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Affect Following First Exercise Session as a Predictor of Treatment Response in Depression

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Abstract

Objective—Remission rates are low with antidepressant treatments either as a first step or even with a second step. Furthermore, despite extensive investments from NIH and Industry, novel treatments are not yet available in clinical care for depression. Predictors of treatment response very early in the course of treatment can avoid unnecessarily lengthy trials with ineffective treatments and reduce the trial and error process. This paper examines the expression of positive affect immediately following an acute exercise session at the end of the first exercise session as a predictor of treatment response in the NIMH-funded TrEAD (Treatment with Exercise Augmentation for Depression) study, which was conducted from April 2003–August 2007.

Method—122 subjects with DSM-IV diagnosed Major Depressive Disorder were randomized to public health dose (16 kcal/kg/week or KKW) or low dose (4 KKW) of exercise for 12 weeks. Affect following the first exercise session was assessed using the Positive and Negative Affect Scale (PANAS) and depressive symptoms were assessed weekly using the Inventory for Depressive Symptoms – Clinician Rated (IDS-C).

Results—The PANAS Composite Affective (CA) score (positive - negative total) predicted change in IDS-C score ($p < .05$), as well as treatment response ($p < .02$) and remission ($p < .03$) for those in the high dose group but not in the low dose group.

Conclusions—These findings suggest that the composite positive affect following the first exercise session has clinical utility to predict treatment response to exercise in depression and match the “right patient” with the “right” treatment.

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Introduction

Although numerous treatments are available for Major Depressive Disorder (MDD), selecting among these options remains the biggest challenge facing clinicians. Remission rates are low with standard antidepressant treatments with the first ¹ or even second step treatments ² in the short term and even lower remission rates in the long term ². Non-pharmacological interventions like psychotherapy and aerobic exercise have also been shown to be efficacious for the treatment of MDD ³⁻⁵. While treatment outcomes do improve with additional treatment steps, in the absence of reliable predictors and moderators ⁶, the trial and error process required to identify appropriate treatment for a given individual prolongs the disease burden in these patients. Therefore, there is a clear need to identify behavioral or biological markers in order to determine who is most likely to respond to any given treatment. Identification of these markers will lead to early treatment matching, reducing the burden of multiple steps for the patient and ultimately reducing the burden of the illness.

The link between exercise and mental health is well documented. Exercise has long-term benefits for general health, and physically active people are at a lower risk of developing mood and anxiety disorders ⁷⁻¹². Research also supports the use of exercise in the treatment of MDD. Exercise has proven efficacious as a monotherapy ^{5, 13, 14} as well as an augmentation treatment of MDD ^{15, 16}. As an intervention, exercise has the additional advantage of targeting residual symptoms such as insomnia, psychosocial functioning, and cognitive function ¹⁷⁻¹⁹. Despite the benefits of exercise as a treatment, it is like other antidepressant treatments, not universally effective. Determining clinically useful behavioral and biological markers as predictors of response to exercise can improve the process of treatment matching for exercise as an antidepressant.

Post-hoc analyses of prior studies have attempted to identify predictors of response to exercise. Using this baseline model, our preliminary work has already shown that insomnia, TNF-alpha and BDNF are predictive of treatment response and suggest these as possible biological markers for exercise augmentation ^{17, 20, 21}. However, it is clear that identification of multiple predictors is necessary in order for these predictors to have clinical utility (Establishing Moderators and Biosignatures of Antidepressant Response In Clinical Care (EMBARC): Rationale and Design, Trivedi et al Journal of Psychiatric Research resubmitted).

Exercise is not only effective in reducing depressive symptoms, but a single bout of exercise results in acute improvements in affect in patients with MDD ^{22, 23}. However, no study has evaluated whether this acute affective response post-exercise is predictive of long-term treatment outcome. Just as long-term reductions in depressive symptoms are heterogeneous, acute affective responses to exercise also vary across individuals. This variation has important implications for exercise treatment interventions, as positive affective response to an exercise session has been associated with long-term exercise adherence ²⁴. Furthermore, research has identified genetic predictors of affective response ^{25, 26}, indicating this variation

can be attributed to underlying biological mechanisms. It is therefore possible that these biological mechanisms underlying variations in affective response to acute exercise may be the same mechanisms underlying variations in treatment response to exercise.

In this study, we examine positive affect following the initial exercise intervention session as a predictor of final treatment outcomes. The Treatment with Exercise Augmentation for Depression (TREAD) study concluded that exercise augmentation with a public health dose is an effective means to achieve remission in patients who are nonresponsive to initial SSRI treatment, with a number needed to treat of 7.8 compared to the lower dose of exercise^{15, 27}. This paper examines: 1) whether affect immediately following the first exercise session predicts treatment outcomes at the end of the 12-week exercise intervention, 2) whether this predictive effect is moderated by exercise dose, and 3) if the predictive effect is mediated by exercise adherence. We hypothesize that greater post-exercise positive affect will be predictive of greater decreases in depressive symptoms at the end of the intervention. Furthermore, we hypothesize that this effect will be greater in the high dose exercise treatment group. Finally, we hypothesize that the predictive effect of post-exercise affect will be, at least partially, explained by differences in exercise adherence.

Methods

The TREAD trial was a randomized trial comparing two doses of aerobic exercise as augmentation treatment for non-remitted MDD. Full study methodology has been previously published^{15, 28}; included below is a description of the study procedures relevant to the current analysis.

Participants

Participants were recruited through physician referrals and advertisements. Eligible participants signed an IRB-approved informed consent before engaging in any study activities. Inclusion criteria were as follows: (1) men and women aged 18–70 years; (2) diagnosis of nonpsychotic major depressive disorder (MDD) based on the Structured Clinical Interview for *DSM-IV* Axis I Disorders; (3) completion of >2 and <6 months of treatment with a selective serotonin reuptake inhibitor (SSRI) with at least six weeks of adequate dose; (4) moderate residual symptomatology from SSRI monotherapy defined by a score of ≥14 on the Hamilton Rating Scale for Depression; (5) not engaged in regular exercise; (6) capable of exercise; and (7) able and willing to provide informed consent.

Exclusion criteria included: (1) significant medical condition; (2) depression due to a comorbid psychiatric disorder; (3) current pharmacological or psychotherapeutic treatment other than SSRI; (4) treatment resistance, defined as failure of two or more pharmacologic treatments of adequate dose and duration; (5) pregnancy or planned pregnancy.

Procedures

Participants were randomly allocated to one of two exercise groups for a 12-week exercise intervention. The dose of SSRI was kept constant during the exercise treatment. The Low Dose (LD) group was prescribed a dose of exercise at 4 kilocalories per kilogram of body weight (KKW) and the Public Health Dose (PHD) group was prescribed a higher dose of

exercise at 16 KKW, reflecting public health physical activity recommendations and standards²⁹. The LD dose is equivalent to approximately 45 minutes of moderate-to-vigorous exercise per week, and the PHD dose is equivalent to approximately 180 minutes of moderate-to-vigorous exercise per week. Exercise intensity was self-selected and monitored with a Polar 610i heart rate monitor. Participants completed the entire first week of exercise dose under supervision by trained personnel at the Cooper Institute, and had two supervised sessions in the second week. In all subsequent weeks, participants had one supervised session per week and completed the remaining exercise dose in home-based sessions. All study procedures were approved by the local Institutional Review Board.

Measures

The Positive and Negative Affect Scale (PANAS) was administered following the first exercise session of Week 1. The PANAS is a twenty-item scale with two ten-item subscales designed to measure affect. PANAS measures affect as both positive and negative. High positive affect (PA) reflects an individual's feelings using adjectives such as enthusiastic, active, and alert, and low PA is characterized by adjectives such as sadness and lethargy. High negative affect (NA) is a general dimension of subjective distress characterized by anger, disgust, guilt, fear, and nervousness, and low NA is characterized by calmness and serenity. The PANAS has been widely used as a measure of acute affect with good psychometric properties,^{30, 31} with reliability for the immediate assessment at alpha of .89 for PA scores and .85 for NA scores and has been further validated specifically within a psychiatric population³². In addition to the standard Positive and Negative affect scores, we also derived a composite affect score (CA) by combining the two measures in order to assess the overall general affect to the exercise session, accounting for both positive and negative aspects of affect. To evaluate the general affective state at the end of the exercise session, the positive and negative PANAS scores were combined. This was done by the subtraction of the negative PANAS total from the positive PANAS total to produce the CA score.

The Inventory for Depressive Symptoms – Clinician Rated version (IDS-C) was used to measure depressive symptoms. The IDS-C is a 30-item rating scale with excellent psychometric properties and has been widely used in clinical trials³³. The IDS-C was administered weekly by blinded raters. Change in IDS-C was calculated as the Week 12 IDS-C total score minus the Baseline IDS-C total score. If data were missing for the Week 12 IDS-C score, the last assessed value was carried forward. Response and remission were also determined based on the IDS-C total score values. Response was defined as a 50% reduction in IDS-C score, while remission was defined as an IDS-C score of 12 or less at study completion.

Statistical Analyses

Primary analyses—Primary analyses were designed to evaluate the composite affect (CA) score following the first acute exercise session as a predictor of change in depressive symptoms from baseline to exit. The CA score at the conclusion of the first exercise session was used as a predictor of treatment response for the primary analysis. Change in depressive symptoms was calculated using the IDS-C total. A general linear model included main effects for both Exercise Group and CA score along with Group by CA interaction as the

predictors of IDS-C change (decrease from baseline to exit). The main effect of group provides a measure of differences in treatment response, the main effect of CA provides the measure of the ability of affect after an exercise session to predict treatment response, and the interaction tests if the prediction is specific to one or the other of the two treatments. This model was repeated using both the PA and NA subscale scores.

Covariate analyses—To control for the effects of the influence of possible confounding variables a series of covariate analyses were conducted. Gender and family history were included as these covariates were associated with treatment outcome in primary outcome paper¹⁵. We also included fitness (VO_{2max}) and exercise adherence (median percent of weekly KKW dose). The covariate analysis was conducted as a two step process that would include all variables plus two way interaction as a first step. As a second step, all covariates with a p value $<.10$ were retained in the final covariate model³⁴.

Prediction of response and remission analyses—We conducted logistic regression models to examine treatment response (50% reduction from baseline) and treatment remission (IDS-C total score ≥ 12). In these models, exercise group and CA score are the main effects and a group by CA interaction were predictors of response and remission. To examine the utility of the CA score to predict the likelihood of response and remission, we also conducted an ROC analysis and report the Area Under the Curve (AUC) for the ROC. Perfect prediction would have an AUC of 1.0, with an AUC above .90 still providing a clinically useful test; an AUC above .80 is considered meaningful but with modest clinical usefulness^{35, 36}. As an example, the AUC for the PHQ-9 self-report and a clinical diagnosis of MDD is about .88³⁷. Finally, to test for any impact of exercise adherence over the course of the treatment trial, a set of analyses were run that included adherence (as measured by the median number of sessions) added to the general linear models with interaction terms for both Group and CA.

Results

Baseline characteristics of the study sample are provided in Table 1. One-hundred twenty-six subjects completed the baseline assessments and were randomized to an exercise condition. Four subjects did not provide post-baseline data and were excluded from the analyses. Mean changes in IDS-C, response and remission for the total sample and by group and PANAS scores following the initial exercise session are presented in Table 2. T-tests conducted to determine if there were differences in Week 1 PANAS scores (PA, PN, & CA) yielded no significant differences.

CA score as a predictor of change in depressive symptoms

The primary analysis for Week 1 included 118 of the 122 subjects, as 4 subjects did not provide PANAS ratings. There was a significant main effect for Group [$F(1,114)=4.87$ $p < .03$; $\eta^2 = .041$], a marginal effect for CA [$F(1,115)=3.36$, $p < .07$; $\eta^2 = .029$], and a significant Group by CA interaction [$F(1,115)=4.13$, $p < .05$; $\eta^2 = .035$]. As seen in Figure 1, higher CA scores predicted better outcomes (as measured by reduction in total IDS-C scores) for subjects in the PHD group but not in the LD group.

Covariate analysis

The first step of the covariate analyses included gender, family history of mental illness, fitness and exercise adherence and two-way interactions in the model with group and CA. Only the exercise adherence [$F(1,106)=5.98$ $p < .02$; $\eta^2=.04$] and the family history of mental illness by Group interaction [$F(1,106)=3.43$ $p < .07$; $\eta^2=.03$] produced p values $< .10$. The final model that include just these two covariates with Group, CA and the Group by CA interaction. The main effect for median percent KKW of dose [$F(1,106)=5.9=60$ $p < .02$; $\eta^2=.04$], family history of mental illness [$F(1,106)=4.76$ $p < .04$; $\eta^2=.03$], family history of mental illness by Group interaction [$F(1,106)=4.66$ $p < .01$; $\eta^2=.03$] and the Group by CA interaction dose [$F(1,106)=5.01$ $p < .03$; $\eta^2=.04$]. The group by CA interaction remained significant and is not moderated by the either exercise adherence or family history. Note the family history results were previously reported in the primary outcome paper (Trivedi et al 2011).

CA score as a predictor of response and remission

The logistic regression at Week 1, using CA and group to predict response, produced significant main effects for Group [$X^2(3)=3.88$], $p < .05$] and CA [$X^2(3)=5.45$], $p < .02$] and a significant Group by CA interaction [$X^2(3)=5.46$], $p < .02$: odds ratio LD =1.00, PHD=1.10]. Similarly, the logistic regression predicting remission produced a marginal main effect for Group [$X^2(3)=3.07$], $p < .08$], a significant main effect for CA [$X^2(3)=8.56$], $p < .004$] and a significant Group by CA interaction [$X^2(3)=4.55$], $p < .03$: Odds Ratios for LD =1.02, PHD=1.13]. These results indicate that higher CA scores predicted a higher likelihood of response and remission within the PHD group.

In order to better understand the extent to which acute affect following the first exercise session can be used to predict treatment response and remission, ROC analyses were also conducted. Since the models for both response and remission produced a significant interaction with group, separate ROC curves were produced for each group. For the LD group, CA does not predict response [$X^2(1)=.00$], $p < .99$: ROC curve Area Under the Curve .51], but CA does predict response for the PHD group [$X^2(1)=8.4$], $p < .004$: ROC curve Area Under the Curve .76]. The same pattern appears for remission, with CA not predicting remission for the LD group [$X^2(1)=.51$], $p < .48$: ROC curve Area Under the Curve .57], but predicting remission for the PHD group [$X^2(1)=9.2$], $p < .003$: ROC curve Area Under the Curve .81]. ROC curves are presented in Figure 2.

To better understand these results, analyses using the PA and NA subscales of the PANAS were conducted. The model included a significant main effect for Group [$F(1,114)=4.09$ $p < .05$; $\eta^2=.02$], a significant main effect for PA [$F(1,114)=6.14$], $p < .02$; $\eta^2=.05$], and a marginal Group by PA interaction [$F(1,114)=3.34$], $p < .08$; $\eta^2=.03$]. The results for the NA analysis indicated there is no main for Group [$F(1,115)=1.19$ $p < .36$], no main effect for NA [$F(1,115)=.10$], $p < .76$; $\eta^2=.00008$], and a marginal Group by RN interaction [$F(1,115)=3.37$], $p < .07$; $\eta^2=.03$]. These finding are only worth noting because they provide some insight as to why CA finding are more robust than the positive finding alone. For the PHD group higher NA scores predict less symptom reduction, but for the LD groups the contrary is true with higher NA scores predicting greater symptom reduction.

Discussion

The primary goal of this study was to examine affect following the first exercise session as a predictor of treatment response for patients with non-remitted MDD. Our results specifically indicate that greater positive affect following the first exercise session was predictive of greater improvements in depressive symptoms, response and remission at the end of the 12-week exercise intervention. Most interestingly, this effect was moderated by treatment group, such that the predictive value of positive affect was only significant in the high dose exercise group but not in the low dose group.

Previous research has shown variation in affective responses to acute exercise sessions^{32, 33, 25, 26}. Our results suggest that variations in post-exercise affect might be predictive of antidepressant response. In light of these results, it is of interest to determine the underlying mechanism of this effect. Potential explanations for the association of post-exercise affect with the longer-term acute phase antidepressant effect of exercise could be a result of enhanced self-efficacy, improved adherence to the exercise intervention, the patient's perception of early antidepressant effect or the capacity of the underlying neural circuitry to respond. Previous work has linked positive acute affect following a single exercise session with improved exercise adherence over an extended period of time²⁴. However, including adherence in the regression model did not diminish the observed effect of post-exercise affect.

Variations in affective response to an acute exercise session can also be due to the characteristics of exercise itself. For example, high exercise intensity, specifically intensity above the ventilator threshold, results in more negative post-exercise affect^{38, 39}. A unique feature of our exercise intervention in the current study was for participants to self-select their exercise intensity, which has been associated with positive post-exercise affect. The fact that the affective response to exercise is modulated by characteristics of the exercise might also explain the moderating effect of treatment group observed in our analysis. Due to the higher exercise dose, exercise sessions among individuals in the PHD group were of a greater duration (mean duration of 45 minutes vs. 25 minutes) and perhaps the longer sessions may elicit an affective response that is more predictive of treatment outcome. Given that characteristics of the exercise session can alter post-exercise affect, it is possible that tailoring an exercise intervention to elicit positive affect could result in a more effective exercise intervention.

Finally, the predictive relationship between post-exercise affect and long-term antidepressant outcomes may be indicative of common underlying biology. Research has identified genetic associations with variations in post-exercise affect^{25, 26} as well as to antidepressant response to an exercise intervention⁴⁰. It is possible that common genetic polymorphisms may predict both acute affective response and treatment outcomes in response to exercise.

Exercise has been shown to be efficacious in the treatment of MDD but many patients do not improve following an exercise intervention. Given the heterogeneity in treatment response, it is necessary to identify predictors of treatment response in order to optimally treat MDD. Our results suggest that post-exercise affect may be a potential predictor of long-term

antidepressant outcomes. This analysis continues a line of research examining predictors of treatment response to exercise in patients with MDD^{17, 20, 41, 42}. Despite these encouraging findings as a predictor of treatment response following the first exercise session, the current analysis does have limitations. This analysis represents a secondary data analysis, as the TREAD trial was not specifically designed to identify predictors of treatment response. Instead, our results should be viewed as “hypothesis generating” and future trials should be designed to specifically identify predictors of treatment response. Second, the PANAS was only collected post-exercise and therefore we were unable to examine changes in affect pre- and post-exercise. Finally, it is clear that a single predictor will not suffice to guide treatment selection and that a metric comprised of several markers is very likely to be needed to enhance the accuracy of prediction⁴³ (Establishing Moderators and Biosignatures of Antidepressant Response In Clinical Care (EMBARC): Rationale and Design, Trivedi et al Journal of Psychiatric Research resubmitted). As work in the field continues to identify predictors of treatment response, these individual predictors must be integrated into comprehensive algorithms to improve predictive abilities. Ultimately, this work will lead to matching patients with treatments most likely to elicit a treatment response for them.

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Clinical Points

- Optimal treatment of MDD requires identification of treatment outcome predictors
- Post-exercise affect appears to be a potential predictor of depression treatment outcome
- However, predictive capability of this, or any other individual predictor, is limited. Future work should aim to synthesize multiple predictors.

Figure 1.
Prediction of treatment outcomes using PANAS CA score at end of first exercise session (week1).

Response

Area Under the Curve = 0.5120

LD Treatment Group

Area Under the Curve = 0.7645

PHD Treatment Group

Remission

Area Under the Curve = 0.5670

LD Treatment Group

Area Under the Curve = 0.8070

PHD Treatment Group

Figure 2.

ROC analysis of the PANAS CA scores for prediction of Response and Remission.

Table 1

Baseline demographic and clinical characteristics means (standard deviations).

Baseline Variable	All (n=118)	16 kcals (n=58)	4 kcals (n=60)
<i>Demographics</i>			
Age (yrs)	47.1 (10.0)	45.7 (10.4)	48.5 (9.4)
Female no. (%)	96 (81.4)	49(84.5)	47 (78.3)
Race			
White no. (%)	103 (86.3)	49 (81.7)	54 (93.1)
Black no. (%)	12 (10.2)	8 (13.3)	4 (6.9)
Hispanic no. (%)	1 (0.8)	3 (5.0)	1 (1.7)
Other no. (%)	2 (1.7)	1 (1.6)	3 (5.2)
Marital Status			
Single, never married (%)	20 (17.0)	10(17.2)	10(16.7)
Cohabiting (%)	5 (4.2)	3(5.2)	2(3.3)
Married, living together (%)	62 (50.8)	31(53.4)	30(50.0)
Married, living apart (%)	1 (0.8)	0(0.0)	1(1.7)
Separated (%)	1 (0.8)	0(0.0)	1(1.7)
Divorced (%)	27 (22.9)	12(20.1)	15(25.0)
Widowed (%)	3 (2.5)	2(3.5)	1(1.7)
Weight (KG)	86.8 (20.0)	87.0 (23.6)	87.8 (17.7)
BMI	30.6 (6.09)	29.9 (6.3)	31.5 (5.5)
VO ₂ max (l/min)	1.7 (0.6)	1.7 (0.5)	1.8 (0.7)
Age of Onset (yrs)	27.1 (11.3)	27.4 (10.7)	26.8 (12.0)
Length of current episode (mos)	82.1 (97.1)	73.4 (95.0)	90.5 (99.0)
<i>Baseline Symptom Severity</i>			
HRSD ₁₇	17.8 (3.7)	17.6 (3.6)	18.0 (3.8)
IDS-C ₃₀	33.8 (7.5)	33.2 (7.1)	34.7 (7.8)
<i>Function</i>			
Q-LES-Q GA	41.9 (7.6)	41.3(7.6)	42.4(7.5)
WSAS	20.2(8.9)	19.2(7.7)	21.0(9.9)
SF-36 Physical	80.1 (20.4)	80.2 (20.1)	80.1 (20.8)
SF-36 Mental	49.4 (15.4)	49.8 (14.9)	49.0 (16.0)

Body Mass Index (BMI), 17-item Hamilton Rating Scale for Depression (HRSD₁₇), Inventory of Depressive Symptomatology–Clinician-rated (IDS-C₃₀), Quality of Life Enjoyment and Satisfaction Questionnaire, General Activities (Q-LES-Q GA), SF-36, maximal oxygen consumption (VO₂ max), and Work and Social Adjustment Scale (WSAS).

Table 2

IDS-C decrease from baseline and PANAS scores at end of first exercise session: means (standard deviations).

Variable	All (n=118)	16 Kcals (n=58)	4 Kcals (n=60)
IDSC ₃₀ Change	12.2 (11.7)	11.0 (11.6)	13.3 (9.6)
PANAS Positive	29.3 (9.1)	28.7 (8.6)	29.9 (9.6)
PANAS Negative	13.2 (4.4)	13.5 (4.6)	13.0 (4.2)
PANAS Composite	16.1 (11.0)	15.2 (11.0)	16.9 (11.0)