Effectiveness of Aerobic Exercise as an Augmentation Therapy for Inpatients with Major Depressive Disorder: A Preliminary Randomized Controlled Trial

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ABSTRACT

Background: Physical exercise has been shown to reduce depressive symptoms when used in combination with antidepressant medication. We report a randomized controlled trial of aerobic exercise compared to stretching as an augmentation strategy for hospitalized patients with major depression.

Methods: Male or female patients, 18-80 years, diagnosed with a Major Depressive Episode, were randomly assigned to three weeks of augmentation therapy with aerobic (n=6) or stretching exercise (n=6). Depression was rated at several time points using the 21-item Hamilton Depression Scale (HAM-D), Beck Depression Inventory (BDI) and other scales.

Results: According to the HAM-D, there were four (out of six) responders in the aerobic group, two of whom achieved remission, and none in the stretching group. According to the BDI, there were two responders in the aerobic group who were also remitters and none in the stretching group.

Conclusions: The results of this small study suggest that aerobic exercise significantly improves treatment outcome when added to antidepressant medication. However, due to the small sample size the results must be regarded as preliminary and further studies are needed to confirm the findings.

INTRODUCTION

Major depressive disorder (MDD) is a common and important cause of morbidity and mortality worldwide. In western countries the yearly incidence of depression is estimated to be 3-5% and the lifetime prevalence is 17% (1). The most frequently used first line agents for the pharmacological treatment of MDD are specific serotonin reuptake inhibitors (SSRIs). Successful treatment with SSRIs may require up to eight weeks (2, 3). In the first stage of the STAR*D trial in which patients suffering from MDD were treated with the specific serotonin reuptake inhibitor, citalopram, the self-reported remission rate was 32.9% and the observer rated Hamilton Depression scale (HAM-D) remission rate was 27.5% (4). These findings, from the largest prospective study to date, confirm that even with optimal dosage and duration of treatment more than 60% of depressed patients will remain significantly symptomatic and will need some additional treatment. The options available to optimize antidepressant treatment include: a) substitution of a different antidepressant; b) augmentation strategies with lithium, triiodothyronine or another antidepressant; and, c) electroconvulsive therapy (5). There is a need to search for new treatments that will enhance the efficacy of these available options, or even replace them in some cases.

The last decade has witnessed a significant growth of interest in Complementary and Alternative Medicine (CAM) worldwide. Depression is one of the 10 most frequent indications for using CAM (6). The reasons for using CAM in depression include lower incidence of adverse effects, decreased likelihood of negative interactive treatment effects, a holistic approach to the indi-
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Individual’s problems and dissatisfaction with conventional healthcare. In a previous review of the evidence base of various complementary and alternative therapies for depression, exercise was found to have Grade 1 evidence support from a meta-analysis of 14 randomized controlled trials (7), though this evidence was inconclusive (8). A recent Cochrane systematic review found a moderate, non-significant effect of exercise (9).

There are several types of exercise: aerobic exercise such as brisk walking, running or cycling, which aims to improve cardio-respiratory fitness; strength (resistance) exercise such as weightlifting, which improves muscle and bone strength, and flexibility exercise such as stretching, which is designed to improve range of motion. Both aerobic and strength training have been shown to improve depression in randomized controlled studies. Two published randomized controlled trials, comparing aerobic training versus no treatment (10) and anaerobic strength training versus standard general practitioner treatment (11), suggest that training has a positive effect on patients diagnosed with depression. Furthermore, the studies found an association between exercise amount and reduction of symptoms in patients with depression. However, meta-analyses could not determine the effects of exercise on depression because of a lack of good quality research on clinical populations (7, 12). The authors found that most of the studies involved non-clinical populations, were without blinded outcome assessment, lacked intent-to-treat analyses and had short follow up.

Exercise has also been shown to reduce depressive symptoms when used in combination with other medical treatments for depression. A recent study comparing high dose and low dose exercise, given as an augmentation to antidepressant treatment therapy in non-hospitalized patients, found that high exercise dose led to better results (13). Another trial in psychiatrically hospitalized depressed patients compared aerobic exercise to stretching exercise and found a significantly greater effect in the aerobic exercise group (14). A significant effect of aerobic exercise was also found in a mixed group of depressed in- and outpatients in an open label study (15). Of note is an inpatient study in which addition of aerobic exercise to the treatment regimen resulted in greater reduction in depression scores in patients who were in the exercise group than those who were not, as well as an increase in maximum oxygen uptake that was related to improvement in depression (16).

In the present study, we evaluated the effect of a short-term aerobic exercise program as an adjuvant treatment in patients with MDD undergoing standard antidepressant medication therapy, as compared to the effect of stretching exercise. Most studies have examined the effect of exercise in non-hospitalized depressed patients. The current study was specifically designed to evaluate aerobic exercise as an augmentation treatment for inpatients with MDD.

**METHODS**

**CLINICAL METHODS**

This was an observer-blinded, randomized controlled trial (ClinicalTrials.gov Identifier: NCT00464048). It involved patients with a Major Depressive Episode (MDE) in the context of Major Depressive Disorder (MDD) admitted to the Department of Psychiatry, Hadassah - Hebrew University Medical Center. Inclusion criteria were (1) male or female; (2) diagnosis of MDE in the context of MDD according to DSM-IV criteria, without psychotic features; (3) age 18-80 years; (4) a score >14 on the BDI = Beck Depression Inventory. 

Figure 1: Study Design

**Assessment for eligibility**
Medical evaluation: medical history, physical exam. Psychiatric Evaluation - SCID, ATTH, HAM-D, CGI, BDI, VAS

Informed consent

**Randomization**

Preliminary patient exclusion

Aerobic exercise group
Pre-activity GXT
4 sessions per week for 3 weeks
Weekly Blind Assessments: HAM-D, CGI, BDI, VAS

Stretching exercise group
4 sessions per week for 3 weeks
Weekly Blind Assessments: HAM-D, CGI, BDI, VAS

Follow-up assessment
HAM-D, CGI, BDI, VAS

The rate was continuously monitored to evaluate training. The patient was supervised by study personnel, and heart rate was performed individually; during training, the intensity was set to be between 60-80% of the maximal estimated heart rate. The training was performed at a moderate intensity corresponding to a heart rate of 60-80% of the maximal estimated heart rate. The training was performed for 4 sessions per week of 30 minutes walking on a treadmill with the recommendations of the Centers for Disease Control and the American College of Sports Medicine (21), aerobic exercise training consisted of four sessions per week of 30 minutes light stretching exercises. Instructions were given to the patients how to perform the exercises and they carried out the program individually supervised by study personnel. The length of both exercise programs was 21 days involving a total of 12 sessions.

Severity of depression was rated using the Hamilton Depression Scale (HAM-D 21 items), Clinical Global Impression Scale (CGI) (observer-rated) and Beck Depression Inventory (BDI) and Visual Analog Scale (self-rated). Patients were evaluated at five points in the study: week 0, week 1, week 2, week 3, and one week after conclusion of the study. All patients were rated by the same investigator who did not work on the inpatient unit, was unaware of the participant's group assignment and had no contact with the participants other than for the purpose of rating. The statistician who performed the data analysis was also blind to treatment allocation. Adverse effects were assessed at the beginning of the study and at the end of every week of the exercise program using a checklist.

The study was approved by the Internal Review Board (Helsinki Committee) of Hadassah – Hebrew University Medical Center. All patients gave written informed consent. It was not possible to blind patients to the intervention; therefore patients were told that the aim of the study was to compare the effects of two different types of exercise on mood.

**Statistical Analysis**

Univariate differences between groups were analyzed using the Student t test or chi square. One way ANOVA with repeated measures was used to examine effects over time followed by Neuman Keuls post hoc tests. Intent to treat analysis was performed with last observation carried forward. The primary outcome criterion for the study was response to exercise intervention defined as ≥ 50% reduction in pretreatment HAM-D score at the end of the follow-up period. Secondary outcome criteria were ≥ 50% reduction in pretreatment BDI score at the end of the follow-up period, remission rates defined as final HAM-D total ≤ 6 or a final BDI total ≤ 9.4 and rating scale scores in the two groups compared over the entire treatment period from baseline to the post-treatment assessment. We also compared length of hospitalization of both groups defined as the number of days between the beginning of training and discharge from hospital.
RESULTS

Of 69 patients with MDE in the context of MDD admitted to the Department of Psychiatry during the research period (June 2009 - August 2011), 28 fulfilled the inclusion criteria for this study. Of these 15 agreed to participate and were recruited. Three patients dropped out before starting the exercise program (two changed their minds and one had an abnormal exercise test). There were no dropouts during the course of the study from baseline to the post-treatment assessment.

The groups were compared on the following parameters: age, gender, presence of depression in the family, years of schooling, number of depressive episodes (including current episode), duration of current episode, antidepressant treatment history form (ATHF) score, and initial scores on the four depression rating scales. There were no significant differences (p<.05) in background and demographic characteristics between the stretching and the aerobic exercise groups at the beginning of the research, although there was a trend for the stretching group to be older and slightly more depressed according to the BDI (p=.06). On the other hand the aerobic group tended to greater resistance to antidepressant treatment as indicated by the ATHF (p=.08) (Table 1).

Differences in response and remission rates between the two exercise groups were examined according to the HAM-D and BDI final total scores. The results are shown in Table 2. In the aerobic exercise group there were four responders according to the primary outcome criterion, >50% reduction in pretreatment HAM-D score at the end of the follow-up period, corresponding to a 66.6% response rate, as compared to no responders in the stretching group (χ²=6.0; p=0.014). Two responders in the stretching group also achieved remission with final HAM-D scores ≤6 (33.3%) (p>0.1). On the BDI there were two responders in the aerobic exercise group who also achieved remission with BDI scores <9.4 and no responders in the stretching group (p>0.1).

For each depression scale a one way repeated measures ANOVA was performed from baseline to post-treatment assessment. Repeated measures ANOVA of HAM-D scores yielded no significant exercise effect (F[1,10]=0.42, p=0.52), a significant time effect (F[4,40]=13.2,

Table 1: Comparison of the background and demographic characteristics of the treatment groups at the beginning of research; df=10, N=6 for each exercise group (aerobic, stretching).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aerobic</th>
<th></th>
<th>Stretching</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean</td>
<td>33.17</td>
<td>Mean</td>
<td>53.50</td>
<td>0.06</td>
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<tr>
<td></td>
<td>Std.Dev.</td>
<td>13.41</td>
<td>Std.Dev.</td>
<td>18.78</td>
<td></td>
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<tr>
<td><strong>Gender</strong></td>
<td>Female</td>
<td>66.6%</td>
<td>Female</td>
<td>83.3%</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>History of depression in family</strong></td>
<td>Positive</td>
<td>67%</td>
<td>Positive</td>
<td>33%</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Years of schooling</strong></td>
<td>13.00</td>
<td>1.67</td>
<td>9.33</td>
<td>6.19</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Number of depressive episodes</strong></td>
<td>4.17</td>
<td>3.54</td>
<td>3.50</td>
<td>2.93</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Duration of current depressive episode</strong></td>
<td>40.33</td>
<td>20.02</td>
<td>20.20</td>
<td>16.29</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Antidepressant Treatment History Form (ATHF) score</strong></td>
<td>10.00</td>
<td>5.55</td>
<td>5.33</td>
<td>1.75</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Hamilton Depression Scale (HAM-D)</strong></td>
<td>29.00</td>
<td>5.06</td>
<td>27.50</td>
<td>7.66</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Beck Depression Inventory (BDI)</strong></td>
<td>28.33</td>
<td>6.28</td>
<td>35.33</td>
<td>5.28</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Clinical Global Impressions Scale (CGI)</strong></td>
<td>4.33</td>
<td>0.52</td>
<td>4.50</td>
<td>0.55</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Visual Analog Scale (VAS)</strong></td>
<td>17.00</td>
<td>9.29</td>
<td>12.33</td>
<td>13.16</td>
<td>0.63</td>
</tr>
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</table>

Table 2: Response and remission rates in the two exercise groups (Response defined as >50% reduction in pretreatment HAM-D or BDI scores. Remission defined as HAM-D final score ≤6, or BDI final scores ≤9.4). BDI= Beck Depression Inventory. HAM-D= Hamilton Depression Scale.

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>Exercise Program</th>
<th>No. Subjects</th>
<th>No. Responders</th>
<th>% Responders</th>
<th>X² square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td>Aerobic</td>
<td>6</td>
<td>4</td>
<td>66.66</td>
<td>2</td>
<td>33.33</td>
</tr>
<tr>
<td></td>
<td>Stretching</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>χ²&lt;0.05*</td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>Aerobic</td>
<td>6</td>
<td>2</td>
<td>33.33</td>
<td>2</td>
<td>33.33</td>
</tr>
<tr>
<td></td>
<td>Stretching</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>χ²&lt;0.5</td>
<td></td>
</tr>
</tbody>
</table>
p=5.71462E-07) and no interaction (F[4,40]=1.6, p=0.19) (Figure 2). For BDI scores there was a significant exercise effect (F[1,10]=10.44, p=0.008), a significant time effect (F[4,40]=10.6, p=5.98577E-06) but no interaction (F[4,40]=1.1, p=0.38). Neuman Keuls post hoc tests showed BDI scores were significantly lower among the aerobic group than the stretching exercise group at all-time points: after one week (p=0.02), two weeks (p=0.001) and three weeks (p=0.003) of treatment and one week following the study (p=0.0002) (Figure 3). For CGI scores there was a significant exercise effect (F[1,10]=7, p=0.02), a significant time effect (F[4,40]=8.5, p=4.36289E-05) and a significant interaction (F[4,40]=2.62, p=0.04). Post hoc Neuman Keuls tests showed that the aerobic group CGI scores were significantly lower than the stretching group scores after three weeks of treatment (T4, p=0.03) and one week following the study (p=0.0004) (Figure 4). For VAS scores there was a significant exercise effect (F[1,10]=6.16, p=0.03), a significant time effect (F[4,40]=15.4, p=1.05903E-07), but no interaction (F[4,40]=1.8, p=0.14). Neuman Keuls post hoc tests showed that the VAS scores of the aerobic exercise group were significantly higher than those of the stretching exercise group after two weeks of treatment (T3, p=0.04), after four weeks (T4, p=0.02) and one week after conclusion of the study (T3, p=0.0006) (Figure 5).

Mean duration of hospitalization, measured as the number of days between the beginning of training and discharge from hospital, was shorter in the aerobic group than the stretching group (38.83±25.36 days versus 61.16±52.4 days) but the difference was not statistically significant (p=0.38).

ADVERSE EFFECTS
No adverse effects were reported by the participants in either exercise group.

DISCUSSION
In this study, we evaluated the effect of a short-term aerobic exercise program as an adjuvant treatment for hospitalized patients with major depression as compared to the effect of stretching exercise. Both groups showed improvement over time on the four depression scales used in the study. Improvement in the aerobic group was significantly greater than in the stretching group on three of the four scales (CGI, BDI and VAS). We found that response and remission rates were significantly higher in the aerobic group on HAM-D and BDI scales. Response to exercise intervention, defined as ≥50% reduction in pretreatment HAM-D score at the end of the follow-up period, was the primary outcome criterion of the study. No significant difference was found in the duration of hospitalization between the two groups.

The results of our study are in accordance with previous trials indicating a positive effect of aerobic exercise as an augmentation treatment for depression. Our findings...
resemble those of four previously published studies. Knubben et al. (14) showed a positive effect of short term aerobic exercise lasting only 10 days among hospitalized depressive patients. The uncontrolled study of Dimeo et al. (15) showed a significant effect after only 12 days. The duration of exercise in our study was longer, three weeks, and included a one week follow up. In contrast, the study of Martinsen et al. (16), which was also positive, lasted nine weeks. Studies in outpatients tend to be longer, the majority lasting 8-12 weeks. Trivedi et al. (13) found a positive effect of aerobic training among depressed outpatients, while Krogh et al. did not (22). A meta-analysis by Krogh et al. (12) suggested a short-term effect of exercise on depression, but this effect does not seem to last in the longer term beyond cessation of the exercise program. This meta-analysis mainly included trials performed outside clinical settings, only half of which were blinded. Our study is unique in that it is a blinded trial performed among hospitalized patients suffering from severe depression. The improvement was on all four depression scales indicating that exercise improves both objective and subjective depression parameters. We planned to recruit a total of 40 patients for this study in order to detect a difference significant at p<0.05 with a power of 80%, based on effect size observed in the previous controlled study of Knubben et al. (14) and using the program Power and Precision (Release 3.1, 2007). The number of patients actually recruited was much smaller than this. Out of 28 patients who fulfilled the inclusion criteria, only 15 agreed to participate in the study. However, all 12 patients who started the exercise program completed it. We calculated the power of our recruited sample to detect a significant effect using our primary outcome variable, 50% reduction in HAM-D score from baseline. On this basis our sample had 74% power to detect a significant effect of aerobic exercise at p<0.05 two tailed. The small number of patients who agreed to take part is most likely related to the low level of motivation for participation in programs of this type among patients suffering from depression. The fact that despite this small sample size significant results were obtained suggests a strong effect of the aerobic treatment. Treatment-resistant depression (TRD) has several definitions. One of these definitions refers to inadequate response to at least one antidepressant trial of adequate dose and duration (23). The cutoff for definition of resistant depression in our study was above two according to the ATHF (18); all the patients were resistant except one. Our results show that aerobic exercise augments the effect of standard antidepressant pharmacotherapy and improves depression even in resistant depressive inpatients. However, because of the small sample size in our study the results must be regarded as preliminary and consideration of aerobic exercise as part of the regular treatment plan in patients with resistant depression requires replication in further clinical trials.
REFERENCES


