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Exercise and severe major depression: Effect on symptom severity and quality of life at discharge in an inpatient cohort

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ABSTRACT

Background: Exercise is a potential treatment for depression. However, few studies have evaluated the role of adjunct exercise in the treatment of severely major depressed inpatients. The goal of this study was to evaluate the effects of add-on exercise on the usual treatment of severely depressed inpatients. *Methods:* Fifty participants were randomized to an exercise (exercise + usual treatment) or a control (usual treatment) group. Twenty-five patients were randomly allocated to each group. The participants in the exercise group performed three sessions per week throughout the hospitalization period, with a goal dose of 16.5 kcal/kg/week plus the usual pharmacological treatment. Depressive symptoms and the Quality of Life (QoL) of the participants were assessed at the baseline, the second week, and discharge. *Results:* A significant group × time interaction was found for depressive symptoms and the physical and psychological domains of QoL. Differences between groups occurred at the second week and discharge with respect to depressive symptoms and the physical and psychological domains of QoL. There was no difference in the remission rate at discharge (48% and 32% for the exercise and control group, respectively). An NNT of 6.25 was found. No significant baseline characteristics predict remission at discharge. *Conclusion:* Add-on exercise is an efficacious treatment for severely depressed inpatients, improving their depressive symptoms and QoL. Initial acceptance of exercise remains a challenge.

1. Background

Depression is a highly prevalent condition with a life-long prevalence of approximately 12% in Brazil and 17% in the United States (Andrade et al., 2003). Moreover, depression is a leading cause of disability worldwide, accounting for 40.5% of the disability-adjusted life years (DALYs) caused by mental and substance-use disorders (Whiteford et al., 2013).

Currently, the first option for the treatment of depression is pharmacological antidepressants (Nemeroff, 2007). Despite the wide use of such antidepressants, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that only approximately 18% of patients remitted after 14 weeks of an adequate trial of a single agent (citalopram). In the second phase, after switching or augmentation of treatment, the remission rates ranged from 18% to 30% (Sinyor et al., 2010).

In severe depression, electroconvulsive therapy (ECT) is indicated as the most effective strategy; however, the side effects (memory impairment, nausea, headache, and temporary confusion) and the cardiovascular and neurological risks limit its broader use (Nemeroff, 2007). Also, despite approximately 50% of patients submitted to ECT were satisfied with the results, only 36% would only 36% would agree to perform an ECT again (Antunes et al., 2009).

Exercise, in contrast, is receiving much attention as a therapeutic option for depression (Daley, 2008; Deslandes et al., 2009; Mura et al., 2014; Schuch and de Almeida Fleck, 2013; Stanton and Happell, 2014; Stanton and Reaburn, 2014; Strohle, 2009). Indeed, several meta-analyses have revealed that exercise has at least a moderate effect on symptom reduction in major depression, serving as a useful strategy for depression of different severities and presenting few side effects (Cooney et al., 2013; Craft and Landers, 1998; Rethorst et al., 2009; Stathopoulou et al., 2006). Despite these

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encouraging results, most studies have evaluated the effects of exercise on moderately depressed outpatients (Cooney et al., 2013; Craft and Landers, 1998; Rethorst et al., 2009; Stathopoulou et al., 2006) and only two evaluated in samples that were also composed by severely depressed inpatients. The studies, however, were not exclusively composed by severely depressed inpatients (one had bipolar patients and the other did not used any criterion excluding bipolar depressed inpatients (Knubben et al., 2007; Martinsen et al., 1985).

Depression significantly affects Quality of Life (QoL) (Angermeyer et al., 2002; Berlim et al., 2004, 2005; Caldieraro et al., 2013), and some evidence points to an inverse relationship between depression intensity and QoL (Caldieraro et al., 2013). Furthermore, some studies have revealed that, even after achieving remission, some inpatients still experience impairments in QoL (Angermeyer et al., 2002; IsHak et al., 2011). In contrast, exercise has positive effects on some QoL domains in healthy individuals (Gill et al., 2011; Gillison et al., 2009) and in moderately depressed patients (Brenes et al., 2007; Carta et al., 2008; Mota-Pereira et al., 2011a; Schuch et al., 2011b).

To the best of our knowledge, no study has evaluated the effects of exercise on depressive symptoms and QoL on a sample composed exclusively of severely depressed (HAM-D > 25) inpatients. The primary aims of the present study were the following: 1) evaluate the effects of add-on exercise to the usual treatment on the depressive symptoms (reduction of symptoms, remission and response rates) of severely depressed inpatients. The secondary outcomes were QoL, adherence and the predictors of response to adjunct exercise on severely depressed inpatients.

2. Methods

2.1. Trial design

The study was a randomized, controlled trial with two parallel arms. It was designed to evaluate the effects of add-on exercise in the treatment of severely depressed inpatients. The study was conducted in a single center in a university hospital (Hospital de Clinicas de Porto Alegre, Brazil). The study was approved by the local ethics committee (07–438) and was registered as a clinical trial (www.clinicaltrials.gov) (Register: NCT01899716).

2.2. Participants

Eligible participants were major depressed inpatients evaluated trough the Mini International Neuropsychiatric Interview (MINI) according to the DSM-IV criteria (American Psychiatric Association, 1994). The inclusion criteria were the following: score of 25 or higher on the Hamilton scale for depression (HAM-D), indicating very severe depression (Hamilton, 1967), not being involved in other physical activity programs during the hospitalization, aged between 18 and 60 years and possession of the capacity to read, understand and sign the informed consent statement. The exclusion criteria were as follows: current use of beta-blocking medications, psychiatric diagnosis of bipolar depression, schizophrenia, anorexia, dependence or abuse of alcohol or other drugs, three or more cardiovascular risk factors on the Physical Activity Readiness Questionnaire (PAR-Q) (Thomas et al., 1992) or any medical condition that limits or contraindicates the practice of exercise.

2.3. Interventions

The participants were randomized in two groups: exercise + treatment as usual (intervention) or treatment as usual (usual care). Randomization was conducted by individuals not directly involved in the study and assigned using opaque envelopes without contact with the outcome assessors.

Exercise + treatment as usual: The intervention group had to complete a weekly exercise dose of 16.5 kcal/kg of weight/week of aerobic exercise with a frequency of three times per week. For example, a participant weighing 70 kg had to perform exercise equivalent to 1120 kcal per week. This amount was divided by three to yield a goal of 373 kcal per session. The exercise dose could be completed using three modalities, stationary bike (CICLE CL 204, CALOI, Brazil), treadmill (ADVANCED 3, ATHLETIC, Brazil) or a "transport" machine (CL 603, CALOI, Brazil). This method was planned to be flexible such that the participants could choose the preferred intensity, instead of a fixed intensity or time of exercise, to complete the daily requirement. This strategy was planned to be consistent with public health recommendations, and because it is flexible, the strategy is feasible for depressed individuals (Dunn et al., 2002, 2005; Trivedi et al., 2011, 2006a, 2006b).

The exercise sessions were performed individually and supervised by a research staff (FBS). The research staff instructed the patients beforehand on the proper use of the exercise machines and on how to complete the targeted exercise "dose". The staff only assisted patients regarding exercise-related topics. No structured or components of motivational or cognitive strategies were used. The participants wore heart-rate monitors (Polar cs200, Finland) during the sessions to evaluate their energetic expenditure during the sessions. The exercise data, including the total time of exercise, average intensity, and energetic expenditure, were collected by the research staff. During the sessions, the participants had the option of listening to music according their preferred local radio station.

The sessions were composed of a warm-up, exercise bout, and cool-down. The warm-up consisted of stretching exercises for the lower limbs, 20 s for each of the following muscular groups: hip extensors, hip flexors, hip adductors, and plantar flexors followed by 4 min of walking at 5 km/h on the treadmill. During the exercise bout, the participants could use different combinations of exercise between or within the sessions according to their preferences. The cool-down was similar to the warm-up. Throughout the study, the participants received other treatments such as antidepressants and/or electroconvulsive therapy (ECT).

Treatment as usual: The participants in the usual care group received their treatment as usual, which consisted of antidepressants and/or ECT. The pharmacological treatments and their respective doses were recorded.

All participants had access to occupational activities. The patients were not receiving psychotherapy. The pharmacological treatments and the date for discharge were decided by staff that were independent of the study.

2.4. Assessments, recruitment and outcomes

The aerobic capacity (VO_2), the clinical diagnosis and the resting heart rate were assessed at baseline. The caloric expenditure was calculated for each session. Patients were recruited during the first 24 h of hospitalization, and outcome assessments were performed at three points: at the baseline (between 24 and 48 h of hospitalization), the second week of the study (after 14–15 days of the baseline assessment) and discharge (0–24 h before discharge).

2.5. Heart rate

The resting heart rate was determined after each participant sat for 5 min using a digital heart rate monitor (Polar cs200, Finland). The maximum heart rate was estimated using the formula proposed by Tanaka (Tanaka et al., 2001). Participants' reserve heart