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Research paper

Efficacy of exercise as an adjunct treatment for clinically depressed inpatients during the initial stages of antidepressant pharmacotherapy: An open randomized controlled trial

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ABSTRACT

Background: Physical exercise as adjunctive treatment for hospitalized patients with major depressive disorder (MDD) has been of increasing interest in the past few years. While preliminary findings are promising, these prior studies have been plagued by inclusion of participants at different stages of medication use at study entry. The present study evaluates the effects of a short (10-days) add-on endurance-training intervention in hospitalized MDD patients on antidepressant medication for less than two weeks.
Method: Thirty-five participants were randomly assigned to one of three study groups: aerobic exercise ($n=14$), placebo (stretching) exercise ($n=11$), or no intervention (control; $n=10$). The study outcome was the change in the Beck Depression Inventory (BDI-II) total score from baseline to the end of the study period.
Results: The intent-to-treat analysis showed significant improvements in BDI-II scores for both the aerobic and the stretching groups. However, comparing pre- to post-study depression changes in these two groups, we found a large effect size in favor of aerobic exercise (Cohen's $d=-1.06$). No significant change in depressive symptoms was found in the control group.
Limitations: The nature of the intervention (i.e., exercise) meant blinding participants to treatments was not possible. Precise information on medication dosage was not available, and the short duration of interventions and lack of follow-up assessment were all limitations.
Conclusions: Endurance-training can be a helpful adjunct treatment for hospitalized patients with severe affective disorders in the initial stages of pharmacotherapy.

1. Introduction

The effectiveness of physical exercise in reducing depressive symptoms has received considerable attention in the past few years, with seven meta-analyses of randomized controlled trials (RCTs) published in the last decade (Stathopoulou et al., 2006; Mead et al., 2009; Rethorst et al., 2009; Krogh et al., 2011; Rimer et al., 2012; Cooney et al., 2013; Josefsson et al., 2014). Even though reviewed RCTs vary substantially in size, type of control group, methodological rigor, and type of exercise modality, these meta-analyses yielded an overall moderate-to-large effect size (from $d=-0.40$ in Krogh et al. to $d=-1.39$ in Stathopoulou et al.) indicating a significant reduction in depression for exercise treatment compared with non-active control condition. Using information from the most recent meta-analysis (Josefsson et al., 2014), exercise programs typically last for 4–16 weeks, are predominantly aerobic in nature (brisk walking, running, stationary cycling), and include 2–3 weekly sessions of 35–40 min duration.

One major limitation to the widespread acceptance of exercise as a therapeutic routine for the treatment of clinical depression is that most of these previous RCTs were undertaken on participants with light-to-moderate levels of depression (Hamilton depression scale score <25, or Beck depression scale score <29). Very little is known about the extent to which physical exercise can reduce depression in individuals with severe symptoms at baseline.

One RCT by Knubben et al. (2007) assessed the efficacy of a short-term adjunctive aerobic training intervention (10 days of 30 min treadmill walking) in 20 inpatients with severe depressive symptoms receiving conventional treatments (antidepressants or sleep deprivation). This was compared with a placebo exercise intervention (10 days of low-intensity stretching and relaxation exercises) implemented in a control sample of 18 inpatients.

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Reduction in depression scores in the endurance-training group was significantly greater. Based on the statistics reported in their study, we estimated the effect size comparing aerobic and placebo interventions to be $d = -1.28$.

More recently, Schuch et al. (2011) evaluated the adjunctive effects of physical exercise (3 weekly sessions of aerobic training until hospital discharge) in 15 severely depressed inpatients under conventional treatment (antidepressants or electroconvulsive therapy). Obtained data were compared to those of 11 control inpatients (who received no intervention except conventional treatment). The mean score on the Hamilton depression scale significantly improved from baseline to discharge in both groups, but there was a difference at discharge in favor of the exercise group. Lack of statistical detail on the magnitude of depression changes in each group makes it impossible to compute a comparative effect size.

Although these two recent RCTs produced evidence that adding physical exercise in the treatment of severely depressed inpatients brings therapeutic benefits, several shortcomings are evident: (1) participants had received antidepressant medication for various amounts of time at study entry, (2) some were receiving other concomitant therapy (e.g., electroconvulsive therapy) in addition to pharmacotherapy, and (3), in Schuch et al., the total duration of the exercise stimulus varied between participants. Accordingly, an improved way to assess the add-on impact of exercise on depressive symptoms in severely depressed inpatients would be to recruit patients being treated only with antidepressant medication, and having identical (or similar) duration of treatment at study entry.

Therefore, in the present study we examined the efficacy of a 10-days long aerobic exercise program as an add-on treatment in severely depressed patients being treated with antidepressant medication (and no other form of therapy) for less than two weeks. Although such a training length may appear too short to be of interest, it can be expected to be effective since combined antidepressants and aerobic exercise was found to increase brain-derived neurotrophic factor (BDNF) levels in as short as two days (Russo-Neustadt et al., 2001). Depression score changes were compared with a control arm of patients being treated with only antidepressants. It was impossible to blind patients to treatment allocation because of the nature of the intervention. But to rule out the possibility of an attention effect, a placebo (stretching) add-on intervention was also implemented.

2. Method

This study was approved by the ethics committee of the psychiatric unit from which our research sample was drawn, and is registered at ClinicalTrials.gov (number NCT02612142).

2.1. Participants

To achieve 80% power with a significance level of $\alpha = 0.017$ and for an effect size of Cohen's $d = -1.28$ (based on Knubben et al. (2007)), the required number of participants per study group was 12 (*t*-tests for differences between 2 independent means; G*POWER, Faul et al., 2007). Because three comparisons were planned *a priori* (aerobic exercise *versus* control; aerobic exercise *versus* stretching; and stretching *versus* control), the criterion α-level for statistical significance was corrected using the Bonferroni procedure ($0.05/3 = 0.017$)

Between July 2011 and July 2015, 124 inpatients admitted for treatment of MDD were considered for participation in the study. Inclusion criteria were as follows: (a) diagnosis of MDD according to the DSM-IV-TR (APA, 2000), (b) antidepressant drug therapy initiated for < two weeks, (c) score of 29 or more on the Beck Depression Inventory (BDI-II, Beck et al., 1996), (d) ability to run or walk briskly and to understand written French. Patients were excluded if they (a) had a medical contraindication for exercise practice, (b) had MDD with psychotic features, (c) were receiving beta-blocking drugs or another form of therapy (e.g., sleep deprivation, electroconvulsive therapy)

Forty-eight out of these 124 screened patients were eligible, and 35 participated in the study (71.4% females, mean age: 45.3 ± 13.2 yrs). Among the remaining 13 depressed patients, 10 declined participation (the main reasons for refusal were lack of interest, and patients were feeling too ill to take part in exercise training), two were disqualified due to medical-related issues (asthma, arthritis), and one had psychotic symptoms.

One of the three study arms (aerobic exercise, stretching, no intervention) was randomly chosen for each participant at the end of an initial individual visit (explanation of study procedures, questions about drug use and drug treatment history, informed consent signature, baseline depression assessment). This was done by running the randbetween function of Microsoft Excel on our laptop, which generated a random number between 1 and 3: 1 = aerobic exercise (AE), 2 = stretching (ST), 3 = no intervention (NI). It resulted in a slightly uneven number of participants in the groups: 14 participants in the AE group, 11 participants in the ST group, and 10 control participants. The assigned intervention was started the day following the initial visit. As mentioned above, information was obtained from each patient as to type and time of onset of their antidepressant drug therapy during the initial visit. Unfortunately, due to stringent privacy legislation in France, access to individual medical records was restricted to medical staff, so that no individual information about daily dosage could be collected. However, given that all patients had recently started antidepressants in the present study (within less than 2 weeks before study entry) and given that one key recommendation for clinical practice is to treat depression at standard doses of antidepressants for a minimum of 4 to 8 weeks before labeling a treatment regimen as ineffective (Adams et al., 2008), we can speculate that all patients were receiving standard doses of antidepressants during the period of the study. These standard dosages can be found in Adams et al. (2008) and are listed in Table 1, along with other measured pretreatment characteristics.

2.2. Procedure

In the aerobic exercise (AE) group, the intervention consisted of 30 min of daily brisk walking or jogging for 10 consecutive days. Participants who missed > 2 training sessions were considered as non-completers. Exercise intensity had to be maintained within 65–75% of age-predicted maximal heart rate, as commonly prescribed in studies using aerobic exercise to alleviate depression (Perraton et al., 2010). Exercise sessions took place outdoors (the EPSMM has a large park with green areas and safe walking paths through its blocks) under the supervision of the first author (PhD in sports sciences). A total of 106 of the 115 training sessions (92.2%) were individual. Nine sessions included 2 patients for whom the exercise intervention had started almost simultaneously. A typical session lasted for approximately 45 min (generally from 5.30 pm to 6.15 pm) including installation, programming and de-installation of a heart rate monitoring device (Polar S725 chest belt and wristwatch).

Patients in the stretching (ST) group also performed a daily 30 min exercise program for 10 consecutive days, but this consisted of stretching exercises instead of endurance training. Several muscle groups (thighs, calves, gluteal, shoulders, back) were stretched for 60 s, with equivalent resting intervals between stretching series. Training sessions were carried out in a room of