Journal of Psychiatric Research 45 (2011) 1005–1011

psychiatric research

Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder

Jorge Mota-Pereira [a,b,*], Jorge Silverio [b], Serafim Carvalho [a], Jose Carlos Ribeiro [c], Daniela Fonte [d], Joaquim Ramos [e]

[a] Porto Psychiatric Department, Hospital Magalhaes Lemos, Porto, Portugal
[b] School of Psychology, University of Minho, Portugal
[c] Research Center in Physical Activity Health and Leisure, Faculty of Sports, University of Porto, Portugal
[d] Radiotherapy Department, Hospital S. Joao, Porto, Portugal
[e] Psychosocial Rehabilitation Department, Hospital Magalhaes Lemos, Porto, Portugal

ARTICLE INFO

Article history:
Received 18 November 2010
Received in revised form
31 January 2011
Accepted 10 February 2011

Keywords:
Exercise
Major depressive disorder
MDD
Treatment-resistant

ABSTRACT

Background: Treatment-resistant major depressive disorder (MDD) is a complex condition, with very low remission rates. Physical exercise has been used, with some encouraging results, as an alternative therapy in other depressive disorders. This study assessed the impact on depression and functioning parameters of a moderate intensity exercise program, as an adjuvant to pharmacotherapy, in treatment-resistant MDD patients.

Methods: 150 individuals with treatment-resistant MDD, defined as taking combined therapy in doses considered adequate for 9–15 months, without showing clinical remission, were initially screened. 33 were randomized to one of two groups: usual pharmacotherapy ($N = 11$) and usual pharmacotherapy plus aerobic exercise ($N = 22$). The exercise program consisted of home-based 30–45 min/day walks, 5 days/week, for 12 weeks, being 1 walk per week supervised.

Results: The exercise group showed improvement of all depression and functioning parameters, as indicated by lower HAMD17, BDI and CGI-S and higher GAF ($p < 0.05$) at last observation compared both to baseline values and to control group. At the end of the study none of the participants in the control group showed response or remission, whilst in the exercise group 21% of participants showed response and 26% remission, although these differences were not statistically significant.

Conclusion: A 12 week, home-based exercise program of 30–45 min/day walks, 5 days/week, improved depression and functioning parameters in treatment-resistant MDD patients, and contributed to remission of 26% of these patients. Moderate intensity exercise may be a helpful and effective adjuvant therapy for treatment-resistant MDD.

1. Introduction

Major Depressive Disorder (MDD) is a complex, multifactorial, multigenic condition, which, as all psychiatric disorders at present, is of unknown pathophysiology (Cichon et al., 2009). Due to the paucity of information regarding the underlying mechanisms, therapeutic approaches to MDD are mainly symptomatical, but aim at achieving full remission (Kurian et al., 2009). However, and despite the combined use of psychotherapy, a variety of antidepressants with optimized dose and duration of treatment, and combined strategies of therapeutic enhancement, remission rates remain modest (Koenig and Thase, 2009; Kurian et al., 2009), with over 60% of patients meeting the criteria for treatment-resistant depression (Trivedi and Daly, 2008). MDD is the leading cause of years of life lived with disability (YLDs) worldwide, accounting for 11.9% of total YLDs, and it is estimated that by the year 2020 it will be second only to ischemic heart disease for disability-adjusted life years (DALYs) lost for both sexes (World Health Organization, 2001). Given this dismal scenario, several non-pharmacological strategies have been considered as possible complementary therapies to help improve MDD prognosis and remission rates, namely exercise, light therapy and sleep deprivation (Howland, 2010).

It has been recognized for several years that performing regular exercise is cardioprotective, decreasing the incidence of cardiovascular diseases such as hypertension, coronary artery disease, type 2 diabetes and atherosclerosis (Powers et al., 2002), and the

* Corresponding author. Hospital Magalhaes Lemos, Rua Prof. Alvaro Rodrigues, 4149-003 Porto, Portugal. Tel.: +351 934 424 377; fax: +351 226 184 084.
E-mail address: dr.motapereira@gmail.com (J. Mota-Pereira).

0022-3956/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2011.02.005

practice of moderate intensity exercise for at least 30 min on most days of the week has been recommended by NIH since 1996 (NIH Consensus Development Panel on Physical Activity and Cardiovascular Health, 1996). Moreover, besides provenly cardioprotective, exercise has shown a positive association with psychological well-being (Hassmen et al., 2000), and therapeutic benefits in older people with depressive disorder (Mather et al., 2002), depression symptoms in patients with Alzheimer's disease (Teri et al., 2003) and MDD (Dimeo et al., 2001; Babyak et al., 2000; Pilu et al., 2007). Although there is still some controversy concerning exercise intensity and frequency, and duration of exercise program, current recommendations are the adoption of a moderate intensity exercise program of at least 30 min on most days of the week, for 10–12 weeks (aan het et al., 2009).

The possible advantages of exercise as an effective therapeutic adjuvant to MDD are, in many ways, attractive: exercise is an inexpensive therapy that brings several health benefits, improves general well-being, and may fill the time lag of 3–4 weeks that antidepressants require before showing therapeutic effects (Fornaro and Giosue, 2010).

However, before adopting this clearly advantageous therapy, there is still a need for more information on how different clinical populations, in diverse settings will respond to different exercise programs. In fact, in their meta-analysis, Lawlor and Hopker concluded that the effects of exercise on depression could not be determined due to the lack of good quality studies, with proper controls, adequate follow-up and undertaken in clinical populations (Lawlor and Hopker, 2001).

In the present randomized, two-arm, parallel assignment study, non-remitted MDD patients undergoing combined pharmacological therapy for 9–15 months with no adjuvant exercise therapy were compared to patients with the same diagnosis that enrolled a 12 week moderate intensity aerobic exercise program.

2. Methods

2.1. Study design

Prospective, randomized, investigator blinded, two-arm, parallel assignment.

2.2. Participants

Between September 2009 and March 2010, 150 individuals attending the out-patient psychiatry clinic at Hospital de Magalhães Lemos, Porto, Portugal, diagnosed with major depressive disorder for more than 9 months and less than 15 months, were screened through an interview with a psychiatrist. Of the 45 individuals diagnosed with MDD according to DSM-IV criteria, taking combined therapy in doses considered adequate (American Psychiatric Association, 2000; American Psychiatric Association, 2005) during this period, without showing clinical remission, 33 met the study criteria and accepted to participate in the study. These were randomized following a 1:2 scheme to one of two groups: control ($N = 11$) and aerobic exercise ($N = 22$). Patients were considered treatment-resistant if they failed to reach symptomatic remission after at least 2 adequate antidepressant trials (Malhi et al., 2005). APA guidelines were followed regarding adequacy of dose and duration of treatment and class of medications administered (American Psychiatric Association, 2000; American Psychiatric Association, 2005). Remission was defined as having an HAMD17 total score ≤ 7. The study protocol was approved by Hospital de Magalhães Lemos Institutional Review Board. All participants provided written informed consent.

2.3. Inclusion and exclusion criteria

Inclusion criteria: 1) males or females aged 18–60 years; 2) able and willing to provide written informed consent; 3) diagnosed for major depressive disorder and taking combined therapy in doses considered appropriate for more than 9 months and less than 15 months, without showing clinical remission; 4) physical fitness to endure moderate intensity exercise confirmed in writing by attending physician; 5) normal ECG.

Exclusion criteria: 1) psychiatric co-morbidities; 2) relevant clinical co-morbidities; 3) psychotic symptoms; 4) imminently suicidal; 5) undergoing psychotherapy; 6) change of pharmacological therapy less than 6 weeks prior to beginning of exercise program; 7) not already participating in regular aerobic exercise.

2.4. Study protocol

Exercise group: 22 individuals were assigned moderate intensity exercise (NIH Consensus Development Panel on Physical Activity and Cardiovascular Health, 1996), in addition to their usual pharmacological therapy. Exercise consisted of 30–45 min/day walks, 5 days/week, for 12 weeks. Of the 5 walks per week, 1 was supervised and the other 4 unsupervised. The supervised weekly walk took place at the Hospital Gymnasium, on a treadmill set to 5 km/h, with an inclination of 0°, in the presence of a Physical Training Teacher. These sessions were not only measured by treadmill speed but also by the GT1M accelerometer. Accelerometer counts above 1952 per minute are considered moderate, and we have evaluated those counts during the exercise session. The chosen speed of 5 km/h was due to the fact that some studies (Freedson et al., 1998; Ekelund et al., 2002) have reported that, on average, speeds above 4.8 km/h will represent around 12.8–13.9 ml kg^{-1} min^{-1} or 3.7–4 METs, which is in accordance with the >3 METs needed for the exercise to be considered moderate. During these sessions, participants were taught walking and behavioral techniques. Behavioral techniques focused on reminding the participant to exercise by placing the tennis shoes at the door entrance, leave a note at the main door reminding them to walk, and use cell phone reminders with a specific tone ring. Social strategies were also adopted, not only be the gymnasium technicians and the doctors, that always stressed the importance of complying with the exercise program, but also by asking the participants' family members to be involved in the process.

At the end of each session, participants were asked by the teacher to perform the remaining 4 walks of that week where they felt more comfortable, trying to reach the same exercise intensity of the treadmill walk. In order to have a measure of the subjective intensity of exercise, a rate of perceived exertion was used: participants were asked to walk in a way that would increase their respiration and perspiration, but without reaching shortness of breath.

All individuals wore an ActiGraph® GT1M LLC two-dimensional accelerometer permanently during the 12 week study period, except when they were sleeping. On their weekly visits to the Hospital Gymnasium, compliance to the exercise on the previous week was confirmed from accelerometer data. Control group: 11 individuals who were not assigned any exercise and remained taking their usual pharmacological therapy. All individuals wore an ActiGraph® GT1M LLC two-dimensional accelerometer permanently during the 12 week study period, except when they were sleeping. Once a week, individuals from the control group went to the Hospital Gymnasium, where they interacted with the teacher, the technicians and with each other for 30–45 min. During these visits, participants received instructions on how to use the accelerometer and data from the previous week was downloaded. These visits were scheduled for

a period when no-one was using the treadmills. Behavioral techniques were also adopted with the control group, and focused on reminding the participant to use the accelerometer by placing it on the nightstand or use cell phone reminders with a specific tone ring. Social strategies were also adopted, not only be the gymnasium technicians and the doctors, that always stressed the importance of wearing the accelerometer every day, but also by asking the participants' family members to be involved in the process. Both groups maintained the pharmacological therapy unchanged during the 12 week study period.

All patients were medicated with non-sedating antidepressants in doses considered therapeutic (Taylor et al., 2009). Clomipramine, maprotiline and amitriptyline were used as tricyclic antidepressants at a dose of 125–150 mg/day; as SSRIs fluoxetine, escitalopram, paroxetine and sertraline were used, at doses of 20–40 mg/day, 20 mg/day, 20–40 mg/day and 100–150 mg/day, respectively; venlafaxine was used as SNRI at a dose of 150 mg/day. When considered appropriate, lorazepam was used as anxiolytic at a dose of 1–2.5 mg/day.

All participants were evaluated at baseline (time 0: before starting the physical activity program), and at 4, 8 and 12 weeks for depressive symptoms, functional assessment, hemodynamic and anthropometric parameters. The Psychiatrist or Clinical Psychologist evaluating HAMD17, CGI and GAF were blinded to the group the patient had been assigned to. Laboratory evaluations were taken at baseline and at the end of the study protocol (12 weeks).

2.5. Depression and functioning assessments

Depression was assessed by the HAMD17 total score (Hamilton, 1960) and the Beck depression inventory (BDI-II) (Kessler et al., 2004). Functioning was assessed using the Global Assessment of Functioning (GAF) (Greenberg and Rosenheck, 2005) and the severity subscale of the Clinical Global Impression Scale (CGI-S) (Guy, 1976). HAMD17 and BDI total scores range from 0 to 52 and 0 to 63, respectively, with higher scores indicating greater depression severity. GAF provides a rating of psychological, social and occupational functioning, ranging from 0 to 100; scores higher than 90 indicate superior functioning, between 90 and 70 slight impairment, and lower than 70 clinical impairment. The CGI-S is a single item scale, ranging from 1 (normal) to 7 (among the most extremely ill patients).

Response and remission rates were based on HAMD17, with response defined as a decrease from baseline to endpoint of $\geq$50% on the HAMD17 total score and remission defined as an endpoint HAMD17 total score $\leq$7.

2.6. Anthropometric and hemodynamic parameters

Body mass index (BMI) was calculated as weight divided by squared height (Kg/m^2). Blood pressure and heart rate were evaluated by oscillometry with a Dinamap Critikon® monitor attached to cuffs of an appropriate size, as recommended (Frohlich et al., 1988). Each participant was asked to sit quietly for 5 min and then four recordings were taken, at 2-min intervals, from the right arm at heart level. The first recording was always rejected; the final value was taken as the mean of the three subsequent recordings.

2.7. Laboratory evaluation

After 12-h fasting, venous blood samples were obtained from an antecubital vein. Serum values of total cholesterol, LDL-cholesterol and HDL-cholesterol were evaluated in clinical laboratories, using validated methods.

2.8. Compliance assessment and definition

All participants included in the exercise group were given a diary and asked to register daily whether or not they had exercised and for how long. Compliance to the exercise program was based on accelerometer data, which was consistent with the participants' diaries. Participants in the control group registered daily at what time they put on and took off the accelerometer.

Compliance was defined as completion of at least 50% of the walks per week during the 12 weeks. This definition was based on three criteria: 1) engaging in physical exercise for 3–5 days per week is in accordance with international recommendations (Haskell et al., 2007); 2) considering that several participants got out of bed specifically and solely to comply to the exercise program, at least 3 sessions in five was considered reasonable and 3) statistical analysis of the results showed that including participants that completed at least 50% of the walks or excluding them, only including those that completed 100% of the walks, did not change statistical significance for any of the studied parameters.

2.9. Statistical analysis

For baseline demographic and clinical characteristics, *t*-tests or Fisher exact tests were used for continuous and discrete variables. Differences between and within treatment groups in the change from baseline to endpoint (12 weeks) and data concerning the 4 time points (baseline, 4, 8 and 12 weeks) were analyzed using an analysis of covariance (ANCOVA) with baseline values as covariates. In the case of significant differences, post hoc tests using the Sidak correction were performed. Differences in response and remission between exercise groups were assessed using the Fisher exact test. Differences on depression and functioning parameters between no response, response and remission groups were analyzed at baseline with ANOVA and with ANCOVA using baseline values as covariates in the change from baseline to endpoint. Tests were considered significant at $\alpha = 0.05$ significance level (two-sided).

3. Results

3.1. Study population and baseline values

Of the 33 participants included in the study, 1 from the control group and 1 from the exercise group only attended the first appointment and were excluded from analysis. 2 participants from the exercise group were excluded due to non-compliance with the exercise program, assessed based on accelerometer data. There was a 6% overall drop-out rate and a 91% compliance to the exercise program. Baseline demographics and psychiatric profile are shown in Table 1. Participants included in the exercise group differed significantly from individuals in the control group, showing greater depression severity (higher HAMD17 and BDI total scores) and worse functioning (lower GAF and higher CGI-S). Both groups showed functional clinical impairment, as indicated by a GAF lower than 70. As for age, gender and BMI, the groups did not differ significantly.

There was no difference in pharmacological agents used between the exercise and the control groups: $p = 0.265$ and $p = 1.000$, for the antidepressants and the anxiolytic, respectively.

3.2. Mean changes from baseline to last observation

The exercise group showed improvement of all depression and functioning parameters, as indicated by lower HAMD17, BDI and CGI-S and higher GAF at last observation compared to baseline values. Also, comparison of the control group with the exercise

Table 1
Baseline demographics and psychiatric profile.

	Control group ($n = 10$)	Exercise group ($n = 19$)	p value*
Age (years)			
Mean (sd)	45.33 (3.11)	48.68 (2.30)	0.385
Range	26–60	26–60	
Gender, n (%)			
Female	8 (80.0)	11 (57.9)	0.110
BMI			
Mean (sd)	29.02 (2.46)	26.30 (1.03)	0.247
HAMD17 total score			
Mean (sd)	13.00 (1.42)	19.32 (1.69)	0.014
BDI			
Mean (sd)	17.83 (1.93)	24.68 (2.07)	0.031
GAF			
Mean (sd)	66.50 (2.76)	53.84 (2.55)	0.003
CGI – Severity			
Mean (sd)	2.67 (0.31)	3.89 (0.30)	0.010

* Independent samples t-test or Fisher exact test.

group concerning last observation shows that the exercise group has lower HAMD17, BDI and CGI-S and higher GAF than the control group (Table 2). Hemodynamic, anthropometric and lipid profile parameters showed no differences, either between-groups or within-groups (Table 3).

3.3. Mean changes over the 12 week study period

Analysis of the 4 time points – baseline, 4, 8 and 12 weeks – shows that mean change on HAMD17 on exercise group is significantly lower than baseline at 4, 8 and 12 weeks, being also lower than the control group at the end of the study (Fig. 1). The mean change on GAF is significantly higher than baseline at 8 and 12 weeks, being also higher than the control group at the end of the study (Fig. 2). BDI and CGI-S mean changes were lower than the control group at the end of 12 weeks (-6.5 ± 10.2 vs 4.3 ± 5.2, $p < 0.05$ and -0.9 ± 1.2 vs 0.3 ± 0.7, $p < 0.05$, respectively).

3.4. Response and remission at the end of the study

At the end of the study none of the participants in the control group showed response or remission, whilst in the exercise group 4 (21%) participants showed response and 5 (26%) remission, although these differences were not statistically significant (Table 4).

There was a difference in pharmacological agents used between responders and non-responders concerning the antidepressants – $p = 0.018$ – with non-responders being more heavily medicated than responders. There was no difference in pharmacological agents used between responders and non-responders concerning the anxiolytic: $p = 1.000$. There was also no difference concerning antidepressants between remitters and either responders or non-responders ($p = 0.524$ and $p = 0.185$, respectively) or the anxiolytic ($p = 1.000$ in both cases).

Table 2
Mean changes of psychiatric profile parameters from baseline to last observation.

	Control group ($n = 10$) Mean change (sd)	Exercise ($n = 19$) Mean change (sd)	p value[a]	p value[b]
HAMD17 total score				
Mean (sd)	0.60 (0.96)	−6.84 (1.47)	<0.0001	0.014
BDI				
Mean (sd)	4.30 (1.65)	−6.47 (2.35)	0.001	0.016
GAF				
Mean (sd)	−5.44 (1.02)	8.05 (2.51)	<0.0001	0.006
CGI-Severity				
Mean (sd)	0.33 (0.236)	−0.89 (0.26)	0.002	0.033

[a] Within-groups from ANCOVA with baseline values as covariate.
[b] Between-groups from ANCOVA with baseline values as covariate.

Table 3
Mean changes of hemodynamic, anthropometric and lipid profile parameters from baseline to last observation.

	Control group ($n = 10$) Mean change (sd)	Exercise ($n = 19$) Mean change (sd)	p value[a]	p value[b]
SBP				
Mean (sd)	6.73 (21.81)	0.26 (11.94)	0.248	0.153
DBP				
Mean (sd)	0.27 (14.75)	−3.79 (9.26)	0.340	0.419
PP				
Mean (sd)	6.45 (19.57)	4.05 (10.18)	0.503	0.140
BPM				
Mean (sd)	1.91 (14.02)	−2.84 (11.77)	0.237	0.410
BMI				
Mean (sd)	0.29 (1.54)	−0.08 (0.95)	0.403	0.206
Total cholesterol				
Mean (sd)	−8.58 (78.54)	12.858 (39.84)	0.742	0.804
HDL-cholesterol				
Mean (sd)	1.11 (21.45)	4.55 (12.55)	0.503	0.493
LDL-cholesterol				
Mean (sd)	−4.39 (53.63)	6.32 (35.48)	0.587	0.814

[a] Within-groups from ANCOVA with baseline values as covariate.
[b] Between-groups from ANCOVA with baseline values as covariate.

3.5. Baseline and endpoint values depending on response to treatment

Participants who remitted showed improvement of all depression and functioning parameters, as indicated by lower BDI (7.0 ± 2.6 vs 17.6 ± 9.9, $p < 0.05$) and CGI-S (1.2 ± 0.5 vs 2.8 ± 1.3, $p < 0.05$) and higher GAF (79.0 ± 7.2 vs 63.4 ± 7.6, $p < 0.05$) at last observation compared to baseline values. GAF baseline values of participants who remitted were higher than baseline values of non-responders (63.4 ± 7.6 vs 49.1 ± 11.3, $p < 0.05$) and, although not statistically significant, participants that showed remission also had lower HAMD17 total scores at baseline than participants that showed only response or no response (13.00 ± 4.6, 22.75 ± 5.3 and 17.64 ± 7.1, respectively, $p > 0.05$) (Fig. 3).

4. Discussion

Although exercise has been recognized for years as important for the general well-being, the effects of exercise on specific populations of diverse psychological conditions has been subject to debate, and although the majority of studies have shown positive results (Babyak et al., 2000) (Blumenthal et al., 2007; Dimeo et al., 2001; Mather et al., 2002; Pilu et al., 2007; Trivedi et al., 2006) others have been less encouraging (Kerse et al., 2010; Sims et al., 2006). This may be due to the different clinical conditions of the studied populations, different degrees of disease severity, pharmacotherapy, study design, outcome assessment and types of exercise programs.

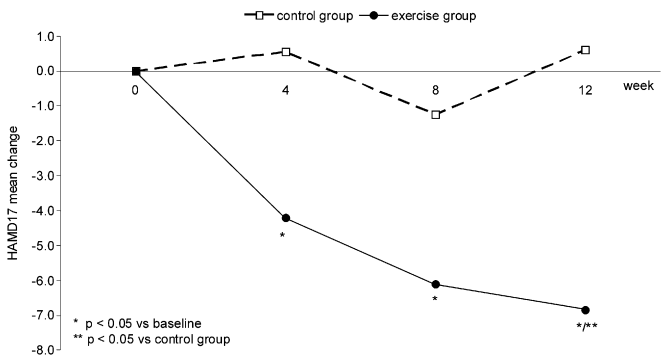

Fig. 1. p-values from ANCOVA with baseline values as covariate.

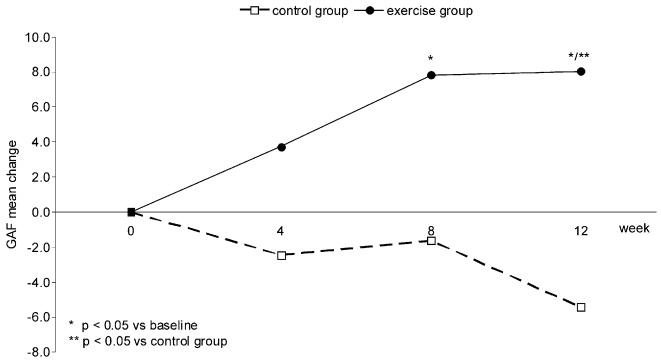

Fig. 2. *p*-values from ANCOVA with baseline values as covariate.

The present study focused on a very specific population of MDD patients who showed no remission and most not even improvement after 9–15 months of combined pharmacological therapy.

Baseline values were different for the exercise group and the control group, with the exercise group showing more severe symptoms. However, since this was a randomized study, any baseline value group difference is due to sampling error, and analysis of data using ANCOVA is appropriate (Van Breukelen, 2006).

All the assessed depression and functioning parameters improved on the exercise group, which has also shown better scores of all these parameters at the end of the study, when compared to the control group. These results are in accordance with previous reports concerning the positive effects of aerobic exercise in patients with MDD (Blumenthal et al., 2007; Pilu et al., 2007; Trivedi et al., 2006), and, beyond that, due to some aspects of this study design, may contribute to the explanation of some questions raised by previous studies, namely some negative ones (Kerse et al., 2010; Sims et al., 2006).

First of all, drop-out (6%) and compliance (91%) rates were encouraging, and compare to similar studies in other depressed populations (Blumenthal et al., 2007; Singh et al., 1997). Others have reported lower adherence rates, suggesting that either health related issues or motivational reasons would be responsible for these (Mather et al., 2002; Sims et al., 2006). We propose that each specific pathology and its severity must be evaluated, and the most adequate exercise program, combined with the proper motivational intervention, should be specifically designed. Since the patients included in this study had particularly severe MDD, we have designed an exercise program that we believed fit their needs: a home-based, walking program, with a motivational group class once week for 12 weeks, which proved effective in encouraging these patients to adhere to the exercise program.

Table 4
Response and remission in the control group and the exercise group.

	Control group ($n = 10$)	Exercise group ($n = 10$)	p value*
No response			
n	10	10	
Baseline mean HAMD17 (sd)	14.00 (4.76)	21.10 (7.64)	
Final mean HAMD17 (sd)	14.60 (4.25)	18.20 (5.63)	
Response			
n	0	4	0.094
Baseline mean HAMD17 (sd)	–	22.75 (5.31)	
Final mean HAMD17 (sd)	–	8.75 (0.96)	
Remission			
n	0	5	0.061
Baseline mean HAMD17 (sd)	–	13.00 (4.64)	
Final mean HAMD17 (sd)	–	4.00 (1.23)	

* Fisher exact test vs no response.

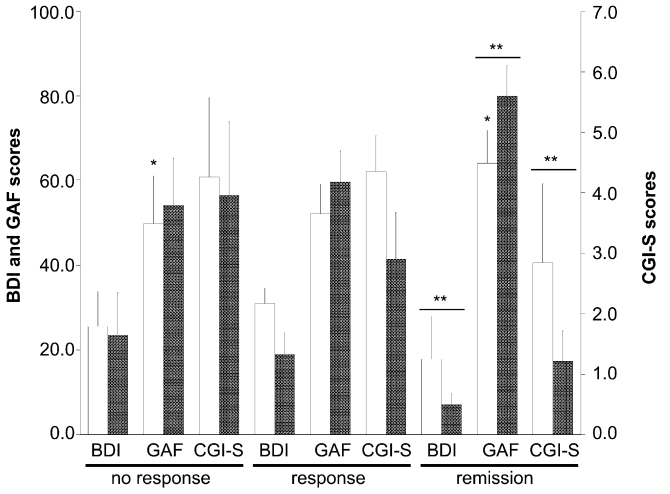

Fig. 3. Bars represent mean ± standard deviation; white bars represent basal values; black bars represent values at the end of the study; $^{*}p < 0.05$ for baseline, from ANOVA; $^{**}p < 0.05$ from baseline to endpoint, from ANCOVA with baseline values as covariate.

The improvement on all assessed depression and functioning parameters in the exercise group was also encouraging. Others have reported similar results in treatment-resistant MDD patients (Trivedi et al., 2006; Pilu et al., 2007), but null responses have also been observed (Kerse et al., 2010; Sims et al., 2006). Some of the positive results found have been questioned due to the lack of control for the effect of social interaction (Pilu et al., 2007), but even studies that did control for this have had dissimilar results (Blumenthal et al., 2007; Kerse et al., 2010; Mather et al., 2002). The possibility that positive effects of exercise in depressed patients may be related to their expectations that physical exercise will be beneficial for their depression has also been raised (Blumenthal et al., 2007). We suggest that, similarly to adherence, the positive effects of exercise in depressive symptoms depend on the underlying pathology and its severity. As such, the best comparators for our results would be studies on treatment-resistant MDD patients (Trivedi et al., 2006; Pilu et al., 2007) to whom exercise was used as an adjuvant therapy in addition to their regular pharmacotherapy.

The present study adds to their findings, insofar as it included a control group to account for the social interaction component. During the weekly visits to the Hospital Gymnasium, the control group interacted with the teacher, the technicians and with each other for 30–45 min, and received as much attention from the study personnel as the study group. They performed the same tasks in the same environment, and the number of steps and daily calories expenditure was measured exactly as in the control group. Also, patients did not have the expectation that it would be better for them to be included in the exercise group, since the information that was conveyed was that this study was designed to evaluate the effect of physical exercise on people taking antidepressant medication. The expected outcome was not mentioned. Our results support physical exercise as a viable and effective adjuvant therapy for patients with unremitted MDD.

Analysis of the 4 time points – baseline, 4, 8 and 12 weeks – showed that the first parameter to significantly decrease was HAMD17 total scores, followed by an increase on GAF scores, and finally a decrease on BDI and CGI-S only significant at the end of 12 weeks. These results suggest that improvement in depressive symptoms precedes improvement in functioning, which has been suggested by others (Bijl and Ravelli, 2000). The fact that BDI only decreased after 12 weeks may be due to a delayed self-perception of improvement, resistance to accept improvement or even disbelief in improvement, since this is a patient self-evaluation. Having

been taking different combination therapies for 9–15 months without feeling better, these patients have lost faith in treatment, and may take some time to recognize they are actually feeling better. As for CGI-S only decreasing after 12 weeks, being preceded by an improvement in HAMD17 and GAF, we can only speculate, but it seems reasonable to suggest that it is the global functioning of the patient and the patient's subsequent perception of improvement that act together as positive enhancers of ameliorating depression as a whole. Response and remission rates are consistent with the improvements shown by the exercise group (Table 4). Although not statistically significant, 21% of the exercise group has shown response and 26% remission, compared to 0% in the control group. These response and remission rates are somewhat lower than previously reported (Blumenthal et al., 2007), which may be due to the fact that these are severely depressed patients, whose response or remission may take longer than the 12 weeks of the study. The follow-up of these patients is currently on-going, and the results may help answering this and other questions, such as if the positive effects of exercise continue after halting the exercise program.

More important than response or remission rates *per se* is restoring psychosocial functioning to an acceptable level (Trivedi et al., 2009; Kennedy et al., 2007), since patients who do not achieve symptomatic remission, as well as patients with remission that maintain residual symptoms, are at greater risk of relapse (Papakostas, 2009).

Our results show that participants who remitted showed improvement of all depression and functioning parameters, while in patients who responded to treatment without remitting and non-responders these changes were not significant, which is in accordance with other studies (Trivedi et al., 2009). This was not a consequence of pharmacotherapy, since non-responders were more heavily medicated than responders concerning antidepressants. Nevertheless, remitted patients maintained a slight functional impairment ($70 < GAF < 90$), which is different from what have been reported for patients with chronic depression (Miller et al., 1998). These different results underline the importance of conducting studies in different populations and pathologies, with different degrees of disease severity, since responses to treatment will certainly vary, and therapeutic approaches have to be adapted in order to achieve the desired asymptomatic remission, crucial so that functional improvement continues beyond acute-phase treatment (Papakostas, 2009). It is reasonable to suggest that, being particularly severe patients, a continued, long-term treatment and a proper follow-up is needed in order to achieve full remission without residual symptoms.

The fact that GAF baseline values of remitters were higher than those of non-responders and, although not statistically significant, remitters also had lower HAMD17 total scores at baseline than responders and non-responders, suggests that this kind of exercise program could benefit particularly MDD patients that show less severe symptoms or are close to remission. The lack of statistical significance in HAMD17 could be due to the small sample population, and we believe this line of research is worth exploring further in larger future studies.

Finally, there was no difference neither in anthropometric or hemodynamic parameters nor in lipid profile, either between or within-exercise groups, which is consistent with findings from another study in post-menopausal women (Agil et al., 2010), suggesting that exercise, at least in these populations, have a positive impact in depressive symptoms but not on these parameters.

5. Limitations of the study

This was a prospective, randomized, investigator blinded, two-arm, parallel assignment study, which controlled for the social interaction component often attributed to physical exercise practice, as well as for the patients' expectation that it would be better for them to be included in the exercise group. One limitation of the study was that there was no assessment of compliance to medication, although there is no indication that patients did not comply. Another variable that was not controlled for was the season: patients were enrolled in the exercise program between September 2009 and March 2010, and it could be possible that the effects of exercise in these patients vary depending on the season of the year, due to temperature, rain, hours of sunlight and day brightness. However, since these patients had been under pharmacotherapy for several months, and across different seasons, without any improvement in treatment, any seasonal effect should have been already experienced.

Patients' fitness was not measured, neither was physiological production of monoamines, serotonin, noradrenaline or dopamine, whose production is supposedly increased by physical exercise. Measurements of oxygen uptake (VO2), carbon dioxide output (VCO2) and minute ventilation (VE) were not performed, and blood lactate concentrations, to monitor improvement in fitness, were also not done. It was our perception that, due to their pathology, such measurements could be too intrusive and distressfull, having the possibility of altering the results and not reflect the remaining exercise periods, which were freely performed. There was also no control of structural conditions, eg, paths taken, topology of the land where the exercise was performed, city or country exercise environment, which may all contribute to the psychological response to physical exercise.

Also, energy expenditure data, which will allow an accurate evaluation of the intensity of the exercise performed by the patients included in the exercise group, is not presented in this paper, since it is not fully analyzed. A manuscript is currently being prepared to report these data. Although the study comprised a small population sample – a total of 29 patients – it was conducted in a very specific population of treatment-resistant MDD patients, which indicates that results may generalize to other populations of patients with similar characteristics.

6. Conclusions

Our results suggest that physical exercise can be used as an effective therapy, adjuvant to pharmacological therapy, in treatment-resistant MDD. A 12 week exercise program of 30–45 min walks 5 times a week resulted in improvement of all studied parameters of depression and functioning: HAMD17, BDI, CGI-S and GAF, and this improvement was not due to social interaction. Moreover, patients in the exercise group showed a 26% remission rate, compared to 0% in the control group. Remitted patients have shown greater improvement in functioning than responders or non-responders, although considering the GAF scores at the end of the study these patients may not be considered free from residual symptoms. Since residual symptoms are predictors of relapse or recurrence, and may be associated with residual psychosocial impairment, these patients are currently being followed-up to assess the impact of continued pharmacological treatment on the disease. This follow-up will also assess if the positive effects of exercise continue after halting the exercise program.

Physical exercise is an attractive option as adjuvant therapy for treatment-resistant MDD patients, for whom even poly-pharmacotherapy has shown poor results. It is safe, has no adverse side effects, can be sustained indefinitely, is readily available and, if home-based, has literally no costs. The currently on-going follow-up of these patients will determine if the observed positive effects of exercise on MDD will last after the exercise program has been stopped.

Funding source

This work was partially funded by a research grant from Servier Portugal.

Author contributions

Author Jorge Mota Pereira designed the study, wrote the protocol, compiled the data, undertook the statistical analysis and wrote the first draft of the manuscript. Authors Jorge Silverio and Jose Carlos Ribeiro supervised the study and reviewed the protocol. Author Serafim Carvalho conducted the clinical evaluation of screened patients and managed the literature searches and analyses. Author Joaquim Ramos supervised the study and conducted the clinical evaluation of screened patients. Author Daniela Fonte managed the literature searches and analyses and undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Conflict of interest

None declared.

Acknowledgments

None.

References

aan hset RM, Collins KA, Fitterling HL. Physical exercise and depression. Mount Sinai Journal of Medicine 2009;76:204–14.

Agil A, Abike F, Daskapan A, Alaca R, Tuzun H. Short-term exercise approaches on menopausal symptoms, psychological health, and quality of life in post-menopausal women. Obstet. Gynecol. Int; 2010. Epub 2010 Aug 16.

American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 2nd. ed.; 2000.

American Psychiatric Association. Guideline watch: practice guideline for the treatment of patients with major depressive disorder. 2nd. edition; 2005.

Babyak M, Blumenthal JA, Herman S, Khatri P, Doraiswamy M, Moore K, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosomatic Medicine 2000;62:633–8.

Bijl RV, Ravelli A. Current and residual functional disability associated with psychopathology: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Psychological Medicine 2000;30:657–68.

Blumenthal JA, Babyak MA, Doraiswamy PM, Watkins L, Hoffman BM, Barbour KA, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosomatic Medicine 2007;69:587–96.

Cichon S, Craddock N, Daly M, Faraone SV, Gejman PV, Kelsoe J, et al. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. American Journal of Psychiatry 2009;166:540–56.

Dimeo F, Bauer M, Varahram I, Proest G, Halter U. Benefits from aerobic exercise in patients with major depression: a pilot study. British Journal of Sports Medicine 2001;35:114–7.

Ekelund U, Tingstrom P, Kamwendo K, Krantz M, Nylander E, Sjostrom M, et al. The validity of the computer science and applications activity monitor for use in coronary artery disease patients during level walking. Clinical Physiology and Functional Imaging 2002;22:248–53.

Fornaro M, Giosue P. Current nosology of treatment resistant depression: a controversy resistant to revision. Clinical Practice and Epidemiology in Mental Health 2010;6:20–4.

Freedson PS, Melanson E, Sirard J. Calibration of the computer science and applications, Inc. accelerometer. Medicine and Science in Sports and Exercise 1998;30:777–81.

Frohlich ED, Grim C, Labarthe DR, Maxwell MH, Perloff D, Weidman WH. Recomendations for human blood pressure determination by sphygmomanometers: report of a special task force appointed by the steering committee. American Heart Association. Circulation 1988;77:A501–14.

Greenberg GA, Rosenheck RA. Using the GAF as a national mental health outcome measure in the Department of Veterans Affairs. Psychiatric Services 2005;56:420–6.

Guy W. ECDEU assessment manual for psychopharmacology. Rockville, MD: National Institute for Mental Health, US Department of Health, Education, and Welfare; 1976.

Hamilton M. A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 1960;23:56–62.

Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Medicine and Science in Sports and Exercise 2007;39:1423–34.

Hassmen P, Koivula N, Uutela A. Physical exercise and psychological well-being: a population study in Finland. Preventive Medicine 2000;30:17–25.

Howland RH. Therapeutic armamentarium for treating depression. Postgraduate Medicine 2010;122:66–93.

Kennedy N, Foy K, Sherazi R, McDonough M, McKeon P. Long-term social functioning after depression treated by psychiatrists: a review. Bipolar Disorders 2007;9:25–37.

Kerse N, Hayman KJ, Moyes SA, Peri K, Robinson E, Dowell A, et al. Home-based activity program for older people with depressive symptoms: DeLLITE–a randomized controlled trial. Annals of Family Medicine 2010;8:214–23.

Kessler RC, Abelson J, Demler O, Escobar JI, Gibbon M, Guyer ME, et al. Clinical calibration of DSM-IV diagnoses in the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMHCIDI). International Journal of Methods in Psychiatric Research 2004;13:122–39.

Koenig AM, Thase ME. First-line pharmacotherapies for depression - what is the best choice? Polskie Archiwum Medycyny Wewnetrznej 2009;119:478–86.

Kurian BT, Greer TL, Trivedi MH. Strategies to enhance the therapeutic efficacy of antidepressants: targeting residual symptoms. Expert Review of Neurotherapeutics 2009;9:975–84.

Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. British Medical Journal 2001;322:763–7.

Malhi GS, Parker GB, Crawford J, Wilhelm K, Mitchell PB. Treatment-resistant depression: resistant to definition? Acta Psychiatrica Scandinavica 2005;112:302–9.

Mather AS, Rodriguez C, Guthrie MF, McHarg AM, Reid IC, McMurdo ME. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: randomised controlled trial. British Journal of Psychiatry 2002;180:411–5.

Miller IW, Keitner GI, Schatzberg AF, Klein DN, Thase ME, Rush AJ, et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. Journal of Clinical Psychiatry 1998;59:608–19.

NIH Consensus Development Panel on Physical Activity and Cardiovascular Health. Physical activity and cardiovascular health. Journal of the American Medical Association 1996;276:241–6.

Papakostas GI. Major depressive disorder: psychosocial impairment and key considerations in functional improvement. American Journal of Managed Care 2009;15:S316–21.

Pilu A, Sorba M, Hardoy MC, Floris AL, Mannu F, Seruis ML, et al. Efficacy of physical activity in the adjunctive treatment of major depressive disorders: preliminary results. Clinical Practice and Epidemiology in Mental Health 2007;3:8.

Powers SK, Lennon SL, Quindry J, Mehta JL. Exercise and cardioprotection. Current Opinion in Cardiology 2002;17:495–502.

Sims J, Hill K, Davidson S, Gunn J, Huang N. Exploring the feasibility of a community-based strength training program for older people with depressive symptoms and its impact on depressive symptoms. BMC Geriatrics 2006;6:18.

Singh NA, Clements KM, Fiatarone MA. A randomized controlled trial of progressive resistance training in depressed elders. Journals of Gerontology Series A Biological Sciences and Medical Sciences 1997;52:M27–35.

Taylor D, Paton C, Kapur S. The Maudsley prescribing guidelines. 10th ed. London: Informa Healthcare; 2009. 173.

Teri L, Gibbons LE, McCurry SM, Logsdon RG, Buchner DM, Barlow WE, et al. Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. Journal of the American Medical Association 2003;290:2015–22.

Trivedi MH, Corey-Lisle PK, Guo Z, Lennox RD, Pikalov A, Kim E. Remission, response without remission, and nonresponse in major depressive disorder: impact on functioning. International Clinical Psychopharmacology 2009;24:133–8.

Trivedi MH, Daly EJ. Treatment strategies to improve and sustain remission in major depressive disorder. Dialogues in Clinical Neuroscience 2008;10:377–84.

Trivedi MH, Greer TL, Grannemann BD, Chambliss HO, Jordan AN. Exercise as an augmentation strategy for treatment of major depression. Journal of Psychiatric Practice 2006;12:205–13.

Van Breukelen GJ. ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]. Journal of Clinical Epidemiology 2006;59:920–5.

World Health Organization. The World Health Report 2001-mental health: new understanding, new hope; 2001.