Research paper

Physical exercise for late-life depression: Effects on symptom dimensions and time course

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ABSTRACT

Background: Physical exercise is increasingly recognized as a treatment for major depression, even among older patients. However, it is still unknown which depressive symptoms exercise affects most, (e.g. somatic vs. affective) and the timing of its effects. Thus, the aim of this study was to examine the changes of depressive symptoms after treatment with exercise.

Methods: We analyzed data from the SEEDS study, a trial comparing the antidepressant effectiveness of sertraline (S) and sertraline plus exercise (S + EX). Exercise was delivered thrice weekly in small groups and monitored by heart rate meters. Patients with late life depression (n = 121) were assessed at baseline, 4, 8, 12 and 24 weeks with the Hamilton Depression Scale. Scores of affective, vegetative, anxiety and agitation/insight factors were analyzed using Multilevel Growth Curve Models and sensitivity analyses (multiple imputation).

Results: Compared with the S group, patients in the S + EX group displayed significantly greater improvements of the affective symptom dimension (total effect size = 0.79) with largest changes in the first 4 weeks and last 12 weeks. Improvements were mainly driven by depressed mood and psychomotor retardation.

Limitations: Sample size; lack of an exercise only treatment arm

Conclusions: Adding exercise to antidepressant drug treatment may offer significant advantages over affective symptoms of depression, rather than somatic symptoms or other dimensions of depression. Compared with standard antidepressant treatment, clinical advantages should be expected both at an early (first 4 weeks) and later stage (after 12 weeks).

1. Introduction

Physical exercise is increasingly recognized as an effective treatment for late-life depression (Heinzel et al., 2015; Schuch et al., 2016b) but its specific effects on symptom dimensions are still largely unknown.

Major depression is regarded as one of the most prevalent and debilitating healthcare problems worldwide, with dire consequences for individuals, families, and society as a whole (Alexopoulos, 2005). Its clinical presentation is highly variable, including both "core"

depressive symptoms, such as low mood and reduced interest for activities, and somatic symptoms, such as sleep and appetite changes. In late life, the diagnosis and treatment of depression are further complicated by specific neurobiological features and by the cooccurence of physical illnesses (Naismith et al., 2012). These factors have a profound impact on response to treatments, which is lower than among younger individuals (Alexopoulos, 2005), and on its clinical presentation, which more frequently includes somatic symptoms, apathy, and psychomotor retardation (Groeneweg-Koolhoven et al., 2017; Haigh et al., 2017; Hegeman et al., 2015; Naismith et al., 2012). Notably, differences in the clinical presentation may correspond to distinct pathophysiological mechanisms and differential responses to treatment (Drysdale et al., 2017). Likewise, different treatments may have differential impact on symptom dimensions (Uher et al., 2012). Since late-life depression is characterized by suboptimal drug response and poor outcomes in the real-world clinical practice, there is an urgent need to improve the present understanding of novel therapeutic strategies and the mechanisms via which they influence the clinical features of depression (Alexopoulos, 2005).

Physical exercise is increasingly recognized as an effective tool for the management of depression. Exercise participation has been found to substantially reduce the severity of depressive symptoms (Ekkekakis, 2015; Schuch et al., 2016b), is well tolerated (Stubbs et al., 2016b), increases physical fitness (Stubbs et al., 2016a), and is among patient preferred treatment options (Luck-Sikorski et al., 2017). Studies on late-life depression broadly confirm the positive results observed among younger samples (Heinzel et al., 2015; Schuch et al., 2016b). However, the question remains whether, among older patients, the efficacy of exercise is due to "non-specific" effects on somatic symptoms (i.e. improvements of sleep, appetite, tiredness) or it also encompasses improvements in "core" depressive symptoms, such as depressed mood and lack of interest (Ekkekakis and Belvederi Murri, 2017). Considerable evidence indicates that physical exercise has the potential to both improve mood in the short term (Ekkekakis et al., 2011) and stimulate long-terms antidepressant mechanisms, such as neurogenesis (Ekkekakis, 2013; Kerling et al., 2017; Schuch et al., 2016a). Therefore, the evaluation of the effects of exercise across different symptom-dimensions over multiple time points may assist clinicians both in terms of monitoring the response to treatment and in guiding the prognosis (Iniesta et al., 2016; Uher et al., 2009).

The aim of the present study was to evaluate the effects of a program of physical exercise on symptom dimensions of late-life depression, taking in account the timing of these changes. The study was based on data from the SEEDS (Safety and Efficacy of Exercise for Depression in Seniors) trial, which randomized patients with late-life depression to antidepressant drugs or antidepressants plus structured physical exercise (Belvederi Murri et al., 2015). Our hypothesis was that patients receiving exercise in addition to antidepressants would display greater and earlier improvements in "core" depressive symptoms, compared to patients receiving only antidepressants.

2. Methods

2.1. The SEEDS study

SEEDS was a randomized trial examining the effectiveness of two exercise interventions, combined with standard antidepressant treatment, against antidepressant treatment alone. Details on the study protocol are available in a previous report (Belvederi Murri et al., 2015). Briefly, the study enrolled 121 participants aged 65 – 85 years diagnosed with Major Depression (DSM-IV TR criteria) from four centers in the region of Emilia Romagna, Italy. Participants were selected by Primary Care Physicians (PCPs) and interviewed by psychiatrists in the context of a liaison program between the Mental Health and Primary Care Departments. Other selection criteria included: a score of 18 or higher on the 17-item Hamilton Depression Rating Scale (HAM-D),

being sedentary (not meeting the recommended levels of physical activity for older adults (Nelson et al., 2007)), absence of other axis I diagnoses, substance or alcohol abuse, severe or unstable physical illness that would prevent them from exercising (e.g. severe cardiovascular disease, osteoarthritis, uncontrolled diabetes, major neurological disorders, severe respiratory disease) and cognitive impairment (Mini Mental State Examination score of 24 or higher). Participants were given information on the study interventions and on the effects of exercise during meetings with their PCPs and study staff.

Of 177 participants who were referred by PCPs for evaluation, 121 fulfilled inclusion criteria and were randomized to study interventions. Participants were assigned to 1) sertraline (S; n = 42); 2) sertraline plus supervised group non-progressive exercise (S + NPE; n = 37), or 3) sertraline plus supervised group progressive aerobic exercise (S + PAE; n = 42). All patients received sertraline at a starting dosage of 50 mg, with later increases according to the clinical course. Participants in the S + NPE arm additionally attended three supervised group non-progressive exercise sessions (NP) per week in groups of 3–6 participants (60-min duration). Patients in the S + PAE group attended exercise sessions with a similar schedule to that of NP but exercised on bikes with a preplanned increase of the workload over the course of the study. The protocol also included brief sessions of interval training. Exercise sessions were supervised by medical and sport-science staff. Heart rate was continuously monitored to adapt the exercise intensity to individual aerobic capacity, which had been assessed by a peak oxygen uptake test. The total duration of the study was 24 weeks. The protocol of study interventions are briefly described in the Supplementary materials (Appendix).

The primary outcome of the study was remission from depression, defined as a total score of 10 or less on the HAM-D at study end. A total of 15 participants withdrew from the study, but where included in the Intention to Treat analyses (Belvederi Murri et al., 2015). Six withdrew from the S group (four unwilling to continue, two for medical problems) and nine from the exercise groups (six unwilling to continue, two for medical problems and one for need of higher level of care). Since the groups receiving sertraline plus exercise displayed similar rates of remission from depression (S + PAE: 81%; S + NPE: 73%), for the aims of the present study they were combined into a sertraline plus exercise group (S + EX, n = 79, remission rate: 77%), to be contrasted with the sertraline-only group (S, n = 42, remission rate: 45%).

2.2. Assessment of symptoms

Depressive symptoms were assessed with the HAM-D at baseline, 4, 8, 12, and 24 weeks. Raters were certified psychiatrists experienced in psychogeriatrics. To improve inter-rater reliability, raters from each center participated in training sessions that included discussion of example cases. Symptom dimension scores were computed based on a previous factor analysis of the HAM-D conducted with a sample of 206 community-dwelling elderly individuals (Onega and Abraham, 1997). The analysis yielded four factors: (1) *affective* (depressed mood, guilt, suicide, work and activities, psychomotor retardation, loss of energy, loss of libido; items 1, 2, 3, 7, 8, 13, 14); (2) *vegetative* (initial, middle, and delayed insomnia, loss of appetite, loss of weight; items 4, 5, 6, 12, 16); (3) *anxiety* (psychological anxiety, somatic anxiety, hypochondriasis; items 10, 11, 15); (4) *agitation/insight* (agitation, lack of insight; items 9 and 17). To compute symptom dimension scores, item scores were summed and divided by the number of items in each factor. For descriptive purposes, at baseline, the participants also completed a battery of instruments assessing cognitive status, disability (Montreal Cognitive Assessment, MOCA) (Santangelo et al., 2014), physical comorbidities (Cumulative Illness Rating Scale, CIRS) (Miller et al., 1992) and other relevant variables (Neviani et al., 2017).