Chapter 4

Moderate Exercise as an Adjuvant Therapy for Treatment-Resistant Major Depressive Disorder: 6-Month Follow-Up

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Abstract

Although several international guidelines recommend exercise to reduce symptoms of Major Depressive Disorder (MDD), data concerning the long-term effects of exercise in depression are still extremely scarce. Therefore, and in order to assess these long-term effects, we have evaluated treatment-resistant MDD patients previously enrolled in a moderate intensity 12 week exercise program at 3 and 6 months after the end of the program, regarding HAMD17, BDI, GAF, CGI-S, WHOQOL-Bref and SF-36. Results show that 47% of patients in the exercise group continued to exercise at follow-up. Those

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who continued to exercise maintained the same depression and functional parameters they showed after the 12 week exercise program, which were all improved compared to the initial values ($p < 0.05$). Those who stopped exercising showed worse HAMD17, GAF and CGI-S ($p < 0.05$) at 6 months follow-up than at the end of the exercise program. All patient groups maintained their QoL scores at 6 month follow-up compared to the scores at the end of the 12 week exercise program, regardless of continuing to exercise or not. Therefore, we suggest that positive effects of exercise on depression and functioning of treatment-resistant MDD only persist if exercise is continued over time. QoL improvements are maintained after 6 months follow-up, even for patients who stop exercising.

**Keywords:** Depression; follow-up; functioning; physical activity; quality of life; relapse; remission

**Introduction**

According to the World Health Organization, there is strong evidence that more active adults have lower rates of depression [1]. Although in no instances should the use of exercise or other complementary and alternative medicine (CAM) therapies preclude the consideration of standard treatment [2], exercise as recommended by the American College of Sports Medicine [3] can be efficacious in reducing symptoms in patients with major depressive disorder (MDD), and some international guidelines for the treatment of depression suggest that exercise may be useful [4].

The 2010 guidelines from the American Psychiatric Association on MDD include suggestions on the use of medication, CBT, exercise and other CAMs [5], and UK national guidelines for treating MDD have explicitly listed physical exercise as a useful and effective intervention for patients with mild depression [6].

However, data concerning the long-term effects of exercise in depression are still extremely scarce [7], and the few existing studies have reported contradictory findings [8-16]. On previous papers, we have shown that MDD patients who enrolled on a moderate intensity 12 week exercise program had improved all depression and functioning parameters at the end of the program [17], with modest improvements on Quality of Life (QoL) [18]. Also, on the previous chapter, we reported the benefits of accelerometer monitoring, namely concerning compliance, exercise patterns and relationship between time spent in MVPA, response to treatment and Quality of Life. In this chapter, we report the assessment of long-term benefits of this exercise program in those patients. Results suggest that positive effects of exercise on depression and functioning of treatment-resistant MDD only persist if exercise is continued over time. However, QoL improvements are maintained after 6 months follow-up, even for patients who stop exercising.

**Participants, Study Protocol and Outcome Measures**

Follow-up of the participants enrolled in the study described in the previous chapter, using the same outcome measures.
Follow-Up

After the end of the 12 week exercise program, all participants were told that the study was finished and individuals assigned to the exercise group were asked to resume their regular daily activities and continue to exercise or not at their will.

They were in no way compelled or coerced to adopt either behavior. All participants were evaluated at baseline (time 0: before starting the physical activity program), at 4, 8 and 12 weeks, and at 3 and 6 months after the end of the exercise program for depressive symptoms, functional assessment and Quality of Life. The study protocol was approved by Hospital de Magalhães Lemos Institutional Review Board. All participants provided written informed consent.

Compliance at Follow-Up 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 was defined as completion of at least 50% of the 5 walks per week during the 6 month follow-up period.

Statistical Analysis

Differences between and within compliance groups at follow-up in the change from 12 weeks to endpoint (6 month follow-up) were analyzed using an analysis of covariance (ANCOVA) with values at 12 weeks as covariates. Differences between no response, response and remission groups were analyzed with ANOVA. In the case of significant differences, post hoc tests using the Sidak correction were performed. Tests were considered significant at \( \alpha = 0.05 \) significance level (two-sided).

Results

Changes from the End of the Study to the End of Follow-Up

47.4% of participants continued to exercise during follow-up. Participants who continued to exercise at follow-up maintained the same average HAMD17, BDI, GAF and CGI-S scores they showed at the end of the 12 week exercise program (13.5 ± 1.8 vs 12.5 ± 1.8, 17.0 ± 2.9 vs 18.7 ± 2.9, 61.6 ± 2.4 vs 61.7 ± 2.4 and 2.8 ± 0.3 vs 3.0 ± 0.3, respectively, \( p > 0.05 \)). Those who stopped exercising had an increase in HAMD17 after 6 months follow-up, compared to their score at the end of the exercise program (17.6 ± 1.7 vs 12.4 ± 1.7, \( p < 0.05 \)), and a decrease in GAF and increase in CGI-S, both compared to their score at the end of the exercise program (54.8 ± 2.3 vs 62.0 ± 2.3 and 3.9 ± 0.3 vs 3.0 ± 0.3, respectively, \( p < 0.05 \)), and compared to the group that continued exercising at 6 month follow-up (54.8 ± 2.3 vs 61.6 ± 2.4 and 3.9 ± 0.3 vs 2.8 ± 0.3, respectively, \( p < 0.05 \)).
There was no statistically significant change in the BDI score. The control group showed no differences at follow-up, either compared to the end of the program or to the other groups – Figures 1 and 2.

All patients maintained their QoL scores at 6 month follow-up compared to the scores at the end of the 12 week exercise program, regardless of continuing to exercise or not.

Figure 1. A. average HAMD17 scores at the end of the 12 week exercise program and at the end of the 6 month follow-up. B. average BDI scores at the end of the 12 week exercise program and at the end of the 6 month follow-up. *p < 0.05 within group; p-values from ANCOVA with values at the end of the 12 week exercise program as covariate.
Figure 2. A. average GAF scores at the end of the 12 week exercise program and at the end of the 6 month follow-up. B. average CGI-S scores at the end of the 12 week exercise program and at the end of the 6 month follow-up. *p < 0.05 within group; **p < 0.05 vs continued exercising; p-values from ANCOVA with values at the end of the 12 week exercise program as covariate.

Patients who continued to exercise improved most of QoL domains, although without reaching statistical significance – Table 1. There was a trend for the change in the environmental WHOQOL-Bref domain to decrease in the order control group > non-compliance group > compliance group, with no difference regarding the other QoL domains.
Table 1. Mean changes on QoL scores from the end of the exercise program to 6 month follow-up

<table>
<thead>
<tr>
<th>Quality of Life Instrument</th>
<th>Control group (n = 10)</th>
<th>Stopped exercising (n = 10)</th>
<th>Continued exercising (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHOQOL-Bref Domains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>1.07 (4.90)</td>
<td>-6.07 (4.90)</td>
<td>-4.37 (5.16)</td>
</tr>
<tr>
<td>Psychological</td>
<td>7.20 (4.27)</td>
<td>1.67 (4.48)</td>
<td>9.26 (4.72)</td>
</tr>
<tr>
<td>Social</td>
<td>-0.76 (6.37)</td>
<td>-5.00 (6.68)</td>
<td>5.21 (7.47)</td>
</tr>
<tr>
<td>Environmental</td>
<td>3.12 (2.82)</td>
<td>2.19 (2.67)</td>
<td>-2.43 (2.82)</td>
</tr>
<tr>
<td>Global QoL</td>
<td>-7.96 (5.06)</td>
<td>-6.25 (5.30)</td>
<td>4.17 (5.59)</td>
</tr>
<tr>
<td>SF-36v2 Domains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>4.09 (5.20)</td>
<td>-8.00 (5.46)</td>
<td>1.11 (5.75)</td>
</tr>
<tr>
<td>Role-physical</td>
<td>6.82 (7.59)</td>
<td>-1.88 (7.96)</td>
<td>3.47 (8.39)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-0.73 (6.15)</td>
<td>-5.10 (6.45)</td>
<td>-9.11 (6.80)</td>
</tr>
<tr>
<td>General health</td>
<td>-0.46 (5.49)</td>
<td>-3.70 (5.76)</td>
<td>1.67 (6.07)</td>
</tr>
<tr>
<td>Vitality</td>
<td>-6.82 (6.09)</td>
<td>-1.88 (6.38)</td>
<td>11.81 (6.73)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>-1.14 (8.60)</td>
<td>2.50 (9.02)</td>
<td>4.17 (9.51)</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>-3.03 (9.11)</td>
<td>0.00 (9.56)</td>
<td>10.19 (10.07)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>-0.46 (6.92)</td>
<td>1.00 (7.26)</td>
<td>10.00 (7.65)</td>
</tr>
</tbody>
</table>

All p values, both within-groups and between-groups from ANCOVA with values at 12 weeks as covariate, are not significant (p > 0.05).

Table 2. Trend analysis of QoL change from the end of the exercise program to 6 month follow-up

<table>
<thead>
<tr>
<th>Quality of Life Instrument</th>
<th>linear-by-linear association</th>
<th>linear regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>χ² value</td>
<td>p value</td>
</tr>
<tr>
<td>WHOQOL-Bref Domains</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>1.161</td>
<td>0.281</td>
</tr>
<tr>
<td>Psychological</td>
<td>0.060</td>
<td>0.807</td>
</tr>
<tr>
<td>Social</td>
<td>0.735</td>
<td>0.391</td>
</tr>
<tr>
<td>Environmental</td>
<td>4.175</td>
<td>0.041</td>
</tr>
<tr>
<td>Global QoL</td>
<td>2.212</td>
<td>0.137</td>
</tr>
<tr>
<td>SF-36v2 Domains</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>0.219</td>
<td>0.640</td>
</tr>
<tr>
<td>Role-physical</td>
<td>0.105</td>
<td>0.746</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>0.786</td>
<td>0.375</td>
</tr>
<tr>
<td>General health</td>
<td>0.050</td>
<td>0.824</td>
</tr>
<tr>
<td>Vitality</td>
<td>3.624</td>
<td>0.057</td>
</tr>
<tr>
<td>Social functioning</td>
<td>0.161</td>
<td>0.689</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>0.798</td>
<td>0.372</td>
</tr>
<tr>
<td>Mental Health</td>
<td>0.918</td>
<td>0.338</td>
</tr>
</tbody>
</table>

Trend analysis using linear-by-linear association $\chi^2$ statistics and linear regression. Analysis was performed considering the order control group, non-compliance group, compliance group.

The Vitality domain of SF36-v2 showed an almost significant opposite trend, increasing in the order control group < non-compliance group < compliance group – Table 2.
Response Groups at the End of Study and at the End of Follow-Up

Within the exercise group, the only three patients who either remitted or maintained remission continued to exercise during follow-up. One patient who continued to exercise and two who stopped exercising relapsed during follow-up. The remaining patients maintained the same response status they had at the end of the 12 week exercise program. Within the control group, all patients maintained the same no response status they showed at the end of the study – Table 3.

Table 3. Response groups at the end of the 12 week exercise program and at the end of follow-up

<table>
<thead>
<tr>
<th>At end of study</th>
<th>At end of follow-up</th>
<th>Exercise group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (n=5)</td>
<td>Maintained remission</td>
<td>0%</td>
<td>40% (n = 2)</td>
</tr>
<tr>
<td>Response (n=4)</td>
<td>Relapsed</td>
<td>40% (n = 2)</td>
<td>20% (n = 1)</td>
</tr>
<tr>
<td>No response (n=20)</td>
<td>Maintained response</td>
<td>50% (n = 2)</td>
<td>50% (n = 2)</td>
</tr>
<tr>
<td></td>
<td>Remitted</td>
<td>0%</td>
<td>10% (n = 1)</td>
</tr>
<tr>
<td></td>
<td>Maintained no response</td>
<td>60% (n = 6)</td>
<td>30% (n = 3)</td>
</tr>
</tbody>
</table>

Did not comply = did not complete at least 50% of the 5 walks per week during the 6 month follow-up period; complied = completed at least 50% of the 5 walks per week during the 6 month follow-up period.

Figure 3. Exercise during follow-up and response to treatment. Bars represent mean ± standard deviation; *p < 0.05 versus other response groups; p values from ANOVA.
Exercise during Follow-Up and Response to Treatment

Of all patients within the exercise group, regardless of compliance at follow-up, those who remitted or maintained remission exercised more times per week, both alone and total, than patients who either maintained the same response/no response status they had at the end of the study or relapsed, albeit only reaching statistical significance for those who exercised more alone (2.9 ± 0.6, 0.8 ± 0.3, 0.0 ± 0.0, respectively, p < 0.05) – Figure 3. All patients who either did not change response/no response status or relapsed during the 6 month follow-up completed less than 50% of the 5 walks per week during this period.

Discussion

Although most studies investigating the effects of exercise on MDD have shown positive effects of exercise on depressive symptoms, functioning, Quality of Life or executive control processes, follow-up data is extremely scarce [7]. Two studies examined the long-term effects of aerobic exercise on MDD patients, suggesting that exercising during the follow-up period seems to extend the short-term benefits of exercise [8, 11] and may augment the benefits of antidepressant use [11]. Other studies including major and minor depression and dysthymia, all suggest that the positive effects of exercise programs ranging from 8 weeks to 6 months on depressive symptoms and mood are maintained at follow-up from 4 to 26 months [9, 16]. However, some studies have shown that exercise was as effective as cognitive therapy only [10], social visits [12] or usual medical care [14] on maintaining improvements in depressed patients at follow-up, and in one study there was a trend that did not reach statistical significance [15]. A recent meta-analysis found little evidence of long-term beneficial effects of exercise in patients with clinical depression [13]. These disparities in results may be a consequence of different study designs, control groups, type and severity of depression and clinical settings, underscoring the importance of additional research aiming at understanding the true long-term benefits of exercise on depression.

As for QoL, and although there are no reports on the follow-up of treatment-resistant MDD, one study reports maintenance of QoL at follow-up in MDD patients [19] and two others in other depressed populations [12, 14].

Exercise during Follow-Up, Depression and Functioning Status

Our results show that 47.4% of participants continued to exercise during follow-up, which is a slightly lower adherence rate than the ones reported for other MDD [8, 11] or depressed populations [12], similar to depressive or anxiety disorders patients [14] and higher than other studies in depressed patients [16]. As previously reported, all patients in the exercise group showed improvement of all depression and functioning parameters at the end of the exercise program [17]. There were no differences on HAMD17 average scores at the end of the exercise program between patients who continued exercising during follow-up and those who stopped (12.8 ± 3.1 and 12.2 ± 1.9, respectively, p > 0.05), nor on any other measured outcomes, nor on the average change from baseline to the end of the exercise.
Moderate Exercise as an Adjuvant Therapy

There was also no difference between those who continued to exercise and those who stopped regarding response status at the end of the exercise program ($\chi^2 = 0.549$, $p = 0.760$). Therefore, this adherence cannot be explained by the severity of the patients’ depression status at the end of the exercise program, rate of improvement or response during the program, and is opened to speculation. MDD is a complex, multifactorial, multigenic condition [20], and the outcomes used in this study, although widely accepted as valid, do not fully reflect the way the patient feels. Also, MDD patients are poorly motivated to perform any kind of physical activity, especially the most severely ill, as is the case of treatment-resistant MDD, and in order to prevent any influence on adherence rates at follow-up, patients were not asked or in no way compelled or coerced to continue exercising, thus this represents a true adherence at follow-up, without any external influence. It may be speculated that, in order to sustain acquired exercise behaviors, the motivational strategies, based on the psychological mechanisms responsible for the high adherence to the exercise program, which were discussed in the previous chapter, need to be continued over time, as has been suggested to be the case both on depressed populations and other pathologies [15, 21-23]. Another possible interpretation, according to the Transtheoretical model of behavior change (TTM) for exercise [24], is that although participants reached Stage IV (action) during the intervention, as discussed in the previous chapter, after the exercise program was finished, and the motivation strategies withdrawn, those who continued to exercise had reached Stage V (maintenance) but those who stopped had not, although the reasons for this remain unclear.

Continuation of exercise during follow-up contributed to the maintenance of the short-term beneficial effects of exercise, with patients who stopped exercising showing a worsening of depression and functioning parameters. Although these results are in line with previous reports on MDD [8, 11] and other depressed patients [9, 16], the follow-up data are different. Pharmacotherapy remained unchanged during follow-up and none of the patients, either on the exercise or the control group, entered psychotherapy. Also none of the patients in the control group initiated an exercise program during follow-up. This allows for a better understanding of the true effect of exercise on depression and suggests that it is the continuation of exercise that is truly responsible for the maintenance of a better depression status, as has been reported for adults with fibromyalgia [25-27], healthy sedentary postmenopausal women [28] and older healthy adults [29].

The mechanisms by which exercise exerts its positive effects on mood and depression remain elusive. Several psychological and physiological theories have been put forth, but none has been proven. As for the psychological theories, we believe all of them may have had its part on the positive effects of continuing to exercise in our patients. The distraction hypothesis has been supported by experimental studies that have demonstrated that physical activity was no more efficient in improving mood than an equivalent period of relaxation [30, 31]. The mastery hypothesis [30, 32], Bandura’s theory of self-efficacy [33] and the self-esteem hypothesis [34], which somewhat overlap, are all based on the individual’s belief that exercise will have a positive impact on the way they feel and look, and seem to be the most consistent explanations for the effects of exercise on mood. As their sense of mastery and confidence (self-efficacy) in exercising increases, with the concomitant increase in self-esteem, not only at the psychological level (“I can do it, I am not worthless”) but also at the physical attributes’ level, depressive symptomatology will be reduced. It has been shown that for those with prior depression, self-efficacy mediates approximately 40% of the effect of stressful life events on symptoms of depression [35], and several authors have raised the
possibility that the positive effects of physical activity or exercise in depressed patients may be related to their expectations that it will be beneficial for their depression [36-39]. Moreover, in view of the psychological constructs discussed on the previous chapter, and the psychological mechanisms involved in MDD, all these theories seem reasonable to at least partly explain the positive effects of exercise on MDD patients.

As for the physiological models that have been proposed to explain the impact of exercise on mood, affect and depression, the monoamine hypothesis [40] is based on the theory that exercise increases the brain’s aminergic synaptic transmission, similarly to the effect of several currently used antidepressants. The improved transmission rate of monoamines in the brain, such as serotonin, norepinephrine and dopamine when exercising occurs, is beneficial for depression since these molecules directly affect mood. Although this is believed to be oversimplified [41, 42], several studies have shown that plasma serotonin and homovanillic acid levels are increased by exercise training [43, 44], and both acute and chronic exercise increase norepinephrine, dopamine and DOPA plasma concentrations in healthy untrained men [45-50]. Increases of plasma norepinephrine levels with exercise have been reported to be similar among individuals at the same relative intensity of exhaustive exercise, regardless of the duration of exercise [48]. Also, endurance training decreases plasma concentrations of tryptophan and increases the mean density of the serotonin transporter in platelets, although platelet serotonin levels are similar to the ones found in sedentary individuals [51]. Other studies reported diverse results: 6 months of endurance training in the elderly did not change norepinephrine levels [52], and withdrawal from exercise for two months did not markedly affect the rate of disappearance of norepinephrine in the postexercise period [53]. Exercise training for 9 weeks did not have an overall 5-HT receptor sensitivity in response to aerobic exercise, although 25% of the subjects in the training group demonstrated decreases in receptor sensitivity [54] and comparison of plasma norepinephrine in well-trained and minimally trained individuals showed only minimal differences, both at rest and during exercise [55]. Nevertheless, all human studies have only measured plasma or urine monoamine concentrations, and it is unknown if these are reflected centrally. Although animal studies have shown some discrepancies regarding monoamine changes in several brain areas both after acute and chronic exercise training, there is evidence in favor of changes in the synthesis and metabolism of monoamines with exercise [56], but this remains to be shown for humans.

The endorphin hypothesis [57] proposes that the effects of exercise on affect, specifically euphoria, are the result of the release and subsequent binding of endogenous endorphins to receptor sites in the brain, and has received support from several studies [58-62]. The elevation of circulating endorphin levels after exercise, and the fact that these levels are known to stay elevated for several days after exercise is discontinued, possibly contributes to improvement in mood and increased self-esteem. However, not only plasma endorphin levels do not necessarily represent levels in the brain, due to the blockade of the blood-brain barrier [63], but also it has not been fully proven that such an increase plays a crucial role in mood control [64, 65]. Perhaps more important is the known fact that increased endorphins act as a natural pain reliever [66], thus contributing to reduced pain, which is known to be one of the most common symptoms of depression, sharing several pathways with this pathology [67].

The neurogenic or neurotrophic hypothesis [68] claims that exercise and an enriched environment increase neurotrophic support and neurogenesis, which could contribute to counteract the effects of stress and aging and produce antidepressant effects. Possible
molecules involved include BDNF and IGF-1. BDNF is one of the most active neurotrophins responsible for the stimulation and control of neurogenesis, may enhance brain plasticity by supporting neuron survival, contributing to growth and differentiation of new neurons and synapses, and protecting against stress-induced neuronal damage [69]. The observed transient increase of BDNF serum levels after exercise in elderly women with remitted MDD, the fact that antidepressants increase BDNF, and the observation that healthy controls have higher levels of BDNF than MDD patients [70-72] support this mechanism as a contributor for the beneficial effects of physical activity on MDD. Moreover, following exercise, BDNF levels are increased in rat hippocampus [73, 74]. However, Gustafsson et al. [75] found no difference in basal levels of BDNF between unmedicated MDD patients and healthy controls, although there was also a transient increase of BDNF plasma levels on both groups after exercise. The BDNF protein is downregulated by CORT but exercise overrides the negative effects of stress and high levels of CORT on BDNF, thus producing positive effects on depression [76]. IGF-1 levels are also increased after exercise, and this has been correlated with cognitive improvement [77, 78]. Moreover, exercise increases VEGF levels, a known potent angiogenic factor, via increased ROS production [79], which may be responsible for the observed possible regulation of neurogenesis by exercise [80, 81]. However, and despite several studies supporting the neurogenic hypothesis through several possible mechanisms [82], others have found no evidence of its role on neurocognitive performance in MDD [83].

Another hypothesis for the possible physiological effects of exercise in mood is the circadian rhythm synchronization hypothesis [84]. Numerous lines of evidence have shown that exercise influences melatonin concentrations and can phase shift circadian rhythms, depending on the time of day it is performed [85-95] and on the duration, intensity and frequency of exercise [96]. However, other studies have found no effect of exercise on endogenous circadian periods or melatonin production [97] or had inconclusive results [98, 99]. No studies exist in MDD patients. Given the importance of the melatonergic system in depression, it is imperative that studies in depressed populations are conducted, to evaluate the possible efficacy of exercise or a combination of exercise and agomelatine, on the improvement of depressive symptomatology.

Finally, exercise, itself a stressor, may contribute to an individual’s ability to respond to stressful events in a less stressful way, thus leading to reduced stress reactivity, and may also modify the physiological response to both acute and chronic stress. Given chronic stress is associated with depression, and in light of the several possible mechanisms of MDD, mentioned in the Introduction section, the ability to attenuate physiological reactivity to a stressor may be of particular importance to our patients.

Active people demonstrate less reactivity when exposed to psychosocial stressors [100], with exercising of longer duration – 46 to 120 min – and more than 3 days per week, regardless of physical fitness, being associated with the largest decrease in stress reactivity.

Putative explanations for the stress-buffering effect of exercise involve some of the physiological mechanisms implicated on the effects of exercise in mood and depression, namely BDNF, norepinephrine and the HPA axis. Exposure to stress reduces BDNF and norepinephrine levels in the brain, and, as already discussed, these decreases are counteracted by exercise. Individuals exhibiting a hyperactive HPA axis when exposed to the stress of exercise also have a hyperreactive HPA axis, particularly as demonstrated by increased cortisol, when exposed to psychological stress [101] which may reflect a more efficient response and enhanced sensitivity or adrenal capacity. In support of this hypothesis, a short
bout of resistance exercise in healthy, young, untrained male volunteers did not increase cortisol levels [47], but cortisol levels are elevated in trained subjects compared to sedentary individuals [102], suggesting that HPA axis involvement is not immediate and only occurs after exercise training. Also, in subjects of varying degrees of fitness, adrenocorticotropic hormone increased 2 minutes after completion of exercise and cortisol increased 17-21 min after exercise, the magnitude of these responses being similar among individuals at the same relative intensity of exhaustive exercise, regardless of the duration of exercise [48]. Exercise may act either as a coping strategy, providing a more efficient system for coping with stress by reducing autonomic or HPA recovery time, or by providing acute buffering effects due to vagal or parasympathetic rebound following cessation of the exercise stressor, or still by providing controlled stimulation of the stress response, thus causing systemic adaptations and enabling people to more effectively respond to future psychosocial stress.

None of the above mechanisms, psychological or physiological, is thought to play a solitary role on the effects of exercise on mood and depression. Rather, a combination of all of these should contribute to these effects.

Exercise during Follow-Up and QoL Status

The effects of physical activity and exercise on QoL have been the object of some research, with results varying widely depending on the pathology, type of exercise program and clinical setting. Several cohort studies have found positive associations between regular exercise/higher physical activity and better QoL in patients with depressive symptoms or current depressive disorder [103], but causality could not be established. Some prospective controlled studies have reported increased scores in various domains of QoL after exercise programs in treatment-resistant MDD patients [18] and depressed elders [104], while others have failed to show benefits of physical activity on any domains of QoL in older people with depressive symptoms [15].

All our patients maintained their QoL scores at 6 month follow-up compared to the scores at the end of the 12 week exercise program, regardless of continuing to exercise or not. Although there are no reports on the follow-up of treatment-resistant MDD, this maintenance of QoL at follow-up is in line with results obtained in MDD patients [19] and other depressed populations [12, 14]. Patients who continued to exercise improved almost all their QoL domains during follow-up, albeit not reaching statistical significance, and there was an almost significant trend for the Vitality domain scores of SF36-v2 to increase in the order control group < non-compliance group < compliance group. It has been reported that, in women with fibromyalgia, an aerobic, strength and flexibility exercise program during 24 weeks largely improved vitality [105]. Given that, in our population, vitality did not improve during the exercise program, this almost significant trend after 6 month follow-up, together with the remaining results, supports our previous suggestion that a 12 week exercise program may not be sufficient to improve QoL [18], and indicates that even a 9 month exercise program may not be long enough. The observed trend for the change in the environmental WHOQOL-Bref domain to decrease in the order control group > non-compliance group > compliance group was unexpected and has not been reported. Since this parameter had not changed during the exercise program [18], we can only speculate that, being a known fact that QoL is multidimensional and shows complex interactions with many physical and psychological
variables [38, 106, 107], in this particular population of severely depressed patients the continuation of exercise over time will not only influence physical QoL domains [19, 108] but others as well. Another possibility is that, given the environmental domain of WHOQOL-Bref includes three questions pertaining to factors external to the patient and not controlled nor influenced by him/her, this result is neither a direct nor indirect consequence of the exercise, being simply a random occurrence.

Exercise during Follow-Up and Response to Treatment

Analysis of response at the end of the exercise program and at the end of follow-up showed that the only patient who remitted during follow-up had not responded during the intervention and continued to exercise at follow-up, which suggests that 12 weeks may not be sufficient for these patients to fully benefit from the exercise program, adding to the on-going debate concerning the duration of exercise needed to produce beneficial effects [7]. One patient (20%) who continued to exercise and two (40%) who stopped exercising relapsed during follow-up, all to HAMD17 scores similar to the ones they had before initiating the exercise program. These results are similar to previous reports on MDD showing that patients who continued to exercise were 50% less likely to relapse [8, 11], and add to the findings of Weinstein, Deuster and Kop [109] on the negative effects of exercise withdrawal in mood. Nevertheless, the relapse of the patient who continued to exercise remains unexplained. The fact that the majority of patients maintained the same response status they had at the end of the 12 week exercise program, regardless of continuing to exercise or not, may be suggestive of long-term effects of exercise programs, at least for 6 months, as has been observed in other pathologies co-morbid with depression [110-114].

Finally, the fact that patients who remitted or maintained remission exercised more times per week supports the conclusions from other studies in MDD [8, 11]. However, statistical significance was only reached for those who exercised more alone, suggesting that patients who reached the maintenance stage no longer need to seek social support to continue exercising. In light of the mastery hypothesis [30, 32] and Bandura’s theory of self-efficacy [33], we may speculate that by getting better during the exercise program, patients may have incorporated the belief that “I have committed myself to exercising and I got better; I can do it, and I can continue to do it alone”, which led them to exercise more on their own during follow-up.

This may, however, be an oversimplified interpretation. Depression is an extremely complex pathology, involving several neurochemical systems, circadian rhythms, neuroplasticity, neuroendocrine systems, inflammatory processes, cognition processes, emotion pathways, environmental, social and personal interactions and genetics, and all these certainly play a role on the effects of exercise on MDD. All the physiological mechanisms involved on the effects of exercise on mood and depression, which are discussed above, are also involved in the pathophysiology of MDD. However, other processes involved in depression, which have not shown a clear link to exercise, may also influence these effects.

Thyroid hormones regulate a myriad of physiological functions, and both hypo- and hyperthyroidism induce diverse psychiatric symptoms [115-117]. This is thought to be due to these hormones’ direct effect on CNS, namely in neuronal excitability and regulation of
serotonergic, noradrenergic and GABAergic receptor density [118], all of which are affected by exercise.

The involvement of an inflammatory process in MDD stems from several observations that a number of cytokines are elevated in MDD patients, eg IL-1, IL-6 and TNF-α [119], who also show high levels of other acute phase proteins, chemokines and cellular adhesion molecules including CRP, haptoglobin, MCP-1 and E-selectin [120]. However, no causality has been established, and it remains elusive if this altered immune condition is a cause – or a risk factor – for MDD or secondary to it. On one hand, and supporting the inflammatory process as being involved in the pathogenesis of MDD, it has been reported that acute immune stimulation causes increased anxiety and depressed mood [121, 122], which correlate with increases in IL-6, IL-1 receptor antagonist, TNF-α, soluble TNF receptors and cortisol. Antiviral treatment with interferon-alpha (IFN-α), a cytokine naturally released by the innate immune system in response to viral infections, induces increased levels of several proinflammatory cytokines in the serum and CSF, such as ICAM-1, IL-1, IL-1 receptor antagonist, IL-6, IL-8, MCP-1 and TNF-α, along with their soluble receptors [123], leading to depressive symptomatology [124]. Cytokines influence the synthesis, release and reuptake of virtually all neurotransmitters associated with MDD [125]. Several cytokines are able to activate the HPA axis, and neuroendocrine deregulations have been consistently found in MDD patients. Inflammatory cytokines can disrupt GR function and decrease GR expression [126], and, either by affecting GR translocation or GR-mediated gene transcription, influence transcription of other proinflammatory cytokines [126, 127]. Proinflammatory cytokines such as IL-1β, IL-6 and TNF-α influence neuronal functioning by interfering with apoptosis, oxidative stress, synaptic plasticity and neurogenesis [128, 129], and a blockade of cytokine action leads to a decrease of depressive symptoms. These changes in mood have been suggested to be due to alterations caused by cytokines in the brain reward system [130]. On the other hand, and suggesting inflammatory processes are secondary to MDD, it is known that psychological stress can induce inflammatory processes [131] and is associated with major depression [132]. Chronic stress seems to be accompanied by GR resistance and activation of proinflammatory pathways [133], with the consequent diminished expression of transcripts with glucocorticoid response elements and elevated expression of transcripts with NF-κB response elements [134], suggesting that stress produces functional resistance to glucocorticoids, which enables activation of proinflammatory transcription control pathways. The secretion and production of proinflammatory cytokines are increased in individuals who are stressed and depressed, and, in major depression, antidepressant drugs can return concentrations of these cytokines to normal or suppress their synthesis [135]. Most probably, there is a cause-effect-cause loop, with the endocrine, central nervous system and immune system synergistically interacting with each other to culminate in a general imbalance that results in MDD. As such, for instance, HPA axis hyperactivity will cause glucocorticoid resistance, leading to immune activation, and inflammation can then stimulate the HPA axis activity via both a direct action of cytokines on the brain and by further inducing glucocorticoid resistance. The known contribution of psychological stress to both inflammation and depression also support this synergistic interaction. Given exercise has anti-inflammatory effects [136-139], this is another possible mechanism by which exercise exerts its effects on depression.
Depression is also associated with several cognitive deficits and negative emotional biases [140], namely cognitive retardation, impaired attention and executive function, negative biased attention, long-term memory deficits, impaired free recall and recognition memory tasks, impaired explicit, mood-congruent and autobiographical memory, and altered effortful processing. Given these characteristics, several cognitive-emotional theoretical models of depression have been proposed: a) The Schema Theory [141] postulates that schemas, the foundations of dysfunctional cognition, cause depression. Schemas are hypothetical structures where information is organized in a meaningful and enduring manner, acting as filters that guide attention, information processing and memory. Schemas are latent until activated by emotional distress, and when activated they provide access to a complex system of negative information processing, thus precipitating a depressive episode; b) The Associative Network Theory, proposed by Bower [142], suggests the existence of emotion nodes, which when activated produce emotions. These nodes exist in the context of a neural-like network, and integrate all aspects of emotions, such as autonomic reactions, affective behaviors, and all events and concepts associated with emotions. Activation of emotion nodes enhances their accessibility, and therefore a previously negative emotion will be more likely to trigger more negative emotions; c) The Resource Allocation Model [143] posits that, in depression, cognitive resources are dedicated to and consumed by recurrent and constant thoughts of depressive symptoms, thus being unavailable to be used for cognitive processing; d) The Differential Activation Hypothesis [144] posits that when a previous depressive episode occurred, accompanied by the inherent negative information processing, there is a vulnerability for that mode of negativistic information processing to be activated in face of periods of lowered mood; e) The Response Style Theory, proposed by Nolen-Hoeksema [145], suggests that depressed individuals respond to depressed mood by focusing on their depressive symptoms, and this rumination perpetuates negative feelings; f) The Interacting Cognitive Subsystems Hypothesis [146] suggests that depressive patients have a shift in information processing from a specific to a more generic level of meaning, and this more generic holistic level encodes information in terms of its relation to globally negative views of the self; and g) The Kindling and Episode Sensitization Model [147] focus on the common recurrence of MDD, with kindling referring to an event exceeding the threshold for activation and sensitization pertaining to the lowering of thresholds in face of repeated experiences, thus leading to less activation being needed to reach the threshold. Depression activates a complex network of depression-related emotions that exert a negatively biased influence on processing stimuli, starting a vicious cycle in which it becomes more difficult to activate areas of positive emotions, thereby perpetuating the negative mood. Perhaps the most important common feature of all these theories is the systematic negativity bias that accompanies depression, producing a hyper-reactivity to negative emotion [148, 149], and forcing the existence of a negative loop which leads to cognitive-emotional impairment and all its consequences. If that loop is disrupted, normal processing will ensue and the depressed mood will disappear. In light of the psychological theories on how exercise affects mood and depression, it can be envisioned that exercise may positively influence these psychological constructs involved in depression.

Finally, the brain reward system incorporates many of the psychological and physiological aspects mentioned above, which are involved in depression and exercise. This system integrates experiences of pleasure in response to both external and internal stimuli [150] and mediates reward behaviors such as pleasure and motivation, which elicit approach
behaviors, increase the frequency and intensity of the behaviors, maintain the behaviors, prevent extinction, and induce subjective feelings of pleasure or positive emotional states. It arises from structures localized over multiple brain regions, being mediated by networks of neurons and regions acting both in serial and parallel [151], including the prefrontal cortex, limbic regions, and basal ganglia [152], involves multiple neurotransmitters, including serotonin, dopamine, norepinephrine, neuroendocrine systems, such as the hypothalamic-pituitary-adrenal axis, neuropeptides and hormones [150, 152, 153]. It is an extremely complex system, still far from fully understood [154], and its deregulation has been proposed as one of the many factors involved in MDD, especially due to the anhedonia that represents one of its core symptoms [153]. Several lines of evidence support this involvement, and two non mutually-exclusive neurobiological mechanisms have been suggested to contribute to anhedonia in MDD: hyporesponsivity of structures within the mesolimbic dopamine system related to processing rewards, which have been observed in MDD patients in response to positive stimuli, and hyperresponsivity in cortical regions associated with conflict monitoring, which have also been observed in MDD patients [155]. In MDD patients, the release of catecholamines within the mesocorticolimbic system, a major component of the brain reward system that produces rewarding effects, correlates highly with severity of depression, with patients with more severe symptoms reporting rewarding effects 3.4-fold greater than controls, suggesting that a hypersensitive response in MDD patients may reflect a hypofunctional state [156]. On the other hand, under catecholamine depletion, remitted unmedicated MDD patients show performance deficits on a reward processing task, which correlated directly with the return of depressive symptoms, but no change on control tasks involving working memory or attention, suggesting that the sensitivity of central reward processing systems to reductions in brain catecholamine levels seems to represent a trait-like marker in MDD, and confirming that even remitted MDD patients are more sensitive than control subjects to developing mood changes during fluctuations in catecholamine levels [157]. Moreover, unmedicated MDD individuals had an impaired tendency to modulate behavior as a function of prior reinforcements, particularly in the absence of immediate rewards, expressing a response bias toward a more frequently rewarded cue in the absence of immediate reward [158], suggesting MDD individuals have a reduced hedonic capacity.

Recent imaging techniques have confirmed neuroanatomical functional abnormalities in the subcortical dopaminergic midbrain nuclei, the medial forebrain bundle and in target regions receiving subcortical projections, as well as microstructural abnormalities in the ventral tegmentum and dorsolateral prefrontal white matter, both components of the subcortical reward/aversion circuitry, in subjects with MDD [159]. In addition, MDD is characterized by hyperactivation in regions associated with motor preparation during reward selection, but not cognitive control or ongoing monitoring of potential reward [155]. Functional MRI showed that individuals with MDD have a reduced activation of striatal reward regions during reward selection, anticipation and feedback, but not hyperresponsivity of cognitive control regions during reward selection or reward anticipation. However, they showed hyperresponsivity to the rewarding effects of dopamine-related neuroanatomical substrates, with altered brain activation in the ventrolateral prefrontal cortex and the orbitofrontal cortex, a region associated with assessment of risk and reward, and the caudate and putamen, as well as decreased activation of the middle frontal gyrus and the rostral cingulate gyrus. Depression severity was predicted by activation in bilateral midfrontal gyrus [152].
All these mechanisms may be involved on the positive effects of exercise in depression, and may play a role on the observed results that patients who continued to exercise during follow-up maintained a better depression and functional status.

**Conclusion**

Our results suggest that physical exercise can be used as an effective therapy, adjuvant to pharmacological therapy, in treatment-resistant MDD, with 47% of participants in the exercise group continuing to exercise at follow-up without the need for further motivational strategies. The improvement of all studied parameters of depression and functioning achieved after a 12 week exercise program of 30-45 minute walks 5 times a week was maintained at 6 month follow-up for patients who continued to exercise. These results are in line with previous studies in MDD and add to their findings in that there was no crossover in treatments after completion of the 12 week exercise program – pharmacotherapy remained unchanged during follow-up, none of the patients, either in the exercise or the control group, entered psychotherapy, and none of the patients in the control group initiated an exercise program during follow-up – thus suggesting that it is the continuation of exercise that is truly responsible for the maintenance of a better depression status. However, QoL improvements due to exercise were maintained after 6 months follow-up, even for patients who stopped exercising. Given the importance of effectively address QoL as a component of depression therapeutic approaches, since residual symptoms, and thus poor QoL, are predictors of relapse and recurrence, longer studies, in larger non-remitted MDD population samples are warranted, to further investigate the length of the exercise program on the quality of life of these patients and its true long-term effect, after withdrawal from physical activity. Additional measures are advised to increase exercise adherence rates at follow-up, in order to achieve maximal benefits for MDD patients.

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