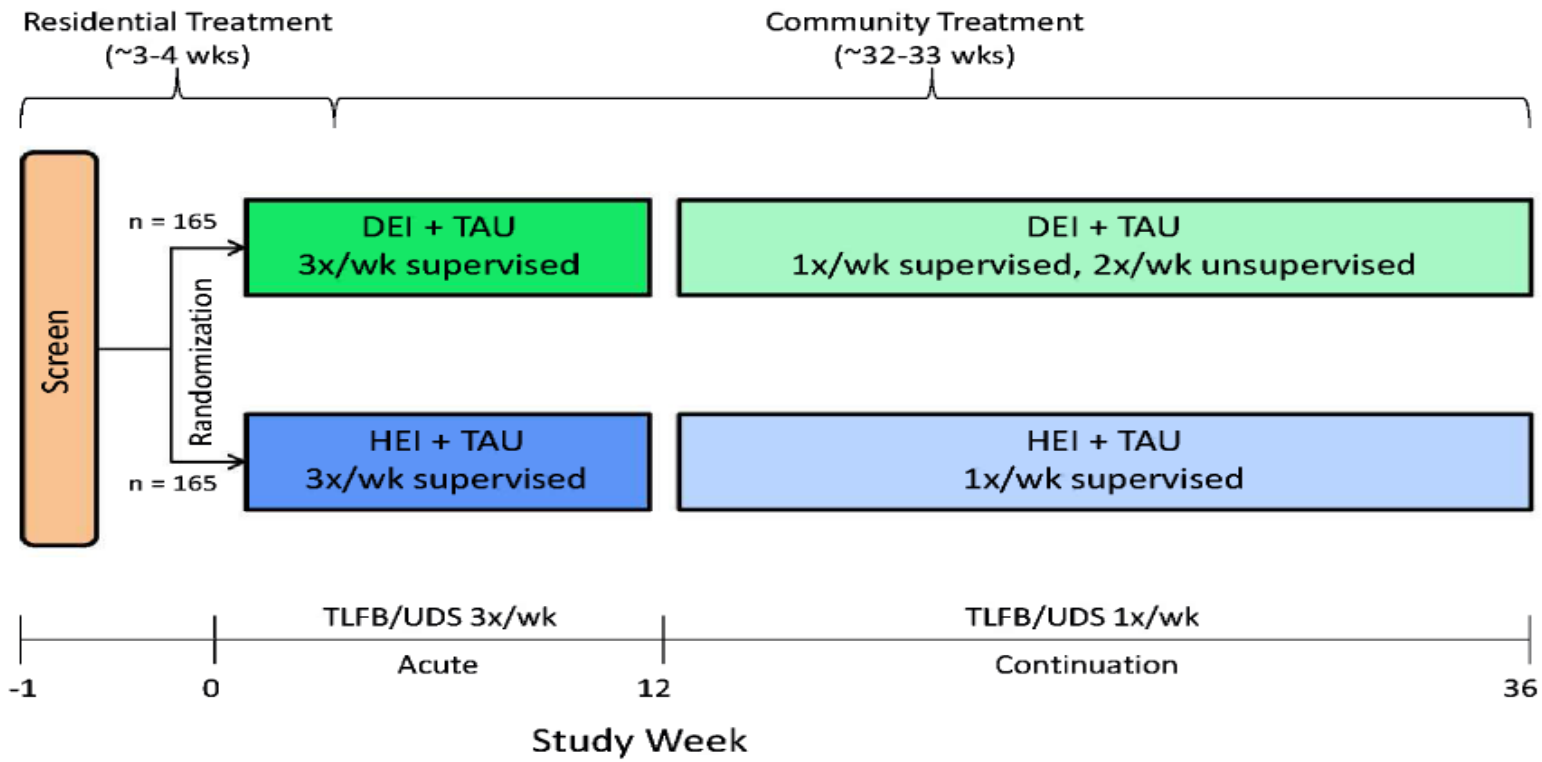
Brown (2003). Cooper Institute Conference on Physical Activity and Mental Health.

Rationale - Conclusions

- Exercise would provide a novel treatment approach for SUD and would meet many of the guidelines for an effective SUD treatment
- Exercise appears feasible as a treatment for substance use disorders
- Neurobiological effects of exercise show plausible mechanisms related to SUD treatment
- Exercise is likely to provide additional health benefits to individuals with substance use disorders

CTN 0037 - STRIDE STimulant Reduction Intervention using Dosed Exercise

STRIDE Design



DEI = Dosed Exercise Intervention Augmentation
HEI = Health Education Intervention Augmentation
TAU = Treatment as Usual

STRIDE Design

- *Design:* Multisite, randomized, controlled trial
- *Participants:* 300 individuals with stimulant abuse/dependence
- *Sites:* 9 Community Treatment Providers (CTPs)

Study Sites

Wave 1	
Arapahoe House	Denver, CO (Florida Node)
Gateway Community Services	Jacksonville, FL (Florida Node)
Gibson Recovery Center	Cape Girardeau, MO (Ohio Valley Node)
Nexus Recovery Center	Dallas, TX (Texas Node)

Wave 2	
Memorial Hermann Prevention and Recovery Center	Houston, TX (Texas Node)
Morris Village	Columbia, SC (Southern Consortium Node)
Penn Presbyterian	Philadelphia, PA (Delaware Valley Node)
Charleston VAMC	Charleston, SC (Southern Consortium Node)
St. Luke's-Roosevelt Hospital	New York, NY (Long Island Node)

Primary Aim & Outcome

- *Primary Aim*: to compare percent days of abstinence between the Exercise and Health Education groups, during days 22-84 post-randomization (Acute Phase)
- *Primary Outcome*: percent days of abstinence as measured by the Timeline Follow Back and UDS 3 times per week

Secondary Aims

1. To compare time to relapse between the Exercise and Health Education groups
2. To evaluate withdrawal symptoms between the Exercise and Health Education groups
3. To evaluate drug use and related outcomes for all substances during the acute phase (randomization – 12 wks)
4. To compare time to dropout from substance abuse treatment between the Exercise and Health Education groups
5. To evaluate drug use and related outcomes during the entire course of the study (randomization – 9 mos)

Exploratory Aims

- To determine if there are additional health benefits to using exercise augmentation in the treatment of substance use disorders
  - sleep
  - cognitive function
  - mood
  - quality of life
  - anhedonia
  - weight gain

Unique Features of STRIDE

- Transition from residential treatment to outpatient treatment and aftercare
- Duration of study and frequency of intervention
- Supervised intervention sessions
- Behavioral adherence program
- Web-based monitoring

Recruitment

- Participants recruited from treatment settings with a residential component
- Eligible participants are those requiring a 21-30 day stay in an RTP and who will be referred to follow-up care close to the RTP
- Participants remain in the study as they transition to outpatient treatment

Inclusion Criteria

- Age 18-65
- Stimulant abuse or dependence
- Stimulant use within 30 days of admission
- Medical clearance including maximal exercise test using ACSM guidelines
- Body mass index (BMI) $\leq$ 40 kg/m2 or BMI $>$ 40 kg/m2 and cleared by medical personnel to exercise

Exclusion Criteria

- Medical condition contraindicating exercise
- Current opiate dependence
- High suicide/psychiatric risk/psychotic disorder
- Pregnancy
- Physically active (consistent activity >20 min per week more than 3x per week) for 3 months prior to enrollment
- Concomitant treatments: beta blockers; methadone, buprenorphine or other opioid replacement therapy

Visit Schedule

- For supervised Exercise and Health Education visits:
  - 12 weeks: 3x week
    - First 21-30 days while in residential treatment
    - Continuation after treatment to follow-up care
  - 6 months: 1x week

Exercise Intervention

- Exercise Dose: 12 kcal/kg/week (KKW) (equivalent to ~120-150 min of exercise per week, or 30 min 4-5 times per week)
- Exercise Intensity: 70-85% maximal heart rate
- Exercise Modality: Walking or running (treadmills)
- To maximize tolerability and adherence, exercise will be gradually ramped up to the required dose and intensity over the course of 3 weeks

Exercise Intervention

- Early sessions focus on training participants to collect and record all exercise variables of interest (kcal, duration, rating of perceived exertion, pre- and post-heart rate, etc.).
- Later supervised sessions allow participants to exercise more independently, but facilitators will be available for questions, troubleshooting barriers, etc.
- During 6 month follow-up, the remainder of exercise sessions needed to fulfill the prescription will be completed at home.
- Heart rate monitors used to verify intensity (supervised sessions).
- Pedometers used to track typical activity levels.

Health Education Intervention

- Educational readings, discussions, videos, and websites
  - e.g. healthy eating, preventive health care, accessing health resources
- Participants help select topics
- Pedometers used to verify typical activity levels

Challenges in Implementing the Study

- Maximizing adherence in both Exercise and Health Education groups
- Retaining participants in study when they transition to outpatient care
- Retaining participants over the entire 9 month study

Adherence to Exercise and Health Education

A comprehensive Behavioral Adherence Program has been developed and successfully used by our team (Trivedi et al., 2006).

- Includes:
  - Psychoeducation
  - Exercise/HE skills training/self-management skills
  - Exercise/HE planning and goal setting
  - Identifying and overcoming Exercise/HE barriers
  - Behavioral contracting
  - Feedback, incentives and prompting

Adherence to Exercise and Health Education

- Participants use STRIDE website to enter Exercise/Health Education activity
- Adherence reports are generated in real time
- Facilitators work with all participants not achieving 100% adherence to develop tailored plans for each participant based on problem-solving person-specific barriers
- Example: A participant in the exercise group is having muscle soreness, as well as difficulty finding the time to schedule exercise sessions. The EF will help the participant to develop a plan for stretching to aid in soreness, as well as work with the participant to help find a way to fit exercise sessions into their schedule.

Why evaluate augmentation treatments of substance abuse?

- Population prevalence for stimulant abuse is 0.5% (1.4 million users)
- In standard treatment, 13% achieve abstinence
- Abstinence rates for the best treatments:
  - Similar across different types of substance abuse
  - Range from 25-30%
- No one treatment works for all individuals – novel treatment approaches are needed

Why Exercise & Health Education?

- Evidence supports efficacy of exercise with other disorders
- Exercise as augmentation effective with other substance abuse disorders (e.g. nicotine dependence)
- Plausible neurobiological and psychological mechanisms proposed
- Novel treatments badly needed for drug abuse

Why evaluate high dose exercise?

- Use of high dose exercise ensures exercise has highest probability of showing efficacy in this early efficacy study
- High dose effective in trials for other conditions
- Consistent with public health recommendations
- High levels of adherence in other studies
- If efficacious, next study can evaluate dose response
- More important to use attentional control and treatment as usual comparators now to establish efficacy than to compare with low dose exercise

Summary

- Good Rationale for the study of Exercise
- Need Definitive Evidence for Efficacy
- Need the Development of Easy to Use tools to Ensure Exercise Implementation in Real World Practice