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Rationale for Using Exercise in the Treatment of Stimulant Use Disorders

Tracy L. Greer, Ph.D.[a]; Kolette M. Ring, B.A. [a]; Diane Warden, Ph.D., M.B.A.[a], Bruce D. Grannemann, M.A.[a]; Timothy S. Church, M.D., Ph.D., M.P.H.[b]; Eugene Somoza, M.D., Ph.D.[c]; Steven N. Blair P.E.D [d, e]; Jose Szapocznik, Ph.D.[f]; Mark Stoutenberg, Ph.D.[f]; Chad Rethorst, Ph.D. [a]; Robrina Walker, Ph.D.[a]; David W. Morris, Ph.D. [a]; Andrzej S. Kosinski, Ph.D.[g]; Tiffany Kyle, Ph.D.[h]; Bess Marcus, Ph.D.[i]; Becca Crowell, M.Ed., Ed.S.[j]; Neal Oden Ph.D.[k]; Edward Nunes, M.D.[l] ; Madhukar H. Trivedi, M.D.[a];

[a] The University of Texas Southwestern Medical Center at Dallas

[b] Preventive Medicine Laboratory, Pennington Biomedical Research Center

[c] Cincinnati Addictions Research Center (CinARC); Department of Psychiatry, University of Cincinnati College of Medicine

[d] Department of Exercise Science, University of South Carolina

[e] Department of Epidemiology and Biostatistics, University of South Carolina

[f] Department of Epidemiology and Public Health, University of Miami, Miller School of Medicine

[g] Department of Biostatistics and Bioinformatics, Duke University Medical Center, Duke Clinical Research Institute

[h] The Center for Drug-Free Living

[i] Department of Family and Preventive Medicine, The University of California, San Diego

[j] Nexus Recovery Center, Inc

[k] The EMMES Corporation

[l] New York State Psychiatric Institute/Department of Psychiatry, College of Physicians and Surgeons of Columbia University

Corresponding Author:

Madhukar H. Trivedi, M.D.

Department of Psychiatry, The University of Texas Southwestern Medical Center at Dallas

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Abstract

Novel approaches to the treatment of stimulant abuse and dependence are needed. Clinical data examining the use of exercise as a treatment for the abuse of nicotine, alcohol, and other substances suggest that exercise may be a beneficial treatment for stimulant abuse. In addition, exercise has been associated with improvements in many other health-related areas that may be adversely affected by stimulant use or its treatment, such as sleep disturbance, cognitive function, mood, weight, quality of life, and anhedonia. Neurobiological evidence provides plausible mechanisms by which exercise could positively affect treatment outcomes in stimulant abuse. The National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) CTN-0037 Stimulant Reduction Intervention using Dosed Exercise (STRIDE) study is a multisite randomized clinical trial that compares exercise to health education as potential treatments for stimulant abuse or dependence. If effective, exercise may provide an additional approach to the treatment of stimulant use disorders.

Key Words: stimulant abuse, stimulant dependence, exercise, health education, behavioral intervention

Introduction

Outcomes in the treatment of substance use disorders suggest a need for innovative modest treatments. Stimulant use disorders are chronic, relapsing illnesses with few highly efficacious treatments (1). In

Treatment as Usual (TAU; i.e., the standard treatment one would receive at a substance use treatment facility) for substance use disorders, typically only about 13% of participants achieve abstinence (1). Abstinence rates for treatments designed to augment TAU vary widely – ranging from 14%-60% (2, 3, 4, 5) – depending on the outcome variable and primary endpoint selected. Currently, the best treatments for cocaine and other stimulant abuse are behavioral treatments that combine cognitive behavioral therapy (CBT) with contingency management (1, 6). However, it is clear that new treatments are still needed for stimulant abuse and dependence.

Exercise is a promising new treatment option for stimulant abuse and dependence. There have been a number of studies of the effectiveness of exercise in improving outcomes with alcohol, other substance abuse, or tobacco, with the impact of exercise on smoking cessation receiving the most attention. There are also a number of studies of the impact of exercise on improving depressive symptom severity and other chronic diseases. As a whole, this literature suggests that exercise may have good potential to impact outcomes with substance use disorders. As a result, the STimulant Reduction Intervention using Dosed Exercise (CTN-0037; STRIDE) study was developed to assess the feasibility of the use of exercise as an augmentation to usual care in individuals with stimulant use disorders.

This review will examine the existing literature that provides the rationale for studying exercise as a treatment for stimulant use disorders. In addition, a brief description of the ongoing STRIDE CTN-0037 trial that resulted from the culmination of this information will be described.

Exercise as a Treatment for Substance Abuse

Exercise and Smoking Cessation

Randomized controlled trials examining exercise to improve outcomes in smoking cessation provide some of the most convincing support for investigating the use of exercise (most frequently, vigorous intensity exercise) to improve outcomes in stimulant abuse treatment. Several controlled trials found vigorous high intensity exercise to improve outcomes in smoking cessation (7, 8, 9), although others did not find this effective (10, 11, 12). These older studies, however, had small samples and other methodological limitations.

Marcus et al. (9) evaluated a 12 week vigorous intensity high dose supervised exercise intervention (target of 60-85% of heart rate reserve, three supervised sessions per week at 30-40 minutes per session) added to a 12 week group cognitive behavioral smoking cessation program as compared with cognitive behavioral intervention plus attentional control (health and lifestyle sessions) in 281 women. Participants who exercised were significantly more likely than participants in the health education control group to achieve continuous abstinence at three time points: 1) after 12 weeks of treatment (19.4% vs 10.2%, $p = 0.03$), 2) three months following treatment (16.4% vs 8.2%, $p = 0.03$), and 3) one year following treatment (11.9% vs 5.4%, $p = 0.05$).

Marcus and colleagues (13) later completed a randomized controlled trial assessing exercise for a shorter duration of time and with more moderate intensity. The study examined an 8-week moderate intensity exercise program (target of 59-69% of maximum heart rate, one supervised session and 4 additional weekly sessions of at least 30 minute duration) added to an 8-week group cognitive behavioral smoking cessation program, compared to a cognitive behavioral program plus equal staff time, in 217 women. There were no differences in 7-day point prevalence abstinence (i.e., the number of participants abstinent 7 days after completing the program) between the groups at 8 weeks. The exercise group had better abstinence at 3-month follow-up, but not at 12-month follow-up, with no differences at any time point between the groups. In a post hoc analysis, among those with a higher level of exercise participation, however, the likelihood of smoking cessation was greater.

In a similar study of smoking cessation in 205 recovering alcoholics, moderate intensity exercise and behavioral counseling was superior to behavioral counseling and nicotine gum or usual treatment one week after participants quit smoking, but there were no differences at 6 or 12 month follow up (14). Interventions in this study were of variable lengths of time, however.

Exercise and Alcohol Use

In two small controlled trials evaluating the efficacy of exercise with alcohol use, exercise improved outcomes. In one study with 58 inpatients in alcohol rehabilitation, abstinence was better post treatment

and at 3 and 18-month follow-ups (15), although subjects were not randomized to intervention and control groups, and control group sizes were very small. In a sample of college students who were drinking heavily, an exercise program reduced alcohol use compared with a control group, although sample sizes again were small (16).

Exercise and Other Substance Use

While randomized controlled trials in patients abusing substances other than tobacco or alcohol are not yet available, some studies report benefits such as increased abstinence and reduced substance use that are associated with the use of exercise. Exercise resulted in higher abstinence at follow-up for patients receiving substance abuse treatment (15). In two trials with adolescent substance abusers (17, 18), exercise increased abstinence and less substance use was reported. Furthermore, in a post hoc analysis of data from 187 participants in two randomized trials evaluating contingency management in the treatment of substance abuse disorders (19, 20), participants that reported exercise-related activities had an increased length of abstinence (21).

A recent pilot study (22) showed that cannabis use and cravings were significantly reduced following 10 sessions of moderate aerobic activity over a 2-week period. Follow-up evaluations indicated that cannabis use returned to pre-exercise levels after the 2-week program was completed; however, these preliminary data offer further support for exercise in substance using individuals. In another recent pilot study of moderate-intensity aerobic exercise added to treatment for 16 individuals with substance dependence, participants had significantly more days with no drug or alcohol use (i.e., abstinence) at the end of treatment compared to the beginning of treatment, and 66.7% of the sample had been continuously abstinent at the end of a 12-week intervention (23).

Exercise and Drug Withdrawal

In a review of 12 studies evaluating the effect of one session of exercise versus a passive control condition on smoking cravings, withdrawal symptoms, or smoking, nine out of ten studies evaluating cravings showed reduction in cravings during and after exercise (24). Eight out of nine reported decreased withdrawal symptoms such as stress, anxiety, tension, poor concentration, irritability and restlessness

during and following exercise, although exercise interventions were of variable intensity (24). These studies, however, measured abstinence within periods of only minutes or hours following exercise. Other studies have examined outcomes over a longer period of time and noted reductions in stress, anxiety, irritability and restlessness at several points during the first few weeks of abstinence during exercise based smoking cessation intervention (25, 26).

Ussher et al. (27) evaluated the impact of brief moderate versus light intensity exercise on alcohol urges and mood, but found effects on urges only during the intervention itself with no improvements post intervention. However, the authors suggest some possibilities for the lack of post-intervention effects, including the fact that much of the sample had a concomitant psychiatric disorder, and the possibility that exercise may have a different effect on withdrawal from central nervous system (CNS) stimulants such as tobacco as compared with CNS sedatives such as alcohol.

Exercise as a Treatment for Major Depressive Disorder

The investigation of exercise as a treatment for depression further supports the use of exercise as a treatment for stimulant use disorders. Observational studies and clinical trials suggest beneficial effects of exercise on depression and anxiety (28). The results of several randomized controlled trials evaluating the use of exercise as a monotherapy (29, 30), augmentation (31, 32) or combination (33, 34, 35) in the treatment of depression suggest that exercise is efficacious in improving the symptoms of depression. However, recent meta-analyses caution that many trials have methodological limitations, and few methodologically sound trials have been conducted, the results of which provide more modest support for the use of exercise in depression (36, 37). Despite these cautions, much of this literature provides additional support for the feasibility of exercise trials for stimulant users.

As a precursor to a randomized controlled trial entitled, TReatment with Exercise Augmentation for Depression (TREAD) (38, 39), Trivedi et al. (40) conducted a pilot study in 17 subjects with MDD who received a therapeutic dose of antidepressant medication for at least 6 weeks, and had some benefit, but residual symptoms remained (HRSD score of greater than or equal to 14). Participants received 12 weeks of 16 KKW (kcal/kg/week) of aerobic exercise in supervised and home based sessions. There was a

nearly 6-point reduction on the Hamilton Rating Scale for Depression (HRSD) in the intent to treat group and more than a 10-point improvement in the 8 completers, despite a mean of about 4 months of antidepressant treatment prior to study entry. Improvements in quality of life were also observed. This pilot study also assisted with developing a home-based exercise program, and suggested that beginning with supervised exercise but tapering to home-based exercise is generalizable to routine clinical care and essential for participants to be likely to incorporate exercise into their ongoing routines.

The TREAD study (38, 39) evaluated improvement in depressive symptoms as well as functioning and quality of life in 126 subjects with MDD. Participants had received 2-6 months of selective serotonin reuptake inhibitor (SSRI) treatment, at least 6 weeks at an adequate dose, but still had residual depressive symptoms as reflected by an HRSD score of greater than or equal to 14. Subjects received 24 weeks of either a higher-dose (16 KKW) or lower-dose (4 KKW) of exercise, avoiding the pitfalls of the other trials such as group exercise, un-blinded outcome evaluation, and lack of rigorous standardized diagnosis of MDD (38). The first 12 weeks included individualized aerobic exercise prescription, self monitoring tools and an interactive website to maximize adherence, and a combination of supervised and home based sessions – 3 supervised sessions in week 1, two in week 2 and one per week in weeks 3-12 to maximize scheduling flexibility and minimize burden. The second 12 weeks included home-based exercise only. Both doses were associated with significant reductions in depressive symptom severity over 12 weeks, with adjusted remission rates of 28.3% and 15.5% for the 16 KKW and 4 KKW groups, respectively, which showed a trend toward significance ($p<0.06$) (39). These studies provide support for the use of exercise in psychiatric conditions and also helped to address design considerations applicable for future trials in this area.

Additional Beneficial Effects of Exercise

Stimulant use is detrimental to a number of important health outcomes, including sleep (41, 42) and cognitive function (43). Exercise has been shown to improve both sleep quality in many (44, 45, 46, 47, 48) although not all studies (49). Several studies have also shown improvements in cognitive function associated with exercise (50, 51, 52, 53, 54, 55). Similarly, exercise has been shown to improve quality

of life in those with depression and other chronic medical illnesses (40, 48, 56, 57, 58, 59), although it only improved quality of life in the physical domain in one small study (60). Furthermore, weight gain is a common concern following cessation of abused substances that may increase risk of substance use relapse (61, 62, 63), and regular exercise has the potential to prevent or reduce post cessation weight gain. These positive health benefits associated with exercise indicate that it may therefore be important not only in directly impacting stimulant use, but also in improving these outcomes.

Possible Mechanisms of Action of Exercise

Exercise may improve outcomes through any of several possible mechanisms. Exercise is likely to impact the underlying biology of addicted persons, as well as act as a behavioral treatment intervention. The mechanisms by which exercise may exert an effect on use of alcohol or substances are unknown. Possible mechanisms are described by Read et al. (64), Brown et al. (65), Ussher et al. (27) and Meeusen et al. (66).

Meeusen (66) notes that exercise results in changes in synthesis and metabolism of central dopaminergic, noradrenergic, and serotonergic systems, all of which are implicated in addiction. For example, activation of the serotonergic system from cardiovascular exercise may be a mechanism by which exercise impacts alcohol urges (67, 68) since reduced serotonin levels are found with alcohol dependence (69). Exercise may also achieve effects via the endogenous opioid system and dopaminergic reinforcement mechanisms (70, 71, 72) similar to the effects induced by alcohol and drug use (73, 74). Unlike alcohol and drug use, however, physical activity is associated with increases in dopamine receptor densities in the reward pathways of the animal brain that persist for days after physical activity ends (75, 76, 77), which may be particularly salient for the treatment of stimulant abuse.

Another possible advantage of exercise as an intervention for stimulant use disorders is the evidence of improved hippocampal function seen with exercise. There is clear evidence in animal studies that exercise increases brain derived neurotrophic factor (BDNF) levels and has been shown to induce molecular changes in the hippocampus. The most recent evidence suggests that molecular changes in the hippocampus may directly impact upon several factors associated with contextual learning. Specifically,

Greenwood et al. (78) have demonstrated improvements in hippocampal-dependent contextual learning and memory in rats. Similar results have been found for exercise-induced hippocampal neurogenesis and improvement in spatial memory in rats and mice (79, 80, 81). Therefore, exercise augmentation may provide specific benefits for participants with a history of substance abuse since this disorder has been associated with memory impairments that would be influenced by hippocampal function (43). Reduction in sugar cravings and increased blood glucose levels also could assist with alcohol urges (82). Additionally, exercise may decrease reactivity to stress (83) and decrease the use of alcohol (or substances) as a way of coping with stress (84). Improving self-efficacy (85, 86) may be another mechanism for improving outcomes.

It has also been suggested that exercise may be a distraction (87), allowing attention to be diverted from urges to drink (27) or a lifestyle change that can substitute for use of substances such as alcohol (88, 89). Finally, the effect of exercise on related health outcomes may mediate its efficacy on substance use. There is evidence that exercise improves anxiety, depression and self-concept in those also abusing alcohol (90, 91, 92, 93), which may then mediate improved outcomes. Exercise has been shown to reduce depression and anxiety during alcohol treatment (94, 95, 96) and with smoking cessation (97, 98). Reduction in depression symptoms in alcohol dependent participants receiving cognitive behavioral therapy mediated improved outcomes in drinking, suggesting that exercise may improve drinking outcomes via reductions in depression and anxiety (99).

Feasibility of Exercise with Stimulant Using Individuals

Existing studies utilizing exercise interventions have shown that good adherence to the interventions can be achieved in a variety of populations. Adherence, or attendance at exercise sessions, did not appear to differ meaningfully in the two studies of vigorous and moderate intensity exercise by Marcus and colleagues with an attendance at exercise sessions of 67.3% for vigorous intensity exercise (three sessions per week) (9) and 70.5% for moderate intensity exercise (one supervised session per week). Attendance was similar in the vigorous intensity trial even though the weekly attendance requirement was three times as high. Adherence rates have been similarly good in studies of exercise in depression, with rates of 71%

for the public health dose of 17.5 KKW and 72% for the 7 KKW dose in the DOSE study (30) and 99.4% for the 4 KKW dose and 63.8% for the 16 KKW dose in the TREAD study (39). Studies in other health-related conditions provide further support that good adherence rates to exercise can be achieved. The DREW study with postmenopausal women (100, 101) had adherence rates of 94.6% for the exercise dose of 4 KKW, 89% for the dose of 8 KKW, and 93% for the dose of 12 KKW. LIFE, which was a 12 month study in mobility impaired participants 70-89 years of age, achieved a retention rate of 94% at 12 months; and the exercise group had adherence rates of 71% and 61% at 6 and 12 months respectively (102). These studies suggest that exercise interventions may be successfully implemented with stimulant using individuals.

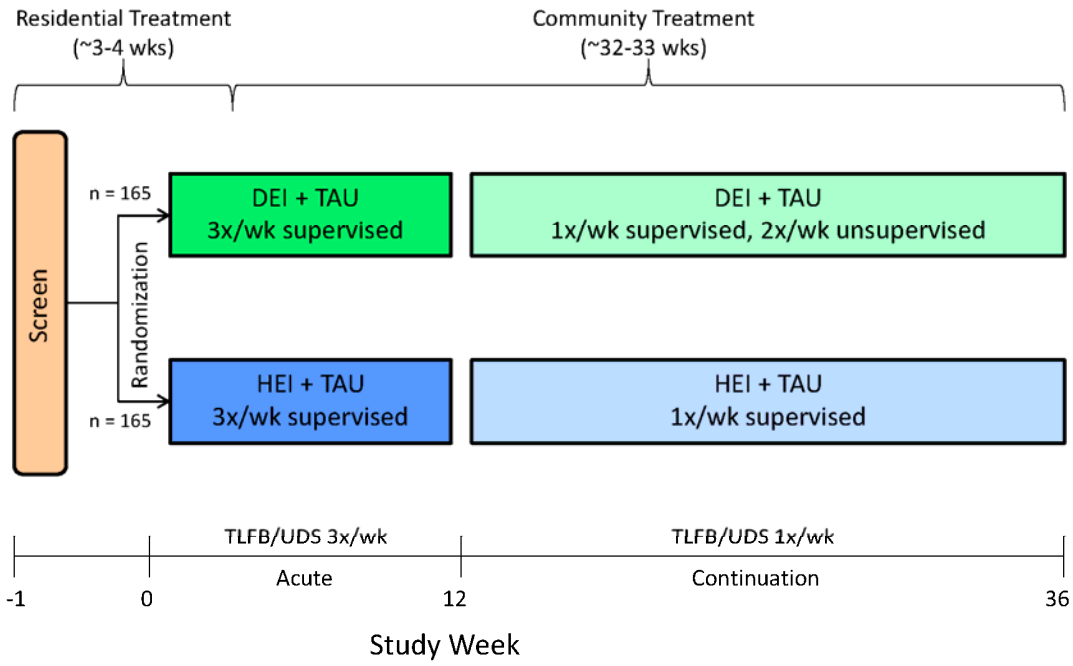
Developing a Trial to Examine Exercise in Stimulant Users: The CTN-0037 STRIDE Study

The converging evidence suggesting that exercise may positively impact stimulant use disorders led to the development of the CTN-0037 Stimulant Reduction Intervention using Dosed Exercise (STRIDE) study. This work is supported by the National Institute on Drug Abuse through the Clinical Trials Network for the Texas Node [3U10DA020024-06S1], Madhukar H. Trivedi, M.D., Principal Investigator; and the Stimulant Reduction Intervention using Dosed Exercise (STRIDE) study [2U10DA020024-06], Madhukar H. Trivedi, M.D., Lead Investigator. STRIDE is a multisite randomized, controlled trial aimed at comparing the augmentation of treatment as usual with either an exercise or health education intervention in a stimulant abusing population. Information on the selection of the primary outcome for the trial, the selection of study sites, and details of the protocol are provided elsewhere (103, 104, 105). A brief description of the trial is provided below.

The STRIDE study is designed as a two-group, randomized controlled trial and includes individuals diagnosed with stimulant abuse or dependence (cocaine, methamphetamine, amphetamine or other stimulant, except caffeine or nicotine) who begin substance use treatment in a residential setting. A schematic of the study flow is shown in Figure 1, as described in Trivedi et al. (105). Participants who provide informed consent and meet all inclusion criteria are randomized to one of two treatment arms:

DEI (Dosed Exercise Intervention Augmentation): Usual Care Augmented with Vigorous Intensity High Dose Exercise

HEI (Health Education Intervention Augmentation): Usual Care Augmented with Health Education.



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

Participants receive 3 months of acute phase intervention followed by an additional 6 months of intervention with less frequent supervision. Both groups receive drug abuse treatment as usual (TAU; i.e., usual care), which begins while the participant is in a residential setting, typically followed by community treatment. The two treatment conditions are structured such that they are similar with respect to number of visits to allow for equivalent contact between groups. Participants randomized to the exercise condition begin with supervised exercise sessions 3 times per week during the 12-week acute phase of the study. Supervised sessions are conducted as one-on-one (i.e., individual) sessions, although other participants may be exercising at the same time. Supervised sessions are monitored closely through the use of heart

rate monitors. Additional exercise sessions may be completed for those needing more than three sessions a week to achieve the target dose. Vigorous intensity high dose exercise is prescribed at a dose of 12 kcal/kg/week (KKW), with intensity ranging from 70-85% maximal heart rate. This dose is equivalent to ≥150 min of moderate exercise per week (i.e., approximately 30-50 min, 3-5 days per week). Participants randomized to the health education condition also begin with visits 3 times per week during the 12-week acute phase. The health education sessions are also conducted as one-on-one (i.e., individual) sessions, although other participants may be receiving health education at the same time. Health education sessions consist of information on health-related topics distributed via methods such as didactics, websites, audio and video materials, and written materials. During the 6-month continuation phase, the frequency of supervised intervention visits for both the exercise and health education groups reduces to one time per week.

This study aims to answer the following question: "Can exercise be used to improve the effectiveness of substance use treatment?" If exercise is found to improve outcomes for substance use disorders, the public health significance would be great. A novel component of treatment would be available for substance users that may not only aid in acute treatment, but may also aid in the long-term prevention of subsequent relapse. Furthermore, additional health benefits for substance users could be realized, including improved cardiovascular status, decreased risk of diabetes, cardiovascular disease, metabolic syndrome and certain cancers, and increased longevity.

Design Considerations

The STRIDE study includes some important design elements geared to enhance adherence to the interventions. A comprehensive behavioral intervention approach to facilitating and monitoring adherence to the study interventions has been developed (38, 105) to help retain participants in the interventions and optimize participant adherence. This multi-component behavioral adherence plan incorporates empirically-validated behavioral strategies to reinforce participation in the interventions and reduce salient participant- and disease-related barriers to intervention adoption and maintenance. These strategies include: 1) multidisciplinary psychoeducation about adherence and the use of behavioral reinforcers for

attendance/adherence to the intervention (e.g., water bottles, pen and notepad, gift cards); 2) written reference materials; 3) skills training (e.g., instruction in appropriate exercise form, intensity); 4) weekly exercise prescription (for participants randomized to exercise); 5) self-monitoring of adherence and performance (e.g., heart rate, RPE, tracking of HEI topics); 6) adherence feedback from study website and intervention facilitators; and 7) weekly intervention planning (individually-tailored plan).

Additionally, the study staff is encouraged to have an ongoing partnership with participants to develop and review a proactive plan to overcome any anticipated barriers that may arise and prohibit participants from completing the intervention. Site staff is trained to be aware of warning signs such as mood changes, decrease in motivation, change in living situation, medical problems and relapse, any of which may adversely impact adherence. Study staff discuss with each potential participant prior to randomization the study responsibilities and time commitment, and they proactively talk through any anticipated barriers or concerns. The site staff reviews participant specific barriers as a team on a weekly basis.

Conclusion

Exercise appears to be a promising intervention for individuals with stimulant use disorders. Evidence of clinical efficacy from studies of exercise in smoking cessation, alcohol abuse, depression, and other chronic disorders suggest that exercise may directly impact stimulant use, as well as mediate other important health related outcomes, such as withdrawal symptoms, mood, quality of life, sleep, and cognitive function. The STRIDE study was designed to examine exercise augmentation, compared to health education augmentation, of treatment as usual in stimulant abusing individuals. If exercise were to have an impact on acute and longer-term outcomes when added to usual substance abuse treatment, this would be of substantial public health importance. Exercise has limited side effects compared with medications, is not likely to interact with concurrent pharmacotherapy (40), is lower in cost (106), can be performed at home, can be continued indefinitely if effective in diverting relapse, and may be useful with vulnerable populations such as pregnant women. Exercise may also improve overall health and functional status (40) and reduce the cost burden associated with substance use disorders.

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Competing Interests:

Madhukar H. Trivedi, M.D. is a consultant to or on speaker bureaus for Abbott Laboratories, Inc., Abdi Ibrahim, Akzo (Organon Pharmaceuticals Inc.), AstraZeneca, Bristol-Myers Squibb Company, Cephalon, Inc., Cyberonics Inc., Eli Lilly & Company, Evotec, Fabre Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products, LP, Johnson & Johnson PRD, Meade Johnson, Medtronic, Neuronetics, Otsuka Pharmaceuticals, Parke-Davis Pharmaceuticals, Inc., Pfizer Inc., Sepracor, SHIRE Development, Solvay Pharmaceuticals, VantagePoint, and Wyeth-Ayerst Laboratories. He receives research support from the Agency for Healthcare Research and Quality (AHRQ), Corcept Therapeutics, Inc., Cyberonics, Inc., Merck, National Alliance for Research in Schizophrenia and Depression, National Institute of Mental Health, National Institute on Drug Abuse, Novartis, Pharmacia & Upjohn, Predix Pharmaceuticals (Epix), Solvay Pharmaceuticals, Inc., and Targacept.

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Kolette M. Ring, B.A. declares that there is no conflict of interest.

Bruce D. Grannemann, M.A. declares that there is no conflict of interest.

Timothy S. Church, M.D., Ph.D., M.P.H. declares that there is no conflict of interest.

Eugene Somoza, M.D., Ph.D. declares that there is no conflict of interest.

Steven N. Blair, P.E.D. receives royalties from Human Kinetics for Active Living Every Day.

Jose Szapocznik, Ph.D. declares that there is no conflict of interest.

Mark Stoutenberg, Ph.D. declares that there is no conflict of interest.

Chad Rethorst, Ph.D. declares that there is no conflict of interest.

Diane Warden, Ph.D., M.B.A. has owned stock in Bristol Myers Squibb and Pfizer, Inc. in the last 5 years and has received funding from the National Alliance for Research in Schizophrenia and Depression.

David W. Morris, Ph.D. declares that there is no conflict of interest.

Andrzej S. Kosinski, Ph.D. declares that there is no conflict of interest.

Tiffany Kyle, Ph.D. declares that there is no conflict of interest.

Bess Marcus, Ph.D. declares that there is no conflict of interest.

Becca Crowell, M.Ed., Ed.S. declares that there is no conflict of interest.

Neal Oden, Ph.D. declares that there is no conflict of interest.

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Author Biographies

Dr. Tracy L. Greer is an Assistant Professor in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas. She is the National Project Director for the STimulant Reduction using Dosed Exercise (STRIDE; CTN-0037) study, a multisite clinical trial funded by NIDA and conducted within the Clinical Trials Network, which aims to study the efficacy of exercise vs. health education as an augmentation to treatment as usual for persons with stimulant abuse and dependence. She has been a Co-Investigator on numerous clinical trials funded by NIH and industry during the past ten years. Her primary interests include exercise as a treatment for psychiatric conditions and the examination of targeted treatments for cognitive impairments associated with psychiatric conditions, with a primary focus on stimulant use disorders and major depressive disorder.

Kolette M. Ring, B.A. is a Clinical Data Specialist in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas. She is the Project Coordinator for the STimulant Reduction using Dosed Exercise (STRIDE; CTN-0037) study. Her primary research interests include studying the effects of physical activity on mental health.

Diane Warden, Ph.D., M.B.A. is an Associate Professor of Psychiatry at the University of Texas Southwestern Medical Center at Dallas. She received her B.A. from the University of Pennsylvania, Ph.D. from Bryn Mawr College and M.B.A. from the University of Texas at Dallas. Her primary research interests include treatment outcomes in depression, and substance abuse and dependence, and co-morbid medical and psychiatric disorders. Dr. Warden was senior project director for the largest multi-site clinical trial ever conducted in psychiatry, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. She has 28 years experience in research and health care management, holding senior leadership roles in behavioral healthcare organizations for nearly 20 years.

Mr. Grannemann is a faculty associate in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas. He earned a Masters of Clinical Psychology from the University of Arkansas and additional training in Psychometrics and Social Psychology at the University of Texas at Arlington. He has worked at UT Southwestern for over 20 years on the evaluation of clinical treatments for depression. He has also been part of the team of researchers developing and testing the use of exercise as an augmentation treatment for both depression and substance abuse.

Tim Church, M.D., M.P.H., Ph.D. is a Professor, the John S. McIlhenny Endowed Chair and is the director of the Laboratory of Preventive Medicine at the Pennington Biomedical Research Center in Baton Rouge, Louisiana. Dr. Church earned his Medical Degree and PhD (structural and cellular biology) from Tulane University School of Medicine in New Orleans. He completed a residency in preventive medicine at Tulane during which time he obtained a Masters in Public Health. He is a PI, Co-I, or investigator on a number of NIH grants, most of which address issues related to exercise and health including exercise and the treatment of diabetes, exercise and cancer survivorship, and exercise and maintenance of function in the elderly. He is an author on more than 100 peer-reviewed publications, and has received several awards for his research.

Dr. Gene Somoza is a psychiatrist with a Ph.D. in physics and a strong interest in developing mathematical models in medicine and psychiatry. He has 26 publications in this area. He also has a reasonable amount of research experience in basic science attained mainly during his three years as a Research Associate at the School of Medicine of the Universidad Autonoma de Madrid. His mentors there were Drs. Rodriguez Delgado and Francis DeFeudis. This resulted in 19 publications. Recently, his focus has been on substance abuse treatment research (approximately 50 published articles in this area), which has included being a PI in approximately 25 clinical trials and an investigator in 15 others. This work was done as Director (and Founder) of the Cincinnati Addiction Research Center (CinARC) for the past 16 years. This Center is closely associated with the Cincinnati VA Medical Center and the University of Cincinnati Department of Psychiatry and Behavioral Neuroscience. The funding for this research has come from NIDA (90%), the VA Cooperative Studies Program (5%), and Pharmaceutical Companies (5%), with a total funding of $M60 over this period. Currently (for the past 12 years) he has been Director of the Ohio Valley Node of NIDA's Clinical Trials Network (CTN) composed of his research center (CinARC) together with 30 Community Treatment Programs within a 15-state region in the Midwest. Approximately 160 individuals are currently working on conducting his clinical trials. He also has 28 years of clinical experience in psychiatry (with a strong focus on addictions) mainly at the Cincinnati VAMC. He started this as the Director of the Psychiatric Evaluation Center where he directly evaluated, or made final decisions on, approximately 20,000 patients over a seven year period, and supervised a registered nurse, a master's level social worker, and numerous psychiatric residents. He also worked at the University of Cincinnati Psychiatric Emergency Services (PES) for 12 years. Afterwards he became Director of the substance abuse programs at the Cincinnati VAMC where he supervised a staff of approximately 35 individuals (MDs, psychologists, RNs, social workers, psychiatric residents, and fellows). Over the past year he has been spending a great deal of time on the dissemination of medication-assisted treatment (MAT) for opiate dependent individuals. This has involved training primary care physicians on using suboxone, working with single-state agency directors (SSADs) to fund MAT in their states, giving seminars at large SSAD-sponsored meetings for substance abuse treatment

providers, attempting to make naloxone injections available to addicted individuals and their families in order to reduce the prevalence of opioid overdose deaths, and serving on Ohio governor's committees dealing with the interaction between opioid treatment and the criminal-justice system.

Steven N. Blair is a Professor in the Departments of Exercise Science and Epidemiology/Biostatistics at the Arnold School of Public Health at the University of South Carolina. Dr. Blair is a Fellow in the American College of Epidemiology, Society for Behavioral Medicine, American College of Sports Medicine, American Heart Association, and American Academy of Kinesiology and Physical Education; and was elected to membership in the American Epidemiological Society. He was the first president of the National Coalition for Promoting Physical Activity, and is a past-president of the American College of Sports Medicine and the American Academy of Kinesiology and Physical Education. Dr. Blair is the recipient of three honorary doctoral degrees--Doctor *Honoris Causa* degree from the Free University of Brussels, Belgium; Doctor of Health Science degree from Lander University, U.S.; and Doctor of Science *Honoris Causa*, University of Bristol, UK. He has received awards from many professional associations, including the Honor Award from the American College of Sports Medicine and the Robert Levy Lecture and Population Science Research Awards from the American Heart Association. He also was granted a MERIT Award from the National Institutes of Health, and is one of the few individuals outside the U.S. Public Health Service to be awarded the Surgeon General's Medallion. He has delivered lectures to medical, scientific, and lay groups in 49 states and 49 countries. His research focuses on the associations between lifestyle and health, with a specific emphasis on exercise, physical fitness, body composition, and chronic disease. He has published over 550 papers and chapters in the scientific literature, and is one of the most highly cited exercise scientists, with over 27,000 citations to his work. He also was the Senior Scientific Editor for the U.S. Surgeon General's Report on Physical Activity and Health.

José Szapocznik, Ph.D., is Professor and Chair, Department of Epidemiology and Public Health, Director of the Center for Family Studies, Director of the Clinical Translational Science Institute and of the Florida

Node Alliance of the National Drug Abuse Treatment Clinical Trials Network, all at the University of Miami Miller School of Medicine. He is also Professor of Psychology, Educational and Psychological Studies and Architecture, all at the University of Miami. Dr. Szapocznik has served on the faculty of the UM Miller School of Medicine for over 35 years and has long distinguished himself as a pioneer in the field of substance abuse, specifically in the national effort to prevent and treat adolescent drug abuse and other behavior problems among minority youth using family based approaches. Szapocznik's Brief Strategic Family Therapy has received national and international recognition for its success as a family-based intervention, including listing in the National Registry of Effective Prevention Programs. Dr. Szapocznik has authored 250+ scholarly publications. His manual on Brief *Strategic Family Therapy for Adolescent Drug Abuse* is the only adolescent treatment manual published as part of the National Institute on Drug Abuse's *Treatment Manual Series*. Dr. Szapocznik also leads a major interdisciplinary program of research on the relationship between the built environment, behavior and health. This work has focused on aspects of the built environment that affect school-age Hispanic children's behavioral adjustment, the psychological and physical adjustment of Hispanic elders, and most recently the risks to weight gain and disease inherent in immigration. The latter includes studies of the pathophysiology of weight gain and the mechanisms through which gain in adiposity bring about progress in metabolic syndrome indicators. This highly interdisciplinary program of research, funded by the Robert Wood Johnson Foundation, the National Institute of Mental Health, the National Institute of Environmental Health Sciences and the National Institute of Diabetes, Digestive and Kidney Diseases, includes architects, behavioral scientists, endocrinologists, epidemiologists, exercise physiologists, geneticists, nutritionists, psychologists, psychiatrists and statistical methodologists. Dr. Szapocznik has a distinguished record of service to the National Institutes of Health and has served on the national advisory councils for the National Institute on Mental Health, the National Institute on Drug Abuse and the National Center on Minority Health and Health Disparities. He was also the first-ever behavioral scientist appointed to the NIH-wide AIDS Program Advisory Committee (now the NIH Office of AIDS). Dr.

Szapocznik has also served as Principal or Co-Principal Investigator on over $100 million in NIH-funded grants and contracts.

Mark Stoutenberg, Ph.D. is a Research Assistant Professor in the Department of Epidemiology & Public Health at the University of Miami. He received his B.A. in History from Columbia University, an M.S. (2004) and Ph.D. (2008) from the School of Education at the University of Miami and an MSPH from the Department of Epidemiology & Public Health at the University of Miami in 2011. His primary research interests include investigating novel approaches for using exercise interventions to improve health outcomes and designing community-based lifestyle modification programs as a means of primary chronic disease prevention. In 2009, Dr. Stoutenberg was a recipient of a NIDA CTN Fellow award and has since transitioned into a role in the STRIDE Study as the National Exercise Specialist and a local Node Coordinator. Dr. Stoutenberg is also actively involved in integrating physical activity into a patient-centered care program for cancer patients at the University of Miami Sylvester Comprehensive Cancer Center.

Chad D. Rethorst, Ph.D. is an Assistant Professor in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas. He obtained a Ph.D. in Kinesiology from Arizona State University and a masters degree in Counseling and Sport Psychology from Boston University. Prior to joining the faculty at UTSW, he completed a T32 fellowship in the Department of Psychiatry at the University of Rochester Medical Center. His research focuses on the effects of physical activity on mental health, specifically conducting intervention research examining the efficacy of exercise as a treatment for depressive and substance abuse disorders.

Robrina Walker, Ph.D. is an Assistant Professor of Psychiatry at the University of Texas Southwestern Medical Center in Dallas, TX and the Scientific Director of the Texas Node of NIDA's Clinical Trials Network. Dr. Walker obtained her Ph.D. in Clinical Psychology from Virginia Tech and completed post-

doctoral training in addiction treatment at the Dallas Veterans Affairs Hospital. She has worked on 10 NIDA-funded, one NIAAA-funded, and two Veterans Affairs-funded studies, with the majority being randomized clinical trials evaluating behavioral or medication treatments for adolescent and adult substance use disorders. Dr. Walker's primary research interests are in behavioral treatments for addictive behaviors.

David W. Morris, Ph.D. is an assistant professor of psychiatry at the University of Texas Southwestern Medical Center in Dallas (UTSW). He was the outcomes manager for the STAR*D and CO-MED trials, as such was responsible for all aspects of data collection including rater training and certification. Dr. Morris also trained and certified all raters for the NIMH funded REVAMP study and B-SNIP study, and is currently performing this duty for the EMBARC study and the CTN 0037 trial. He has specific expertise in the development and implementation of clinical assessment procedures, and training and certification of clinical raters, having performed in this capacity for many of the largest federally funded multi-center psychiatric treatment trials to date. Dr. Morris received his Ph.D in clinical psychology from the University of Tulsa, and completed an NIMH research fellowship at UTSW Medical Center prior to joining the UTSW faculty.

Andrzej S. Kosinski, Ph.D. is an Associate Professor in the Department of Biostatistics and Bioinformatics at the Duke University. He received his B.S. from the AGH University of Science and Technology, Krakow, Poland; M.Sc. in Applied Statistics from University of Oxford, England; and a Ph.D. in Biostatistics from the University of Washington. He research interests include design of clinical trials, statistical methods for evaluation of diagnostic tests, and measures of agreement. He has received research grants from the American Heart Association and participated in research supported by the National Institutes of Health and industry.

Tiffany Kyle, Ph.D., is Director of Research at The Center for Drug-Free Living in Orlando, Florida, a Volunteer Professor in the Department of Epidemiology and Public Health at the University of Miami, and a Research Professor in the Department of Psychology at the University of Central Florida. She earned a Ph.D. in Clinical Psychology from the University of Central Florida and has more than ten years of experience conducting research on the treatment of substance use disorders within community settings.

Bess Marcus, Ph.D., is Professor and Chair of the Department of Family and Preventive Medicine at the University of California, San Diego. Dr. Marcus is a clinical health psychologist who has spent the last 25 years conducting research on physical activity behavior and has published over 175 papers and book chapters as well as four books on this topic. She has developed a series of assessment instruments to measure psychosocial mediators of physical activity behavior and has also developed low-cost interventions to promote physical activity behavior in community, workplace, and primary care settings. Dr. Marcus has participated in numerous national and international committees and review groups including the American Heart Association, American College of Sports Medicine, Centers for Disease Control and Prevention, and National Institutes of Health. She has served on panels that have created recommendations regarding the quantity and intensity of physical activity necessary for health benefits. She was a contributing author to the Surgeon General's Report on Physical Activity and Health and is on the executive committee for the development of a National Strategic Plan for Physical Activity. Dr. Marcus serves or has served on the Editorial Board of the Journal of Physical Activity and Health, Journal of Behavioral Medicine, Psychology, Sport and Exercise, Journal of Lifestyle Medicine, Research and Sport, and Journal of Mental Health and Physical Activity. Dr. Marcus serves on the national advisory panel for the Centers for Disease Control and Prevention course on Physical Activity and Public Health. Dr. Marcus has also conducted a series of NIH-funded studies on the efficacy of physical activity to enhance smoking cessation and minimize weight gain in women smokers. Dr. Marcus is currently Principal Investigator or Co-investigator on 10 National Institutes of Health grants on physical activity behavior including trials of primary and secondary prevention in adults. These studies involve

interdisciplinary teams that include experts in cardiology, primary care, public health, epidemiology, cost-effectiveness, and women's health. Dr. Marcus is currently involved in several studies examining different channels (print, phone, email, Internet) for promoting physical activity in order to determine both efficacy and cost-efficacy. These studies are conducted with a variety of populations including healthy adults, pregnant women, adults with substance use or abuse issues, patients in primary care practices, Spanish-speaking Latina women, and Spanish-speaking Latino men. Dr. Marcus has two ongoing RO1 grants to promote physical activity behavior in Latina women. In one study being conducted in the Northeast she is using a print-based approach to increase physical activity in Spanish-speaking Latinas. In the other study being conducted in San Diego she is using an Internet-based approach to increase physical activity in Spanish-speaking Latinas. These studies build on the print and technology-based physical activity studies she has been conducting with men and women for the past 25 years. Dr. Marcus has had continuous NIH funding for this line of work for the past 18 years. Dr. Marcus actively mentors graduate students, interns, post-doctoral fellows and members of the faculty and teaches courses on physical activity and obesity.

Becca Crowell, M.Ed., Ed.S is the executive director of Nexus Recovery Center, a women's drug treatment center in Dallas, Texas. She has a B.A., M.Ed. and Ed.S from the University of Florida and is a licensed professional counselor (LPC) and a Licensed Chemical Dependency Counselor (LCDC). Nexus participates in community-based drug treatment research in cooperation with the University of Texas Southwestern Medical School through the NIDA funded Clinical Trials Network. Ms. Crowell has co-authored several articles about these research activities and has presented on gender specific treatment and treatment of pregnant women.

Dr. Oden joined The EMMES Corporation in 1993 as a biostatistician. He has more than 10 years experience in the statistics of vision research. Currently, Dr. Oden works on variety of projects, including serving as a senior statistician at the Data and Statistics Center for the NIDA Clinical Trials Network. In

this role, Dr. Oden has been involved in designing and supporting 3 clinical trials, and has performed methodological work on combining results of time-line-follow-back and urine drug screens to measure abstinence outcomes. Dr. Oden has also supported as a senior statistician The Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) study, sponsored by NIH. SCORE is a multi-center clinical trial assessing the efficacy and safety of standard care versus triamcinolone acetonide injection(s) for the treatment of macular edema associated with central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). Dr. Oden developed a Bayesian method to predict enrollment in multicenter clinical trials and performed statistical research on closed testing for controlling family wide error for trials with more than 2 arms. Previously, he was the Principal Investigator and Director of the Coordinating Center for the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity Study Project (STOP-ROP), sponsored by the National Eye Institute. In this role, he directed day-to-day activities at the Coordinating Center, interacts with clinical and other staff, both internally and externally, negotiates with outside vendors, and has direct responsibility for staff, funding, and budgetary issues. He was active in presentations at major study meetings, and publication of study-related informational materials, and maintains good rapport with key study personnel and support staff. He was integrally involved in, and has considerable expertise in, the planning and implementation of data analyses, and the technical aspects of the databases and information systems.

Edward V. Nunes, M.D. is a Professor of Clinical Psychiatry in the Department of Psychiatry at Columbia University College of Physicians and Surgeons, a research psychiatrist at the New York State Psychiatric Institute (NYSPI), and Co-Chairman of the NYSPI Institutional Review Board. Following study at Dartmouth College (earned A.B. in Psychology and Chemistry in 1977) and University of Connecticut School of Medicine (earned M.D. in 1981), Dr. Nunes completed an internship in internal medicine at St. Elizabeth Hospital in Boston (1982) and a psychiatry residency (1982-1985) and a research fellowship in clinical psychopharmacology (1985-1987) at the New York State Psychiatric Institute. During his fellowship training, he developed an interest in treatment of addictions and co-

occurring psychiatric disorders and clinical trials design and analysis, which became the foci of his research career. Dr. Nunes has been principal investigator or collaborator on numerous NIH-funded R01s and, since 2000, has served as principal investigator of a node in the National Institute on Drug Abuse (NIDA) Clinical Trials Network (now in its third funding period), which has led three multi-site clinical trials. He has authored over 175 book chapters and articles and edited a recently published volume on diagnosis and treatment of co-occurring psychiatric and substance use disorders. He has received consecutive career development awards from the National Institute on Drug Abuse (K20, two K02s, and K24) and serves as a research mentor to numerous junior faculty members and fellows at the NYSPI.

Madhukar H. Trivedi, M.D. is currently a Professor and Chief of the Division of Mood Disorders in the Department of Psychiatry at the University of Texas Southwestern Medical Center at Dallas. He holds the Betty Jo Hay Distinguished Chair in Mental Health. Dr. Trivedi is an established efficacy and effectiveness researcher in the treatment of depression. Dr. Trivedi has focused his research on pharmacological, psychosocial, and other nonpharmacological treatments for depression. Dr. Trivedi has been a principal investigator in multiple clinical trials funded through NIMH and the Texas Department of Mental Health. He is the Principal Investigator of the NIDA-funded "Stimulant Reduction Intervention using Dosed Exercise (STRIDE)" study that tests the effectiveness of adding exercise to treatment as usual in improving drug treatment outcomes. Dr. Trivedi is also Principal Investigator of the Texas Node of the NIDA-funded Clinical Trials Network. Additionally, he was the Principal Investigator of three NIMH grants entitled "CBASP Augmentation for Treatment of Chronic Depression (REVAMP)," "TReatment with Exercise Augmentation for Depression (TREAD)," and "Computerized Decision Support System for Depression (CDSS-D)." He was the Principal Investigator of the Depression Trials Network "Combining Medications to Enhance Depression Outcomes (CO-MED)" trial, which focused on the use of specific antidepressant combinations to increase remission rates by treating a broader spectrum of depressed patients and by capitalizing on additive pharmacological effects. He was also the Co-Principal Investigator of the NIMH-funded project entitled "Sequenced Treatment Alternatives to Relieve

Depression (STAR*D).” Most recently, Dr. Trivedi has been selected to Lead the team conducting the EMBARC project. This project is at the core of the NIMH’s initiative to identify a biosignature for depression. This work will focus on neuroimaging, EEG, clinical and behavioral phenotypes and other blood-based biological markers. His ongoing work as the Lead PI of the EMBARC study provides an extensive background for his contribution to the Neurobiological Markers employed in the study. Note this grant is designed to be a linchpin in the development of a biosignature for depression and is unique in its design to evaluate biomarkers from across full spectrum possible biological markers. As the lead site, he will be able to provide new clinical research opportunities to work at cutting edge of translational research in depression. Dr. Trivedi has received numerous awards including the Gerald L. Klerman award from the National Depressive and Manic-Depressive Association Scientific Advisory Board-NDMDA and the Psychiatric Excellence Award from the Texas Society of Psychiatric Physicians-TSPP. Dr. Trivedi has mentored multiple psychopharmacology postdoctoral fellows and research track residents over the past many years in Mood and Anxiety Disorders and is the Principal Investigator of an NIMH-funded Postdoctoral T32 training program. He is or has been a member of several institutional review groups of the NIMH. Dr. Trivedi has published over 380 articles and chapters related to the Diagnosis and Treatment of Mood Disorders.