Chapter 5

Exercise Intervention in Treatment-Resistant Major Depressive Disorder: Benefits of Accelerometer Monitoring

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Abstract

Although there are several reports on the benefits of exercise on Major Depressive Disorder, none has monitored these exercise programs with accelerometers. We have conducted a 12 week home based moderate intensity exercise program in 33 treatment-resistant Major Depressive Disorder patients and, based on accelerometer data, determined compliance, exercise patterns and relationship between time spent in MVPA, response to treatment and Quality of Life. Patients were diagnosed according to DSM-IV criteria, and, from 150 initially screened, 33 met study criteria and were included. Four patients were excluded due to non-compliance/drop-out, thus a total of 29 patients finished the study. Patients were randomized either to a moderate intensity exercise program, which consisted of 30-45 min/day walks, 5 days/week, for 12 weeks, plus usual pharmacotherapy (N=22) or regular daily activities plus usual pharmacotherapy (N=11).

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All participants wore an ActiGraph® GT1M accelerometer during the 12 weeks. Moderate to very vigorous physical activity (MVPA), HAMD17, BDI, GAF, CGI-S, WHOQOL-Bref and SF-36 were assessed. Results show a trend for increasing time spent in MVPA from no response to response and remission (p = 0.028), and medium to strong correlations between time spent in MVPA and better depression and functioning parameters. There was also a trend for increasing time spent in MVPA and improvement of some QoL domains, namely WHOQOL-Bref Physical domain and SF-36 Physical Functioning and General Health Domains (p < 0.05). Participants showed preference for exercising on weekdays and on specific periods of the day (p < 0.05). Therefore, we suggest that future implementation of effective exercise augmentation therapy programs in MDD patients should consider objective measures that allow the quantification of exercise and assessment of exercise patterns.

**Keywords:** Accelerometer; walking; exercise; physical activity; major depression

**Introduction**

It is known that one of the main symptoms of Major Depressive Disorder (MDD) is increased tiredness, and depression has been associated with low physical activity, with the percentage of low-level daytime activity being directly related to the severity of depression [1]. Despite several available therapeutic approaches to MDD, remission rates remain modest [2], and exercise has been proposed as a possible adjuvant therapy, given several lines of evidence showing its positive effects on depressive symptoms, functioning, QoL and executive control processes [3-6]. In fact, exercise is currently recommended by several international guidelines not only to prevent depression but also as a stand-alone or adjuvant therapy for MDD, and for all phases of MDD treatment - acute, continuation and maintenance - as long as there is no medical contraindication to exercise [7-12]. Data generally support at least a modest improvement in mood symptoms for patients with major depressive disorder who engage in aerobic exercise or resistance training, and the advantages of exercise are attractive: exercise is safe, well tolerated, brings several health benefits, improves general well-being and can be sustained indefinitely at literally no costs [3], thus having the potential to restore psychosocial function and eliminate residual symptoms, consequently reducing the risk of relapse [13]. Chronic or treatment resistant MDD patients, who are poorly motivated to perform any kind of physical activity, adhere very well to exercise programs, with encouraging improvements in their depression and functional status [5]. Additional benefits of physical activity and exercise on health include increased muscle strength, enhanced cardiovascular function, increased sleep quality, control of hypertension, hypercholesterolemia, and diabetes, as well as improved physical appearance.

However, many studies have shown several methodological limitations that prevent the effective implementation of exercise programs among the most conventional treatments, and only 10% of healthcare professionals currently recommend exercise to their patients [14]. Moreover, studies to date in MDD patients rely solely on self-reported measures, which have been questioned by several authors, given the differences found concerning self-reported compliance and compliance calculated based on objective measures in other pathologies [15, 16], and may be the reason for the on-going controversy regarding exercise intensity and frequency necessary to produce positive effects [17, 18].
Accelerometers not only provide an objective measure of exercise intensity and energy expenditure but also, and perhaps most importantly, information concerning exercise patterns, which may be crucial for the future implementation of effective exercise programs in MDD patients.

Therefore, our goal was to determine, based on accelerometer data, compliance to a moderate intensity 12 week exercise program, exercise patterns and relationship between time spent exercising, response to treatment and Quality of Life.

Methods

Participants

From 150 initially screened individuals, attending the out-patient psychiatry clinic at Hospital de Magalhães Lemos, Portugal, between September 2009 and March 2010, 45 were diagnosed with MDD according to DSM-IV criteria, and considered treatment-resistant, defined as failure to reach symptomatic remission after at least 2 adequate antidepressant trials [19]. Of these 45, 33 met the study criteria of 1) not having psychiatric co-morbidities, 2) not having relevant clinical co-morbidities, 3) absence of psychotic symptoms, 4) not imminently suicidal, 5) not currently undergoing psychotherapy, 6) no change of pharmacological therapy less than 6 weeks prior to beginning of exercise program, 7) not already participating in regular aerobic exercise, 8) physical fitness to endure moderate intensity exercise confirmed in writing by attending physician and 9) normal ECG.

Study Protocol

Participants were randomized in two groups: 22 were assigned to the exercise group, consisting of a moderate intensity home-based exercise program of 30-45 min/day walks, 5 days/week, for 12 weeks, in addition to usual pharmacotherapy, with 1 walk per week supervised at the Hospital Gymnasium, on a treadmill set to 5 km/hour [3], with an inclination of 0º; 11 participants were assigned to the control group and continued their regular daily activities plus usual pharmacotherapy.

Once a week, individuals from the control group went to the Hospital Gymnasium, where they interacted with the teacher, the technicians and each other for 30-45 minutes, assuring they were allowed to spend the same amount of time with the Hospital staff as individuals in the exercise group. During the 12-week study period all individuals wore an ActiGraph® GT1M accelerometer around the waist during waking hours, except when showering or swimming, given the unit is not waterproof, and these activities were clearly reported in the log diary.

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 and Quality of Life. The study protocol was approved by Hospital de Magalhães Lemos Institutional Review Board. All participants provided written informed consent.
Assessment of Physical Activity

The ActiGraph® GT1M is a two-dimensional accelerometer which measures accelerations and decelerations on two previously chosen axis, over a pre-programmed time interval (epochs), providing information regarding energy expenditure, intensity and duration of everyday activity, that has been widely used in several research and intervention programs, with children, adults and elderly individuals [20-23]. Accelerometer specifications allow for the filtering out of high-frequency vibration movements, thus only detecting normal body motion. Waist wearing was chosen because when the device is intended to collect daily energy expenditure data it should be affixed to the body’s center-of-mass to ensure the most accurate caloric measurements [24]. Accelerometers were set to 1-minute epochs and data were downloaded to a computer weekly. The following cutoff points, in counts/min, were used to differentiate among different activity intensity levels: sedentary < 100, lifestyle 101-759, light 760-1952, moderate 1953-5724, vigorous 5725-9498, very vigorous > 9499 [24, 25].

Participants kept a diary to record when the accelerometer was put on and taken off, whether or not they had exercised and, in the case they had exercised, if they were alone or not. Weekly reports were given to all the participants in the intervention group regarding their compliance to the recommended exercise program and the levels of physical activity attained during the previous week.

Outcome Measures

Depression was assessed by HAMD17 [26] and the Beck Depression Inventory (BDI-II) [27], functioning was assessed using the Global Assessment of Functioning (GAF) [28] and the severity subscale of the Clinical Global Impression Scale (CGI-S) [29]. The WHOQOL-Bref [30] and SF-36 [31, 32] instruments, adapted and validated for the Portuguese population, were used to assess Quality of Life. Response was defined as a decrease from baseline to endpoint of ≥ 50% on the HAMD17 score and remission defined as an endpoint HAMD17 score ≤ 7.

Data Analysis

Primary outputs from ActiGraph® are activity counts and steps, which are summed over each epoch. Counts may then be converted to kcals, given the weight of the individual, and to intensity and duration of everyday activity. Steps, kcals and time spent in each activity intensity were averaged to yield a mean value per day, and then analyzed per period of day, per day of the week, per week, per assessment and total (ie, over the 12 weeks). Kcals/kg/week (KKW) and time spent in moderate to very vigorous physical activities (MVPA) in minutes per week were also calculated. Total KKW and total MVPA were calculated by averaging KKW and MVPA throughout the study to yield a mean value per week. All participants wore the accelerometer for a week before engaging in the study, in order to obtain a baseline of their usual daily activity.
Since accelerometers were worn for the entire study period and no data were extrapolated, no minimum daily wear time was considered. Also, no “allowable interruption period” was considered [33] since, given our population consists of treatment-resistant MDD patients, even long periods of time of zero counts during the day should represent true sedentary behaviour and not time during which the accelerometer has been removed. MVPA activity was used to calculate % compliance (MVPA performed x 100/MVPA prescribed).

Statistical Methods

Normality of distributions was determined using the Shapiro-Wilk test. For baseline characteristics, t-tests were used. Differences between and within groups were analyzed either using an analysis of variance (ANOVA) or 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. Correlations between accelerometer data and clinical variables were performed using Pearson or Kendall’s τ-b rank correlation coefficients, depending on the parameters being normally distributed or not, respectively. Trends were tested using linear-by-linear association χ² statistic and linear regression. Tests were considered significant at α = 0.05 significance level (two-sided).

Results

Accelerometer Data at Baseline and during the 12 Week Exercise Program

Baseline demographics, psychiatric and quality of life profiles have already been reported for this population [3, 4], and have shown that the exercise group had greater depression severity and worse functioning than the control group, but since this was a randomized study, any baseline group difference is due to sampling error, and analysis of data using ANCOVA is appropriate [34].

Table 1. Accelerometer data at baseline and during the 12 week exercise program

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Control group (n = 10)</th>
<th>Exercise group (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>total</td>
</tr>
<tr>
<td>Kcals/kg/week</td>
<td>39.8 (19.6)</td>
<td>32.4 (21.1)</td>
</tr>
<tr>
<td>Total counts/day</td>
<td>275,490±129,397</td>
<td>219,772±135,776</td>
</tr>
<tr>
<td>Total steps/day</td>
<td>8,176 (3,767)</td>
<td>5,989 (3,822)</td>
</tr>
<tr>
<td>Time lifestyle/day</td>
<td>231.2 (72.1)</td>
<td>170.3 (96.7)</td>
</tr>
<tr>
<td>Time light/day</td>
<td>91.2 (56.7)</td>
<td>75.1 (61.4)</td>
</tr>
<tr>
<td>Time moderate/day</td>
<td>29.4 (25.2)</td>
<td>21.9 (16.4)</td>
</tr>
<tr>
<td>Time vigorous/day</td>
<td>0.06 (0.01)</td>
<td>0.72 (1.88)</td>
</tr>
<tr>
<td>Time MVPA/week</td>
<td>206.5 (176.5)</td>
<td>158.2 (118.3)</td>
</tr>
</tbody>
</table>

All values are mean (sd); all times in minutes; MVPA = Moderate to Very Vigorous Physical Activity. a,p < 0.05 within-groups from ANCOVA with baseline values as covariate; b,p < 0.05 between-groups from ANCOVA with baseline values as covariate.
Baseline physical activity has shown no differences between groups, but during the study the exercise group showed almost all parameters significantly higher than the control group, and increased time spent in MVPA/week compared to baseline – Table 1.

Compliance According to Accelerometer and Diary Data

There was an overall compliance of 97% to the exercise program, calculated based on accelerometer data (considered “true compliance”) and a 91% compliance calculated based on diary data (self-reported compliance) [3]. Comparison of percent true compliance and self-reported compliance per week – Figure 1 – showed that self-reported compliance was below true compliance on all weeks, although only statistically significant on weeks 11 and 12.

![Figure 1. Compliance per week according to accelerometer data and to diary data. % MVPA = MVPA performed*100/MVPA prescribed; % times exercised = times self-reported exercise*100/5; p-values from ANOVA.]

Total Time Spent in MVPA and Response Groups

In order to ascertain if response to treatment depended on time spent in MVPA, total time spent in MVPA according to response group – no response, response, remission – was analyzed, considering aggregated data from both groups. There was a trend for increasing time spent in MVPA in min/week from no response to response and remission (216.1 ± 103.8, 303.2 ± 18.7 and 314.0 ± 104.9, respectively), confirmed by linear-by-linear association $\chi^2$ statistic ($\chi^2 = 4.843, p = 0.028$) and linear regression ($F = 5.647, p = 0.025$).
In order to determine the influence of time spent in MVPA, energy expenditure and average times exercised per week on clinical parameters, correlation analysis was performed, considering aggregated data from both groups. Table 2 shows all statistically significant correlations. Total time spent in MVPA and average times exercised per week showed significant favorable correlations with all depression and functioning parameters. There was a trend for increasing time spent in MVPA and improvement of some QoL domains, namely WHOQOL-Bref Physical domain and SF-36 Physical Functioning and General Health Domains (linear-by-linear association \( \chi^2 \) statistic: \( \chi^2 = 4.598, p = 0.032; \chi^2 = 5.425, p = 0.020 \) and \( \chi^2 = 5.599, p = 0.018 \), respectively; linear regression: \( F = 5.305, p = 0.029; F = 6.488, p = 0.017 \) and \( F = 6.749, p = 0.015 \), respectively).

Table 2. Correlation coefficients between accelerometer/diary data and clinical variables change from baseline to last observation

<table>
<thead>
<tr>
<th></th>
<th>Total MVPA</th>
<th>Total KKW</th>
<th>TPWA</th>
<th>TPWD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAMD17</td>
<td>-0.383</td>
<td>-0.637</td>
<td>-0.627</td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>-0.440</td>
<td>-0.396</td>
<td>-0.540</td>
<td>-0.457</td>
</tr>
<tr>
<td>GAF</td>
<td>0.490</td>
<td>0.651</td>
<td>0.538</td>
<td></td>
</tr>
<tr>
<td>CGI-S</td>
<td>-0.420</td>
<td>-0.577</td>
<td>-0.501</td>
<td></td>
</tr>
</tbody>
</table>

MVPA = Moderate to Very Vigorous Physical Exercise in minutes per week, during the whole study period; KKW = kcals/kg/week during the whole study period; TPWA = Average times exercised per week during the whole study period, based on accelerometer data; TPWD = Average times exercised per week during the whole study period, based on diary data. All correlations are significant at \( p < 0.05 \). All Pearson correlation coefficients.

Exercise Preferences

Given one of our goals was to gather data, which will allow the most efficient implementation of an exercise program in MDD patients, exercise preferences were analyzed. Analysis of self-reported times exercised per week over time have shown that there was always a preference to exercise with company rather than alone, but only significant at week 12 – Figure 2. As for total time spent in MVPA per day of the week and per time of day – Figure 3 – there were no differences within the control group, but the exercise group showed a preference for week-days, the morning period until lunch time (9:00 AM – 13:00 PM) and the afternoon period (4:00 PM – 7:00 PM).

Discussion

Although there are no studies with accelerometer data in treatment-resistant MDD patients, other psychiatric pathologies have shown reduced motor activity compared to controls [35], and unmet physical activity guidelines on overweight and obese adults with severe mental illness, with an average MVPA of 120 min/week [36]. Our population has
shown average steps/day below the recommended 10,000 [37], both at baseline and during the study, for both groups. Also, counts/day and MVPA were lower than the ones reported for patients with schizophrenia and healthy European adults, at baseline and during the study for the control group, and at baseline for the exercise group, with values for the exercise group reaching similar levels [38, 39]. Kcals/kg/week, both at baseline and during the study, for both groups, were also lower than the ones reported in severely mentally ill patients [40].

During the study the exercise group showed all parameters significantly higher than the control group except for time light/day and time vigorous/day, and increased total counts/day, time moderate/day, time vigorous/day, KKW and time spent in MVPA/week compared to baseline. Thus, patients in the exercise program not only accomplished but exceeded the recommended 150 min/week MVPA [9, 12].

We can speculate that this may have stemmed from the exercise program design. We have designed an exercise program that would not only comply with current exercise recommendations for MDD patients [9, 11] but that would also have the duration considered to be necessary for exercise to have positive effects on depressive symptoms [41]. Moreover, and considering that the patients included in this study were treatment-resistant and thus particularly severe MDD patients, we have followed the recommendations from the American Psychiatric Association and the Canadian Psychiatric Association that exercise intensity and frequency should be the ones the patient prefers and will adhere to [7, 8], and have used several motivational strategies throughout the study. Also, cultural factors may play a role in this high MVPA. In Portugal there is the generalized concept, engrained among the population, that to exercise and to be outdoors is good and positive in almost all situations, and most especially in face of illness. Therefore, not only patients will have a self-motivation to exercise and go outdoors, they will also be encouraged to do so by their family, friends, neighbors and co-workers. Moreover, the climate and environment are pleasant and encouraging for walks, during which patients will have the added advantage of interacting socially with people they meet along the way.

Compliance

One extremely important issue concerning exercise programs in patients is compliance, since if compliance is poor not only the exercise will not have the desired effect but also the conclusions drawn from the studies will be of limited interest. Different adherence rates have been reported for other depressed populations [42-44] and the observed 97% overall true compliance was extremely high, especially considering the severity of MDD in these patients.

We propose that this adherence rate can be explained considering mainly the psychological theories that have been proposed by several authors.

It is extremely challenging to motivate these patients to start to exercise, mainly due to their anhedonia and loss of energy, but also their low self-esteem and self-confidence, feelings of guilt or worthlessness and social withdrawal, all core symptoms of MDD. These patients, especially ours, who were treatment-resistant, only want to stay at home, in bed or on the couch, alone, in the dark, with no personal or social contact at all. Besides all this, the prevalence of pain in depressed patients, yet another reason for them not to want to engage in any kind of physical activity, is estimated to be 65% [45]. Therefore, we have relied on mainly three theories of exercise adherence to implement strategies that would lead these
patients to start exercising: a) Bandura’s Self-Efficacy Theory [46], which has been shown to have the strongest support as a correlate of exercise and physical activity [47-50], especially pertaining adherence during the adoption phase of exercise behavior [51]; b) Self-Determination Theory [52, 53], whose constructs have been shown to predict exercise behavior in both healthy and clinical populations [54-56]; and c) TTM, initially developed as a model to explain and propose interventions to deal with addictive behaviors [57], but that has since been extensively applied to other behaviors, such as exercise acquisition [58, 59], with good results for promoting exercise adoption.

Bandura’s Self-Efficacy Theory is the most widely used competence-based approach to exercise. This theory posits that both perceived self-confidence and self-efficacy will lead to a behavioral change which will enable the person to achieve the intended goal [60], in our case the initiation of the exercise program. Perceived self-efficacy is defined by Bandura [61] as: “peoples' judgments of their capabilities to organize and execute courses of action required to attain designated types of performances”, and is influenced by four intrinsic and extrinsic variables [61, 62]: 1) Prior success and performance attainment; 2) Imitation and modeling, particularly of people similar to oneself; 3) Verbal and social persuasion and 4) Judgments of physiological states, such that states of relaxation can be achieved.

Given the psychopathology of MDD, patients will have no a priori self-efficacy, and the first variable will negatively influence them, since being anhedonic and feeling they have very little energy, prior successes are inexistent; the second variable, in our opinion, will not influence them in any way, given their social withdrawal; the third and fourth variables, however, will influence their self-efficacy positively, as long as the external motivation is adequate. Given both self-efficacy expectations – “I can do it” – and outcome expectations – “I will get better” – are crucial to the success of this initial adherence, we have adopted several strategies that have shown efficacy in encouraging people to exercise: after establishing a strong therapeutic alliance, we have promoted a task-orientation approach, a mastery motivational climate, incited patients to adopt mastery-approach goals, drove them to reach intrinsic motivation both at the contextual and situational levels, constantly used positive reinforcement strategies, developed impression management and implemented the use of accelerometers by all patients.

A strong therapeutic alliance is paramount for the success of this type of program. It is known that interpersonal interactions strongly affect the likelihood that change will occur, that the clinician is a significant determinant of treatment outcome, that both patient and doctor expectations for change have powerful effects in the patient and that statements reflecting motivation for and commitment to change predict later behavior change. The motivational interviewing approach, as we have used, is a clinical method of counseling characterized by a collaborative relationship between doctor and patient: the doctor seeks to find and elicit intrinsic motivation for change in the patient, while acknowledging and respecting the autonomy of the individual in accepting the responsibility for change, expressing empathy through acceptance, listening and respect, avoiding arguing for change, inviting but not imposing new perspectives and supporting self-efficacy, in such a way that the doctor’s personal belief and expectations about the patient’s capability to change exert a powerful effect on outcome [63]. The choice of a task-orientation approach, a mastery motivational climate and the encouraging of patients to adopt mastery-approach goals, were based on numerous studies that have shown these are the most suitable motivation methods to lead people to enroll in exercise programs. Task-orientation sets the goal of action on
developing mastery, improvement, or learning, with a self-referenced demonstration of ability, and success is perceived when mastery or improvement has been attained. The goal of action for an ego-oriented approach is to demonstrate ability relative to others or to outperform others, making ability other-referenced, and realizing success when others are out-performed [64]. Given the psychopathology of our patients, an ego-oriented approach would have been profoundly detrimental. Also, a task-involved person will develop adaptive achievement behaviors, since as the person is trying to demonstrate mastery or improvement, he/she will be more likely to persist in the face of failure, to put more effort into the task and to be interested in the task [64-66]. Task-orientation fosters perceptions of competence and success for individuals who are either high or low in perceived competence, encourages the exertion of effort, and leads individuals to construe competence based on self-referenced criteria and to be primarily concerned with mastery of the task [67]. Given our patients were extremely low in perceived competence before the start of the exercise program, task-orientation was clearly the right choice: “this exercise program is for you to get better. It doesn’t matter to be better or even equal to others, the only thing that matters is for you to get better”.

Moreover, task-oriented individuals feel satisfied when they have mastery experiences and perceive a sense of accomplishment during their exercise participation [68], and also experience greater enjoyment in performing the activity than those who are high in ego orientation and low in task orientation [69]. It was our goal that patients enjoyed their walks as they got better, and it has been shown that task-involvement fosters positive affect in physical activities [70]. Task-orientation leads people to try harder and perform better, and seems to be important for continued participation in physical activity. In our case trying harder fights anhedonia and performing better reflects on depression improvement, and as depression improves patients will try even harder and improve more. It is a positive reinforcement cycle.

For this task-involvement to be achieved, the creation of a mastery motivational climate, supporting effort, cooperation, and putting emphasis on learning and task mastery [71] is important in optimizing positive (i.e., well-being, persistence, task perseverance, adaptive achievement strategies) and attenuating negative responses. Evidence supports that perceptions of a mastery motivational climate are associated with more adaptive motivational and affective response patterns than perceptions of a performance climate [70]. Being MDD patients, a performance climate would be completely unadvisable, given performance is expected to be low.

Finally, the adoption of mastery-approach goals was followed due to evidence that these, which focus on performing a task as well as possible or surpassing a previous performance on a task, appear to be optimal, being associated with the set of consequences we were seeking for our patients: enhanced intrinsic motivation, information processing and reduced anxiety. The adoption of any of the other approaches – performance-approach goals, which focus on outperforming others, performance-avoidance goals, which focus on not being outperformed by others, or mastery-avoidance goals, focusing on not making mistakes or not doing worse than a previous performance – would be clearly detrimental. It is now clear that task involvement as well as the development of mastery oriented environments will facilitate effective motivational patterns for all participants [72].

Nevertheless, it is possible that our patients started the exercise program with strong task-involved motivation, as we have incited them to adopt this behavior, and, as they got better
and felt better, wished to try to demonstrate normative ability, or avoid demonstrating inability, comparing their ability with healthy people, and thus becoming, at least in part, ego-involved in the task – the exercise program – which is supported by theories that goal states are dynamic and can change as information is processed [73].

The goal of driving patients into reaching intrinsic motivation both at the contextual and situational levels was based on previous research that has concluded that intrinsic motivation is more efficacious in physical activity contexts than extrinsic motivation. Intrinsic motivation pertains to doing something for its own sake, unlike extrinsic motivation, in which the person is driven to do something as a means to attain some kind of external goal [74]. Our emphasis was always on the patient: “do this for your own sake, to feel better and get better”. The importance of reaching motivation at the contextual and situational levels is of particular relevance to these patients, given the first will orient them toward a specific context and the second pertains to the motivation individuals experience when engaging in a specific activity at a given moment in time [75]. In our case, these translate into getting better and engaging in the exercise program, respectively. The strategies adopted to reach these motivational states were the ones that have been shown to be more effective: a) provide an autonomy-supportive motivation [76], which was always done, throughout the entire exercise program, by all the team involved in the study; b) provide positive feedback [77] conveyed in an autonomy-supportive fashion [78], always avoiding controlling or coercive messages, which are known to undermine intrinsic motivation [79] – on their weekly visits to the Hospital Gymnasium, patients were given the accelerometer results from the previous week, together with some kind of positive feedback “Look how good you have done! Keep up the good work! It is really important for your own good to continue to do this”; c) giving them the choice to perform the walks where they wanted, when they wanted and with whom they wanted, given it has been reported that choice facilitates intrinsic motivation concerning physical activity [80]; d) not using a reward or award system, which have been shown to decrease intrinsic motivation [81]; and e) discourage any type of competitive focus. If this undermines intrinsic motivation in healthy people [82], it would have devastating effects in these MDD patients.

If the intrinsic motivation is successful, positive affective outcomes such as satisfaction, interest, enjoyment [83], less fatigue, psychological distress, and perceived exertion [84], and behavioral outcomes, such as the intention to continue engagement in the activity, and dedicating more effort to it [85], will follow. The high compliance we have seen in our patients, and the effects on depression and functional parameters, which will be discussed in the next section, show that the adopted motivational strategies were successful.

The adopted impression management approach was almost secondary to the other used strategies, but nonetheless may have contributed to the observed high compliance. It is well established that we all want to positively impress others, and the impressions we make have important implications for how we see ourselves, how other people treat us, and our success on social outcomes. Given our patients had low self-esteem and self-confidence, feelings of worthlessness and social withdrawal, we envisioned that an impression management approach could help adherence to the exercise program. According to Leary and Kowalski [86], the desire to create particular impressions is powered by three situational determinants: the relevance of creating a particular impression in order to fulfill one’s goals, the value placed on these goals, and the discrepancy between the image that one has already made and the image that one wants to make.
In the case of our patients, these translate into getting better and increasing self-esteem and self-confidence. Also, people who have high fear of negative evaluation, which is the case of our patients, due to their psychopathology characteristics, may be particularly motivated to impression-manage. Impression motivation has been shown to predict future intentions to exercise when considered in conjunction with social pressure to exercise [87] and people who are highly fearful of negative evaluations are more likely to base their intentions to exercise on subjective norms, putting forth greater effort when they think that increased effort will create a desired impression [88]. Also, lower ratings of perceived exertion are reported when exercising next to a person who gives the impression that the exercise is very easy than when they exercise alone [89], and in situations where workloads can be sustained for longer periods because they are largely supplied by aerobic energy pathways, the desire to be perceived as physically fit prompts exercisers to report low perceived exertion. Given our patient’s need to seek for approval of others, these constructs may have influenced compliance.

Finally, the use of accelerometers by all patients may have contributed to increased compliance [90, 91], as well as the weekly reports given to all the participants in the exercise group regarding their performance during the previous week, which may have been an additional incentive to maintain or even exceed those physical activity levels.

All the above constructs also apply within the frame of SDT and TTM. However, TTM, the most well-known stage based model [57, 59], may help explain the behavioral change that the used strategies induced in our patients. TTM posits that four factors mediate the change process: (1) an individual’s self-efficacy for change, (2) the weighing up of perceived advantages and (3) disadvantages of change (decisional balance) and (4) the strategies and techniques individuals use to modify their thoughts, feelings, and behavior (referred to as the processes of change). Should these factors converge positively, a behavioral change will be successfully adopted. Given the observed compliance, we may claim our strategies were successful, and, within the frame of TTM, suggest that our patients were at the precontemplation stage before the initiation of the exercise program, and we have guided them through progression into the contemplation and preparation stages, finally achieving the action stage.

Along with all the mentioned motivational strategies, we have followed the recommendations that exercise intensity and frequency should be the ones the patient prefers and will adhere to [7, 8], which has certainly contributed to the high compliance.

Week-by-week comparison between self-reported and true compliance – Figure 1 – has shown good concordance, with self-reported always being lower, albeit only significant on weeks 11 and 12. Both compliances reached their minimum on week 12. We have previously proposed that the design of an exercise program that fits the specific needs of a particular pathology is crucial for effectively encouraging patients to adhere to the exercise program [3], and now further propose, based on weekly compliance analysis, that treatment-resistant MDD patients may need an extra motivational intervention before the end of a 12 week exercise program, to prevent the decrease in compliance on the last week. This is not surprising, since engaging MDD patients in exercise programs requires motivational and outreach efforts to have any chance at success [92].
Perception of Exertion

Self-reported compliance was always lower than true compliance, which is suggestive of an underperception of exertion, as has been observed in other depressed populations [15, 16], but others have associated depression and poor mental health to overperception of exertion [93, 94]. These disparities between self-perceived and true exertion, as assessed by objective measures, have led several authors to propose great caution when interpreting results based solely on self-reported physical activity [95, 96]. Self-report measures may either under or overestimate true physical activity intensity, not only because they are subject to issues such as recall and response bias, but most importantly because they necessarily reflect the persons’ perception of exertion, which is multidimensional and governed by many physiological and psychological factors [93].

We suggest that, as was the case with compliance, this underperception of exertion observed in our patients was a consequence of the study design and the strategies used to increase compliance. We have told our patients to stop whenever they felt tired, so that the exercise dose would never go beyond the ventilatory threshold – these are anhedonic patients, who feel tired just from getting up from bed and walking to the living room. An excessive dose would inevitably influence compliance, besides being psychologically detrimental. Several studies support an association between underperception of exertion and a positive impact of exercise on mood. Considering the four levels of subjective reporting of sensory experiences during exercise – discrete symptoms, subordinate, ordinate, and superordinate [97] – with the first level being associated to drive, vigorous mood, and determination, the second with cardiopulmonary, leg and general fatigue, the third linked to task aversion and the motivation to adhere to the task and the fourth associated with extreme fatigue and/or physical exhaustion, when telling our patients to stop when feeling tired, it was our intention to keep them in the first level. This aim was based on reports that found that under low effort conditions, or low to moderate levels of tolerance, dissociative coping strategies and problem solving occur. In the case of our patients this may be linked to the distraction hypothesis: they are feeling relaxed and enjoying the exercising, become more aware of the environment, are distracted by whatever surrounds them and other people, and eventually even use that walk time to think about other things, such as what they are going to have for dinner or the TV show they will watch when getting home. All these will distract them from their own psychopathology, at least while walking. On the contrary, higher levels of exercise intensity will shift attention to the overwhelming physiological sensations that dominate focal awareness and would, therefore, be prejudicial. Moreover, moderate-intensity strength training has been found to produce the greatest improvements in post-exercise anxiety, positive affect and negative affect, whilst high-intensity training resulted in increased anxiety and negative affect [98]. Underperception of exertion has been associated to more positive affect when there is a combination of high task and low ego orientation [99], as was the case of our patients, and to increased self-efficacy [100, 101], but only if the exercise intensity is maintained below or at the ventilatory threshold [102], with high self-efficacy being associated with greater positive well-being and less psychological distress [50]. The reasons why self-efficacy is negatively associated with perceived exertion were suggested by Harter [103]: self-judgments about one’s competence and self-worth on meaningful tasks moderate the motivational effects of aversive feedback or physical exertion. Underperception of exertion has also been linked to personality traits of reducers [104] and extraverts [105]. Our
MDD patients are reducers and introverts, due to their pathology, but as they got better some extravert characteristics, such as optimism, may have started to emerge.

Perception of exertion is clearly a multidimensional construct and has to be interpreted from an holistic perspective, comprises several inputs that are perceived differently across the duration of physical activity, and must take into account the different psychological components that reflect signals of motivation and affect, in addition to physical components [106, 107].

Given our results, we may speculate that the observed underperception of exertion and its increase with time in our patients may be a result of their improvement of all depression and functioning parameters [3] and physical functioning [4], as they approach response or remission: finally starting to feel better after several months of severe depression, they will perceive exertion lower as they improve, which is not confirmed by accelerometer data.

Time Spent in MVPA

Another very important issue, which remains unclear, is if the amount of time spent in MVPA influences the outcomes.

Both WHO and The American College of Sports Medicine recommend, for the maintenance of health in adults, at least 150 minutes/week of moderate-intensity aerobic physical activity or at least 75 minutes/week of vigorous-intensity aerobic physical activity or an equivalent combination of moderate- and vigorous-intensity activity. Moreover, to have beneficial effects, aerobic activity should be performed in bouts of at least 10 minutes duration. For additional health benefits, these levels should be doubled [9, 12]. For the reduction of depressive symptoms in patients with MDD, recommendations differ slightly: The American College of Sports Medicine states that at least 30 minutes of moderate-intensity physical activity on most days of the week should be performed [9], but the UK National Guidelines recommend a structured and supervised exercise program of 45 to 60 min, 3 times a week for 10 to 12 weeks [11].

Our results showed a trend for increasing time spent in MVPA and improvement of some QoL domains, and also a trend for increasing time spent in MVPA from no response to response and remission. Moreover, correlation analysis has shown that there were medium to strong correlations between time spent in MVPA and better depression and functioning parameters, corroborating other studies [95, 108, 109]. Therefore, our results suggest that more time spent in MVPA may be more beneficial concerning depression, functioning and QoL parameters.

Exercise Preferences

Given our future major goal of effectively implementing a community based exercise augmentation therapy program for MDD patients, it is important to understand their preferences concerning exercise patterns, in order to maximize efficacy. Self-reported number of walks per week – Figure 2 – showed that, although patients always preferred to exercise in the company of someone rather than alone, this difference was only significant at week 12.
Figure 2. Self-reported times exercised per week. p-values from ANOVA.

These results further support our proposal that these patients may need an extra motivational intervention, which they felt the need to seek. Further analysis of their preferences concerning day of the week and time of day – Figure 3 – showed no differences within the control group, suggesting that these patients maintain a similar basal level of physical activity regardless of the day of the week or time of day. However, the exercise group showed a clear preference for weekdays, with no differences between weekdays. These results are different from the ones reported for healthy populations [90, 110]. Baker et al. reported more activity on weekends compared to weekdays [90], but healthy individuals usually engage in leisure activities on weekends, since they do not have time to do it on weekdays, due to work obligations. On the contrary, the majority of our patients was either unemployed or on sick leave, and thus free to choose the days to exercise. We may speculate they considered their walks a task they had to perform, and since weekends are “to rest” they preferred to complete that task on weekdays. Difference from our results to the ones from Hart et al. may be due to the different age groups [110].

Although there were four preferred periods of day to exercise, the favorite period was from 9:00 to 11:00 AM. Hormones and sleep/wake cycles controlled by circadian rhythms may be in play. In depressed patients, melatonin onset is around 9:30 PM and offset at around 8:45 AM, with aMT6 (urinary melatonin metabolite) acrophase at 4:30 AM [111], which is very similar to healthy populations [112].

On the other hand, cortisol acrophase occurs between 8:30 and 10:00 AM [112] on healthy populations, and since cortisol is associated to activity levels and healthy populations do not seem to differ from patients with schizophrenia considering activity acrophase, which occurs between 10:00 AM and 4:30 PM [113], we may speculate that these preferred exercise periods are at least partially related to these hormones. Also, light is the strongest environmental controller of circadian rhythms, and MDD patients may naturally and unconsciously seek these periods for exercising.
Both the above mentioned hormonal circadian rhythms and light exposure may also explain the decrease in MVPA at night, whilst the period from 1:00 – 2:00 PM coincides with lunch time.

Another fact that has to be taken into consideration is that most MDD patients, particularly our sample which is treatment-resistant, have sleep disturbances, and it is known
that exercise promotes sleep [114]. Therefore, we may further suggest that if their sleep
quality is enhanced they will feel more energy to exercise, especially in the morning period.

**Conclusion**

The use of accelerometers as an objective measurement of physical activity in treatment-
resistant MDD patients is feasible, provides important information concerning exercise
intensity and patterns, and may contribute to the high adherence rates observed. Our results
suggest that more time spent in MVPA seems to be more beneficial concerning depression,
functioning and QoL parameters.

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, further, longer studies, using objective physical activity measurements, in
larger non-remitted MDD population samples are warranted, not only to further investigate
the effects of time spent in MVPA on the improvement of these patients, but also to assess its
ture long-term effect, after withdrawal from physical activity, and to identify characteristics
of optimal exercise programs as an adjuvant therapy for MDD.

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