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Atypical depressive symptoms as a predictor of treatment response to exercise in Major Depressive Disorder

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Abstract

Effective treatment of Major Depressive Disorder (MDD) will require the development of alternative treatments and the ability for clinicians to match patients with the treatment likely to produce the greatest effect. We examined atypical depression subtype as a predictor of treatment response to aerobic exercise augmentation in persons with non-remitted MDD. Our results revealed a small-to-moderate effect, particularly in a group assigned to high-dose exercise (semi-partial eta-squared = 0.0335, $p = 0.0735$), indicating that those with atypical depression tended to have larger treatment response to exercise. Through this hypothesis-generating analysis, we indicate the need for research to examine depression subtype, along with other demographic, clinical and biological factors as predictors of treatment response to exercise.

Introduction

Approximately 30% of patients with MDD achieve remission following initial treatment with an antidepressant medication and a third of patients have significant depressive symptoms even after multiple treatment attempts (Rush et al., 2006; Thase et al., 2005). These data highlight the need for alternative treatments for MDD and have led to the study of exercise as a potential treatment alternative. Meta-analyses of exercise as a treatment for MDD indicate a significant treatment effect on par with that of antidepressant medication and psychotherapy (Cooney et al., 2014; Ekkekakis, 2015; Josefsson et al., 2014; Rethorst et al., 2009; Silveira et al., 2013).

The effective implementation of alternative treatments also requires identification of subgroups of patients with MDD that will benefit from these alternative treatments. One such subgroup is patients with atypical depression. Atypical depression is characterized by mood reactivity along with symptoms increased appetite and/or weight gain, hypersomnia, leaden paralysis, and interpersonal sensitivity. Results from the STAR*D trial indicate poorer treatment response to SSRIs in those with atypical depression (Stewart et al., 2010).

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The purpose of this analysis is to examine the atypical depression as a predictor of treatment response to exercise. Previous analyses indicate that hypersomnia and elevations in BMI are associated with better treatment outcomes to exercise (Rethorst et al., 2013; Toups et al., 2011). Furthermore, it has been hypothesized that treatment response to exercise may vary based on depressive subtypes (Schuch and de Almeida Fleck, 2013). Based on those findings, we hypothesize that those with atypical depression will have a greater treatment response to exercise.

Methods

TREAD was a randomized controlled trial designed to compare the efficacy of two doses of exercise augmentation in reducing depressive symptoms in patients with non-remitted MDD. Complete details regarding the TREAD study design have been published elsewhere (Trivedi et al., 2011); specific details pertinent to the current analysis are presented below.

Participants

Individuals, age 18–70, with a non-remitted MDD diagnosis, based on the Structure Clinical Interview for DSM-IV Axis I Disorders (SCID-I) were eligible for participation. Non-remission was defined as a score of > 14 on the Hamilton Rating Scale for Depression and between 2 and 6 months of treatment with an SSRI, with at least 6 weeks at an adequate dose. Exclusion criteria included: depression due to a comorbid psychiatric disorder, comorbid psychotic disorder, treatment resistant depression (failure of 2 or more pharmacological treatments during the current episode), pregnancy, and presence of a medical condition contraindicating exercise.

Exercise Intervention

Participants were randomized to receive one of two doses of aerobic exercise augmentation: 4 kilocalories per kilogram of bodyweight (KKW) or 16 KKW. The 16 KKW dose was designed to be equivalent to the current physical activity recommendation of 150 minutes per week of moderate intensity exercise. The 12-week exercise intervention began in Week 1 with three exercise sessions supervised by trained personnel at The Cooper Institute. In Week 2, two supervised sessions were conducted with the remaining exercise dose completed during home-based exercise sessions. After Week 2, one supervised exercise session per week was completed with the remaining dose completed during home-based sessions. Supervised exercise sessions were completed on a treadmill or stationary bicycle. Exercise intensity was self-selected during all sessions and monitored with a Polar 610i heart rate monitor.

Outcome Measures

Depressive symptoms were assessed using the clinician rated Inventory of Depressive Symptomatology (IDS-C) (Rush et al., 2000). Atypical depression was categorized by the presence of mood reactivity (score of <2 on item 8) plus 2 or more of the following symptoms: hypersomnia (item 4 score = 2–3), increased appetite or increased weight (item 12 or item 14 score = 2–3), leaden paralysis (item 30 score = 2–3), interpersonal sensitivity (item 29 score = 3) (Novick et al., 2005).

Statistical Analysis

A linear mixed model analysis examined the relationship between atypical depression and depressive symptoms (exit IDS-C, defined as last observed IDS score). Exercise group was included in the model along with the following covariates: baseline IDS-C, age, gender and family history of mental illness. These covariates were chosen due to the significant moderating effect observed in the primary outcome analysis (Trivedi et al. 2011). A final model also included the group $\times$ atypical interaction term. Least square means were calculated for each group in the model. An effect size which measures the percent of variance explained (semi-partial eta-squared) was computed for each term in the model. Effect sizes of .01, .06, and .14 can be interpreted as small, medium, and large effects, respectively.

Results

Of the 122 evaluable subjects, 35 were classified as having atypical depression. Those with atypical depression did not differ from those without atypical depression by age, gender, family history of mental illness, BMI, years of education, race/ethnicity, or marital status ($p > 0.05$). The atypical group did demonstrate greater baseline scores on the IDS-C ($p < 0.001$), which is expected since atypical depression was classified by affirmative responses to five IDS-C items. The median adherence rate in the 4-KKW group (99.4%) was significantly greater than in the 16-KKW group (63.8%) ($p = 0.0005$). Those with atypical depression did not have significantly different adherence to the exercise compared to the rest of the sample ($p = 0.526$; Table 1).

Results from the initial model indicate a non-significant effect of atypical depression ($p = 0.195$). However, the semi-partial eta-squared for atypical of 0.0123 represents a small-to-moderate effect. In the model that included the atypical $\times$ group interaction, both the interaction term ($p = 0.215$) and the atypical term were non-significant ($p = 0.212$). Again, the semi-partial omega-squared for the interaction (0.0112) and the atypical term (0.0114) represent small-to-moderate effects.

The IDS-C total scores for the atypical group and atypical $\times$ exercise group, represented by the least square means, are presented in Table 2. These show a lower level of symptoms in those with atypical depression (21.5 vs. 24.5) that appears to be driven by a differential treatment effect across groups assigned to the high exercise dose (20.8 vs. 26.7, semi-partial eta-squared = 0.0235, $p = 0.0735$).

Discussion

The purpose of this paper was to examine atypical depression as a potential predictor of antidepressant response to exercise. Our results indicate a small-to-moderate effect of atypical depression, with a greater reduction in depressive symptoms among those with atypical depression. Examination of the atypical $\times$ exercise group effect indicates that this effect appears to be driven by a reduced treatment effect observed in the non-atypical depression group assigned to high dose exercise.

These findings are the result of secondary analysis of the TREAD trial, which was not specifically designed to identify predictors of treatment response. The small-to-moderate effect size is indicative of a potential moderating effect of atypical depression on treatment response to exercise despite the non-significant statistical test as this analysis was likely underpowered. An additional limitation of the current study is the lack of a true “control” group. Considering these limitations, the result of this analysis should be viewed as “hypothesis generating” and indicate the need for future studies conducted with the explicit aim of identifying predictors of treatment response. These future studies would allow for more sophisticated analysis of treatment moderators, such as latent class analysis. Furthermore, the small-to-moderate effect size indicates that clinical utility of treatment predictors will likely require integration of multiple predictors into a comprehensive algorithm that would allow clinicians to match patients with the treatment most likely to be effective.

References

- Cooney G, Dwan K, Mead G. Exercise for depression. *JAMA*. 2014; 311:2432–2433. [PubMed: 24938566]
- Ekkekakis P. Honey, I shrunk the pooled SMD! Guide to critical appraisal of systematic reviews and meta-analyses using the Cochrane review on exercise for depression as example. *Mental Health and Physical Activity*. 2015
- Josefsson T, Lindwall M, Archer T. Physical exercise intervention in depressive disorders: meta-analysis and systematic review. *Scand. J. Med. Sci. Sports*. 2014; 24:259–272. [PubMed: 23362828]
- Novick JS, Stewart JW, Wisniewski SR, Cook IA, Manev R, Nierenberg AA, Rosenbaum JF, Shores-Wilson K, Balasubramani GK, Biggs MM, Zisook S, Rush AJ, investigators SD. Clinical and demographic features of atypical depression in outpatients with major depressive disorder: preliminary findings from STAR*D. *J. Clin. Psychiatry*. 2005; 66:1002–1011. [PubMed: 16086615]
- Rethorst CD, Sunderajan P, Greer TL, Grannemann BD, Nakonezny PA, Carmody TJ, Trivedi MH. Does exercise improve self-reported sleep quality in non-remitted major depressive disorder? *Psychol. Med*. 2013; 43:699–709. [PubMed: 23171815]
- Rethorst CD, Wipfli BM, Landers DM. The antidepressive effects of exercise: a meta-analysis of randomized trials. *Sports Med*. 2009; 39:491–511. [PubMed: 19453207]
- Rush AJ, Carmody TJ, Reimnitz PE. The Inventory of Depressive Symptomatology (IDS): Clinician (IDS C) and Self Report (IDS SR) ratings of depressive symptoms. *Int. J. Methods Psychiatr. Res*. 2000; 9:45–59.
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am. J. Psychiatry*. 2006; 163:1905–1917. [PubMed: 17074942]
- Schuch FB, de Almeida Fleck MP. Is Exercise an Efficacious Treatment for Depression? A Comment upon Recent Negative Findings. *Front Psychiatry*. 2013; 4:20. [PubMed: 23565097]
- Silveira H, Moraes H, Oliveira N, Coutinho ES, Laks J, Deslandes A. Physical exercise and clinically depressed patients: a systematic review and meta-analysis. *Neuropsychobiology*. 2013; 67:61–68. [PubMed: 23295766]
- Stewart JW, McGrath PJ, Fava M, Wisniewski SR, Zisook S, Cook I, Nierenberg AA, Trivedi MH, Balasubramani GK, Warden D, Lesser I, John Rush A. Do atypical features affect outcome in depressed outpatients treated with citalopram? *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2010; 13:15–30.
- Thase ME, Haight BR, Richard N, Rockett CB, Mitton M, Modell JG, VanMeter S, Harriett AE, Wang Y. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake

inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *J. Clin. Psychiatry*. 2005; 66:974–981. [PubMed: 16086611]

Toups MS, Greer TL, Kurian BT, Grannemann BD, Carmody TJ, Huebinger R, Rethorst C, Trivedi MH. Effects of serum Brain Derived Neurotrophic Factor on exercise augmentation treatment of depression. *J. Psychiatr. Res.* 2011; 45:1301–1306. [PubMed: 21641002]

Trivedi MH, Greer TL, Church TS, Carmody TJ, Grannemann BD, Galper DI, Dunn AL, Earnest CP, Sunderajan P, Henley SS, Blair SN. Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. *J. Clin. Psychiatry*. 2011; 72:677–684. [PubMed: 21658349]

Highlights

- We examine atypical depressive symptoms as a predictor of treatment response to exercise in MDD
- The presence of atypical depressive symptoms is related to greater treatment response
- This effect appears driven by a blunted treatment response to high dose exercise for those without atypical symptoms

Table 1

Baseline Demographic and Clinical Characteristics

	Total Sample	Atypical	Non- Atypical	
	(n = 122)	(n = 35)	(n = 87)	
Variable	M (SD)	M (SD)	M (SD)	p-value
Age (years)	47.04 (10.0)	48.77 (10.8)	46.34 (9.6)	0.225
Female (%)	82	88.6	79.3	0.229
Race (%)				0.672
White	86.1	85.7	86.2	
Black	11.5	14.3	10.3	
Hispanic	0.8	0	1.2	
Other	1.6	0	2.3	
Education (years)	14.17 (4.6)	13.20 (4.4)	14.57 (4.6)	0.137
Marital Status (%)				0.737
Married/Cohabit	55.7	54.3	56.3	
Never Married	17.2	14.3	18.4	
Div/Sep/Widowed	27	31.4	25.3	
BMI	30.86 (6.2)	30.62 (5.5)	30.96 (6.4)	0.786
Family History of MDD (%)	70.5	74.3	69.0	0.56
IDS-C	34.03 (7.4)	38.34 (6.9)	32.30 (7.0)	<0.001
Exercise Adherence (% of KKW)	65.43 (29.7)	68.71 (28.6)	64.10 (30.2)	0.441

Table 2

Least Square Mean exit depression scores (IDS-C)

	Total	Low Dose	High Dose
Atypical	21.4	22.2	20.8
Non-Atypical	24.5	22.3	26.7