Clinical Research in Practice: The Journal of Team Hippocrates

Volume 8 | Issue 1 Article 9

2022

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Recommended Citation

BLOCK CJ. Determining the optimal exercise intensity level for adjunctive treatment of major depressive disorder. Clin. Res. Prac. Apr 28 2022;8(1):eP2672. https://doi.org/10.22237/crp/1640995680

Clinical Research in Practice
The Journal of Team Hippocrates
VOL 8 ISS 1 / eP2672 / APRIL 28, 2022
https://doi.org/10.22237/crp/1640995680

Determining the optimal exercise intensity level for adjunctive treatment of major depressive disorder

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ABSTRACT A clinical decision report using:

Helgadóttir B, Hallgren M, Ekblom Ö, Forsell Y. Training fast or slow? Exercise for depression: A randomized controlled trial. *Prev Med*. 2016;91:123-131. https://doi.org/10.1016/j.ypmed.2016.08.011

for a patient seeking an exercise regimen to help with depressive symptoms.

Keywords: *depression, depressive disorder, exercise, antidepressant therapy*

Clinical-Social Context

Mr. Sam Farris (pseudonym), a married middle-aged white male with a history of major depressive disorder, was seen in clinic for a follow-up appointment to discuss medication management. Mr. Farris was employed in a professional capacity, had a college education, and stated that he had sufficient financial and social resources. He was physically fit with a normal-range BMI. He exhibited a high level of health literacy. He also had access to health insurance through his employer. Other than major depressive disorder, he had no significant medical history. After trials of two SSRI agents, he was currently taking the SNRI venlafaxine for depression. He reported the drug had moderate efficacy in treating his symptoms; while able to go about his daily activities, he still struggled with depressed mood and motivation.

During the interview, he mentioned that he had struggled with depression since adolescence. He noted that when he was engaged in regular exercise his depression was relatively well-controlled. In particular, he described a period in his late 20's and early 30's when routine weightlifting without talk or pharmacologic therapy seemed sufficient to control his depressive symptoms. However, as his professional and family obligations increased, he stopped regularly exercising. He wanted to restart a regular exercise program to supplement his antidepressant therapy and improve his mental health. Due to time constraints and being out of shape, he wanted to start a lower-intensity exercise program consisting of daily walks and yoga with his wife. However, he was unsure if these low-intensity exercises would be sufficient to improve his depressive symptoms, as he had previously engaged in much more strenuous activities.

Clinical Question

What is the optimal exercise intensity level for adjunctive treatment of major depressive disorder?

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ISSN: 2379-4550
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Clinical Research in Practice
The Journal of Team Hippocrates
VOL 8 ISS 1 / eP2672 / APRIL 28, 2022
https://doi.org/10.22237/crp/1640995680

Research Article

Helgadóttir B, Hallgren M, Ekblom Ö, Forsell Y. Training fast or slow? Exercise for depression: A randomized controlled trial. *Prev Med*. 2016;91:123-131. https://doi.org/10.1016/j.ypmed.2016.08.011 [1]

Description of Related Literature

The advanced search function in PubMed was used to identify randomized clinical trials investigating the role of exercise in the treatment of depression. The search algorithm used was: "("depression") AND ("exercise") AND ("intensity") AND ("randomized controlled trial" OR "randomized clinical trial")". This strategy yielded a total of 274 publications. Titles and abstracts were screened manually to identify relevant studies. Many of the studies identified by this search method were not specifically designed to study the effect of exercise on depression and were eliminated. Of the relevant studies identified, most were designed to investigate the role of exercise in depression in specific patient cohorts, some of the most common cohorts being pregnant women, cancer patients, and patients with heart failure.

After these screening steps, eight relevant studies were identified (Table 1). These studies were then reviewed in detail. We prioritized studies that were (1) conducted in an outpatient setting, (2) used large sample sizes, (3) compared the therapeutic effects of different levels of exercise intensity, and (4) used standard-of-care as the control group. The study from Hughes et al. was eliminated due to small sample sizes (N=14).[2] Studies by Kennedy et al. and Antunes et al. were eliminated for using an inadequate control group.[3,4] The trial performed by Singh et al. excluded patients under 60 years old, which would have excluded Mr. Farris from the study.[5] Mota-Pereira et al. focused their study on participants with treatment-resistant depression, inclusion criteria which would have excluded our patient.[6] The study performed by Knubben et al. was conducted in an inpatient setting, limiting its applicability to outpatient primary care.[7]

Only two studies, Helgadóttir, et al. and Belvederi et al., compared multiple levels of aerobic exercise intensity to a sufficient control. Belvederi et al. compared patients treated with the first-line antidepressant sertraline to patients treated with both sertraline and either low- or high-intensity aerobic exercise over a 24-week period. This study demonstrated a significant increase in the proportion of remitted patients relative to control. No significant difference was observed between the two treatment groups.[8]

Of the trials identified, Helgadóttir, et al. reported the most comprehensive and relevant investigation.1 Helgadóttir, et al. had the largest sample sizes, compared 3 levels of aerobic exercise with a treatment-as-usual control group, and was conducted in an outpatient setting. This paper, published in 2016, was a follow-up study using data from the Regassa trial (described in detail below). Importantly, Regassa used community-based resources and tools that would be available to most primary care providers. By choosing a community-based approach, Regassa also increases the "real-world" applicability of the trial to clinical practice. After the publication of these results in 2016, the same group published a follow-up article which evaluated the effects of exercise on depression one year after the treatment period in the same study group. Due to these strengths, the study by Helgadóttir, et al. was selected for a detailed critical appraisal. Based on these two randomized controlled trials, by the Strength of Recommendation Taxonomy (SORT) criteria, the Grade of Recommendation for this topic is A- based on consistent, high-quality patient-oriented data.[9]

Critical Appraisal

Study methodology: This study utilized data from the REGASSA trial comparing three treatment arms: Treatment as usual (TAU), treatment with internet-based CBT (ICBT), and physical exercise. Patients were randomly assigned to one of these three groups using a computerized approach. Hallgren et al. reported the initial findings from Regassa in 2015.[10] While it was not possible to blind patients to their assigned treatment, researchers were blinded to the participants assigned group. The primary outcome for the study was the change in Montgomery-Asberg Depression Rating Scale (MADRS) score over the 3-month trial period between groups.[11] The MADRS is a 10-question survey in which patients rate different symptoms of depression on a scale from 0 to 6. The study also monitored the relationship between exercise group and heart rate during exercise sessions.

Inclusion criteria for the study included an age range of 18-67 and a score of >=10 on the PHQ-9. Patients with known substance use disorders, severe somatic disorders, and patients who required specialist-managed psychiatric care were excluded. Participant age, gender, educational level, health status, home activity level, height, and weight were collected by a questionnaire at enrollment.

ISSN: 2379-4550

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The TAU arm received standard-of-care therapy from their primary care physician. According to the authors, "most" participants in the TAU group participated in CBT-focused counseling sessions of approximately 1 hour. The average patient attended 8.2 sessions during the 12-week trial period, but the standard deviation in this group was quite large (6.2), demonstrating significant variability in patient participation. Also, approximately 25% of the patients in the TAU group received no documented treatment during the study period.

Patients assigned to the physical exercise arm were further subdivided into three subgroups: light, moderate, and vigorous exercise. The light exercise group engaged in yoga-based stretching and balance classes. These classes did not include mindfulness training, thus avoiding possible confounding due to the documented positive effects of mindfulness on mental health. The moderate exercise group participated in "intermediate-level" aerobics courses. The vigorous exercise group also participated in a high-intensity aerobics course. All three groups were assigned to participate three times per week in these courses, with all classes being 55 minutes in duration. All study participants could continue mental health treatment that had started prior to joining the trial; according to the authors, "most" patients were engaged in some form of care. While most patients receiving care were participating in outpatient therapy, 25% of all patients in the study were taking antidepressants.

The primary measure of treatment response was MADRS score at start of treatment and after 12 weeks of treatment. MADRS is a validated, standard research tool for measuring the severity of depressive symptoms. Patient heart rate was documented at exercise sessions and used to calculate the percent of time spent at maximum heart rate. The authors used chi-square tests to evaluate the distribution of categorical participant characteristics across groups and one-way ANOVA to evaluate the distribution of continuous characteristics. Multiple linear regression models were employed to compare MADRS scores between the three groups before and after treatment. These comparisons were controlled for antidepressant use, and at times stratified by various characteristics (sex, physical activity at baseline, etc.). Also, the authors analyzed change in MADRS score using per protocol analysis, in which "compliers" within the three treatment groups (those who completed 12 or more exercise sessions during the study period) were compared against TAU.

Results:

Patient characteristics: A total of 620 patients were enrolled in the TAU and exercise arms. The average age of the study population was 42.6. 31.8% of the patients were between 50-67 years old. 73.7% of the participants self-identified as women. No data about race, ethnicity, socioeconomic status, or sexual orientation were collected. Male participants exhibited both a significantly greater proportion of participants with no somatic disorders compared to women and significantly greater rates of hazardous drinking. Women in the study were significantly more likely to have achieve tertiary education (defined as >=2 years of post-high school education).

Statistical testing confirmed successful randomization of participant assignments, as participant characteristics were statistically similar across most of the characteristics measured. However, testing identified significant differences in the proportions of participants taking antidepressants and baseline MADRS scores. 34.3% and 30.3% of the moderate- and high-intensity group participants, respectively, were taking antidepressants. This contrasted with much lower rates in the TAU (21.6%) and light exercise (22.6%) groups. MADRS scores at baseline were slightly higher in the moderate-intensity (22.8) and high-intensity (22.4) groups than the TAU (20.9) and low-intensity (21.3) groups.

Compliance with protocol: Approximately 32% of the participants in the exercise groups attended no documented exercise sessions, while 40% attended the protocol-recommended minimum of 12 sessions over the study period. For comparison, per the original Regassa report in 2015, approximately 25% of the patients in the TAU arm received no documented treatment over the study period.

Primary analysis: The primary outcome measured in this study was the reduction in MADRS score after 12 weeks of treatment. All four groups demonstrated significant decreases in MADRS score. However, all three exercise groups significantly outperformed the TAU arm. On average, participants in the TAU group reduced their MADRS score by 5.3 (95% CI -6.3, -4.4). Score reductions were significantly higher in the light exercise (-9.4, 95% CI -11.0, -7.77), moderate exercise (-7.43, 95% CI -9.1, -5.8), and vigorous exercise (-7.8, 95% CI -11.0, -4.6) groups. The differences in the change in MADRS score between exercise groups were not statistically significant. The per protocol analysis comparing compliers to TAU demonstrated similar results, but the effect of treatment was

ISSN: 2379-4550
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much larger for compliers in all three exercise groups. As mentioned above, these comparisons were adjusted for baseline antidepressant use.

Secondary analysis: Next, the authors stratified the results by patient gender and home physical activity level at baseline. Male participants in all three exercise groups demonstrated greater decreases in MADRS score compared to TAU, with no statistical differences observed between the response in the exercise groups. In contrast, female participants in the light and vigorous exercise groups demonstrated significantly greater decreases in MADRS score compared to TAU. For women, the moderate exercise group was not statistically different from TAU. Men also exhibited a larger decrease in MADRS scores than women in all exercise categories, although these differences were not significant. Physical activity levels at baseline were dichotomized into two levels: Inactive and light active participants and moderate to vigorous physical activity levels. Participants at both levels of physical activity demonstrated similar decreases in MADRS score across all three treatment groups.

Conclusions: The results from this study suggest several conclusions. In agreement with previous reports, study participants who engaged in a combination of physical exercise and primary care-guided treatment demonstrated significantly greater decreases in self-reported depressive symptoms. The exercise-associated decrease in MADRS did not demonstrate a dose-dependent relationship, as all three treatment groups exhibited similar declines in depressive symptoms. However, participants who completed the minimum recommended number of exercise sessions demonstrated a greater decline in MADRS score relative to TAU. Neither gender nor baseline level of physical activity were significantly associated with treatment response.

In terms of clinical applicability, this trial had several strengths. By using a randomized and blinded prospective design, the trial offers the highest level of evidence for its conclusions. It was conducted in the outpatient primary care setting, making the results relevant to primary care providers. While approximately 41% of the participants did not engage in their assigned exercise treatment, this level of noncompliance is likely similar to what would be observed in a real-world clinical setting. As expected, per protocol analysis demonstrated a larger effect of exercise in patients who completed the recommended number of exercise sessions during the study period. Consequently, the conclusions from this study are more relevant for patients who have a high likelihood of compliance with an exercise regimen.

Several factors limit the applicability of the study to our case. No data were obtained regarding the race or ethnicity of the participants. The study was conducted in Sweden, a relatively wealthy nation with a strong social safety net and nationalized healthcare system. This contrasts with healthcare access in the United States, which is substantially determined by individual socioeconomic status and insurance provider. The study focused on relatively healthy individuals, excluding those with serious somatic disorders, those with substance use disorders, or psychiatric illnesses requiring specialist care. Consequently, the results of this study are most likely to reflect outcomes in a relatively wealthy, physically healthy adult with no major somatic conditions.

One major limiting factor, the relatively short duration of the trial, was partially ameliorated by the recent publication of a follow-up study on the same participant group.12 This subsequent study compared the effects of TAU versus the three levels of exercise therapy one year after completion. All four groups of patients continued to have lower average MADRS scores at 12 months when compared to baseline. The average MADRS score in the TAU arm decreased over the nine-month gap, while the MADRS scores in the exercise groups remained stable. Despite the large and significant difference between TAU and the treatment arms in the initial study, only the light exercise group demonstrated significantly lower MADRS scores at 12-month follow-up than TAU. While this difference was statistically significant, the difference between the two groups was much smaller than observed at the 12-week endpoint.

Clinical Application

Based on this trial, aerobic exercise appears to be an effective adjunctive therapy for mild- to moderate major depression. The results from this trial indicate that individuals who participate in any level of aerobic exercise, in combination with therapy and/or medication, will see more significant short-term decreases in their depressive symptoms. Patients who engaged in adjunctive light aerobic exercise also had a slightly greater decrease in depressive symptoms one year after participating in treatment.

ISSN: 2379-4550

Clinical Research in Practice
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VOL 8 ISS 1 / eP2672 / APRIL 28, 2022
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Our patient, Mr. Farris, matched the inclusion criteria of this study. Most importantly, he was physically fit and would be able to engage in light aerobic exercise without much difficulty. In addition, he had sufficient access to healthcare and financial resources to engage in an aerobic exercise program. Consequently, despite the limitations of the study, the results are applicable to Mr. Farris. Given that Mr. Farris had successfully performed routine exercise to manage his depression, we believe he had a high likelihood of maintaining a routine exercise regimen. Given the results of this trial, we believe that his planned low-intensity regimen of walking and yoga would have a high likelihood of benefit with minimal risk of harm.

New Knowledge Related to Clinical Decision Science

There is a substantial body of literature on the use of exercise as an adjunctive therapy for depression, yet relatively few studies have interrogated the specifics of the dose/response relationship between exercise intensity and amelioration of depressive symptoms. The Regassa trial provided the first strong clinical evidence on this issue. More importantly, the study context was optimized for the outpatient primary care setting where the majority of patients with major depression initially seek care. For the field of clinical decision science, Regassa provides an example of the type of real-world, contextually valid research that can provide reliable evidence for decision-making in the clinic. Regassa used standardized measures of depression that can be easily implemented into the primary care setting. Finally, the statistical methods used for analysis were standard and relatively easy to understand for the average clinician. While limited by its geographic setting and lack of substantial socioeconomic data about the study participants, the practical and simple design implemented by Regassa permits the primary care physician to directly apply the study results to her clinical practice. By adhering to a similar methodological approach, future randomized trials designed to answer practical clinical decision questions can maximize the applicability and ease of interpretation demonstrated by the Regassa trial.

Table 1. Description of the eight most relevant randomized trials identified by PubMed search and manual screening.

Author	N	Groups	Control type	Outcome	Other considerations
Belvederi, et al., 2015 [8]	121	3 groups: Sertraline, sertraline+ high-intensity aerobic, sertraline+ low-intensity aerobic	Sertraline alone	Patients in both exercise groups had significantly higher remission rates	
Hughes, et al., 1986 [2]	14	Crossover design; no treatment vs moderate intensity exercise	Crossover study	No difference in remission was observed between two groups	Males only
Mota-Pereira, et al., 2011 [6]	33	"Usual pharmacotherapy" vs usual pharmacotherapy + home-based moderate-intensity exercise	Pharmaco-therapy	Patients in the treatment group exhibited increased rates of clinical response and admission that were not statistically significant	Limited to patients with treatment-resistant depression
Kennedy, et al., 1997 [3]	42	No control group; patients randomized to either low- or high-intensity exercise	None	Both groups exhibited decreases in depression	
Antunes, et al., 2005 [4]	46	No treatment vs. low-intensity aerobic exercise	No treatment	Treatment group exhibited significant decreases in both anxiety and depression relative to control	Limited to "sedentary seniors"
Knubben, et al., 2006 [7]	38	Placebo (stretching and relaxation) vs. walking	Placebo	Treatment group exhibited significant decreases in both anxiety and depression relative to control	Conducted in an inpatient setting

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https://doi.org/10.22237/crp/1640995680

Table 1 cont.

Singh, et al., 2005 [5]	60	3 groups: Primary care alone vs low-intensity progressive resistance training (PRC) vs high-intensity PRC	Primary care only	Only high-intensity exercise group exhibited a significant reduction in depression	Study included patients with both major and "minor" depression
Helgadóttir, et al. 2016 [1]	620	Four groups: Treatment-as-usual (TAU), TAU+light aerobic exercise, TAU+moderate aerobic exercise, and TAU+ vigorous aerobic exercise	Treatment-as-usual	All three exercise modalities with TAU demonstrated significantly larger reductions in major depressive symptoms relative to TAU alone	No placebo group; single-blind design

Conflict Of Interest Statement

The author declares no conflicts of interest.

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