Journal of Affective Disorders 191 (2016) 139–144

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Efficacy of exercise as an adjunct treatment for clinically depressed inpatients during the initial stages of antidepressant pharmacotherapy: An open randomized controlled trial

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ARTICLE INFO

Article history:
Received 14 August 2015
Received in revised form
23 November 2015
Accepted 26 November 2015
Available online 30 November 2015

Keywords:
Add-on therapy
Endurance-training
Severe depression
Antidepressant drugs

ABSTRACT

Background: Physical exercise as adjunctive treatment for hospitalized patients with major depressive disorder (MDD) has been of increasing interest in the past few years. While preliminary findings are promising, these prior studies have been plagued by inclusion of participants at different stages of medication use at study entry. The present study evaluates the effects of a short (10-days) add-on endurance-training intervention in hospitalized MDD patients on antidepressant medication for less than two weeks.
Method: Thirty-five participants were randomly assigned to one of three study groups: aerobic exercise ($n=14$), placebo (stretching) exercise ($n=11$), or no intervention (control; $n=10$). The study outcome was the change in the Beck Depression Inventory (BDI-II) total score from baseline to the end of the study period.
Results: The intent-to-treat analysis showed significant improvements in BDI-II scores for both the aerobic and the stretching groups. However, comparing pre- to post-study depression changes in these two groups, we found a large effect size in favor of aerobic exercise (Cohen's $d=-1.06$). No significant change in depressive symptoms was found in the control group.
Limitations: The nature of the intervention (i.e., exercise) meant blinding participants to treatments was not possible. Precise information on medication dosage was not available, and the short duration of interventions and lack of follow-up assessment were all limitations.
Conclusions: Endurance-training can be a helpful adjunct treatment for hospitalized patients with severe affective disorders in the initial stages of pharmacotherapy.

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1. Introduction

The effectiveness of physical exercise in reducing depressive symptoms has received considerable attention in the past few years, with seven meta-analyses of randomized controlled trials (RCTs) published in the last decade (Stathopoulou et al., 2006; Mead et al., 2009; Rethorst et al., 2009; Krogh et al., 2011; Rimer et al., 2012; Cooney et al., 2013; Josefsson et al., 2014). Even though reviewed RCTs vary substantially in size, type of control group, methodological rigor, and type of exercise modality, these meta-analyses yielded an overall moderate-to-large effect size (from $d=-0.40$ in Krogh et al. to $d=-1.39$ in Stathopoulou et al.) indicating a significant reduction in depression for exercise treatment compared with non-active control condition. Using information from the most recent meta-analysis (Josefsson et al., 2014), exercise programs typically last for 4–16 weeks, are predominantly aerobic in nature (brisk walking, running, stationary cycling), and include 2–3 weekly sessions of 35–40 min duration.

One major limitation to the widespread acceptance of exercise as a therapeutic routine for the treatment of clinical depression is that most of these previous RCTs were undertaken on participants with light-to-moderate levels of depression (Hamilton depression scale score <25, or Beck depression scale score <29). Very little is known about the extent to which physical exercise can reduce depression in individuals with severe symptoms at baseline.

One RCT by Knubben et al. (2007) assessed the efficacy of a short-term adjunctive aerobic training intervention (10 days of 30 min treadmill walking) in 20 inpatients with severe depressive symptoms receiving conventional treatments (antidepressants or sleep deprivation). This was compared with a placebo exercise intervention (10 days of low-intensity stretching and relaxation exercises) implemented in a control sample of 18 inpatients.

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http://dx.doi.org/10.1016/j.jad.2015.11.047
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Reduction in depression scores in the endurance-training group was significantly greater. Based on the statistics reported in their study, we estimated the effect size comparing aerobic and placebo interventions to be $d = -1.28$.

More recently, Schuch et al. (2011) evaluated the adjunctive effects of physical exercise (3 weekly sessions of aerobic training until hospital discharge) in 15 severely depressed inpatients under conventional treatment (antidepressants or electroconvulsive therapy). Obtained data were compared to those of 11 control inpatients (who received no intervention except conventional treatment). The mean score on the Hamilton depression scale significantly improved from baseline to discharge in both groups, but there was a difference at discharge in favor of the exercise group. Lack of statistical detail on the magnitude of depression changes in each group makes it impossible to compute a comparative effect size.

Although these two recent RCTs produced evidence that adding physical exercise in the treatment of severely depressed inpatients brings therapeutic benefits, several shortcomings are evident: (1) participants had received antidepressant medication for various amounts of time at study entry, (2) some were receiving other concomitant therapy (e.g., electroconvulsive therapy) in addition to pharmacotherapy, and (3), in Schuch et al., the total duration of the exercise stimulus varied between participants. Accordingly, an improved way to assess the add-on impact of exercise on depressive symptoms in severely depressed inpatients would be to recruit patients being treated only with antidepressant medication, and having identical (or similar) duration of treatment at study entry.

Therefore, in the present study we examined the efficacy of a 10-days long aerobic exercise program as an add-on treatment in severely depressed patients being treated with antidepressant medication (and no other form of therapy) for less than two weeks. Although such a training length may appear too short to be of interest, it can be expected to be effective since combined antidepressants and aerobic exercise was found to increase brain-derived neurotrophic factor (BDNF) levels in as short as two days (Russo-Neustadt et al., 2001). Depression score changes were compared with a control arm of patients being treated with only antidepressants. It was impossible to blind patients to treatment allocation because of the nature of the intervention. But to rule out the possibility of an attention effect, a placebo (stretching) add-on intervention was also implemented.

2. Method

This study was approved by the ethics committee of the psychiatric unit from which our research sample was drawn, and is registered at ClinicalTrials.gov (number NCT02612142).

2.1. Participants

To achieve 80% power with a significance level of $\alpha = 0.017$ and for an effect size of Cohen's $d = -1.28$ (based on Knubben et al. (2007)), the required number of participants per study group was 12 (*t*-tests for differences between 2 independent means; G*POWER, Faul et al., 2007). Because three comparisons were planned *a priori* (aerobic exercise *versus* control; aerobic exercise *versus* stretching; and stretching *versus* control), the criterion α-level for statistical significance was corrected using the Bonferroni procedure ($0.05/3 = 0.017$)

Between July 2011 and July 2015, 124 inpatients admitted for treatment of MDD were considered for participation in the study. Inclusion criteria were as follows: (a) diagnosis of MDD according to the DSM-IV-TR (APA, 2000), (b) antidepressant drug therapy initiated for < two weeks, (c) score of 29 or more on the Beck Depression Inventory (BDI-II, Beck et al., 1996), (d) ability to run or walk briskly and to understand written French. Patients were excluded if they (a) had a medical contraindication for exercise practice, (b) had MDD with psychotic features, (c) were receiving beta-blocking drugs or another form of therapy (e.g., sleep deprivation, electroconvulsive therapy)

Forty-eight out of these 124 screened patients were eligible, and 35 participated in the study (71.4% females, mean age: 45.3 ± 13.2 yrs). Among the remaining 13 depressed patients, 10 declined participation (the main reasons for refusal were lack of interest, and patients were feeling too ill to take part in exercise training), two were disqualified due to medical-related issues (asthma, arthritis), and one had psychotic symptoms.

One of the three study arms (aerobic exercise, stretching, no intervention) was randomly chosen for each participant at the end of an initial individual visit (explanation of study procedures, questions about drug use and drug treatment history, informed consent signature, baseline depression assessment). This was done by running the randbetween function of Microsoft Excel on our laptop, which generated a random number between 1 and 3: 1 = aerobic exercise (AE), 2 = stretching (ST), 3 = no intervention (NI). It resulted in a slightly uneven number of participants in the groups: 14 participants in the AE group, 11 participants in the ST group, and 10 control participants. The assigned intervention was started the day following the initial visit. As mentioned above, information was obtained from each patient as to type and time of onset of their antidepressant drug therapy during the initial visit. Unfortunately, due to stringent privacy legislation in France, access to individual medical records was restricted to medical staff, so that no individual information about daily dosage could be collected. However, given that all patients had recently started antidepressants in the present study (within less than 2 weeks before study entry) and given that one key recommendation for clinical practice is to treat depression at standard doses of antidepressants for a minimum of 4 to 8 weeks before labeling a treatment regimen as ineffective (Adams et al., 2008), we can speculate that all patients were receiving standard doses of antidepressants during the period of the study. These standard dosages can be found in Adams et al. (2008) and are listed in Table 1, along with other measured pretreatment characteristics.

2.2. Procedure

In the aerobic exercise (AE) group, the intervention consisted of 30 min of daily brisk walking or jogging for 10 consecutive days. Participants who missed > 2 training sessions were considered as non-completers. Exercise intensity had to be maintained within 65–75% of age-predicted maximal heart rate, as commonly prescribed in studies using aerobic exercise to alleviate depression (Perraton et al., 2010). Exercise sessions took place outdoors (the EPSMM has a large park with green areas and safe walking paths through its blocks) under the supervision of the first author (PhD in sports sciences). A total of 106 of the 115 training sessions (92.2%) were individual. Nine sessions included 2 patients for whom the exercise intervention had started almost simultaneously. A typical session lasted for approximately 45 min (generally from 5.30 pm to 6.15 pm) including installation, programming and de-installation of a heart rate monitoring device (Polar S725 chest belt and wristwatch).

Patients in the stretching (ST) group also performed a daily 30 min exercise program for 10 consecutive days, but this consisted of stretching exercises instead of endurance training. Several muscle groups (thighs, calves, gluteal, shoulders, back) were stretched for 60 s, with equivalent resting intervals between stretching series. Training sessions were carried out in a room of

Table 1
Baseline data of study participants.

	AE group ($n=14$)	ST group ($n=11$)	NI group ($n=10$)	p-Value
Age, mean (*SD*)	45.3 (10.6)	41.8 (13.2)	49.1 (16.5)	.46
Sex, *n* (%)				.70
Women	9 (64.3)	8 (72.7)	7 (70.0)	
Men	5 (36.7)	3 (27.3)	3 (30.0)	
Occupational status, *n* (%)				.71
Full-time	6 (42.9)	4 (36.4)	3 (30.0)	
Part-time	3 (21.4)	2 (18.2)	2 (20.0)	
Unemployed	3 (21.4)	4 (36.4)	2 (20.0)	
Retired	2 (14.3)	1 (9.1)	3 (30.0)	
Antidepressant duration, *n* (%)				.79
< 1 week	10	8	6	
< 2 weeks	4	3	4	
Treatment*, *n* (%)				.99
SSRIs (paroxetine, fluoxetine)[a]	9 (64.3)	8 (72.7)	7 (70.0)	
SSNRI (milnacipran)[b]	3 (21.4)	2 (18.2)	2 (20.0)	
dopamine agonist (bupropion)[c]	2 (14.3)	1 (9.1)	1(10.0)	
BDI-II score, mean (*SD*)	36.1 (5.9)	37.8 (8.3)	35.7 (6.7)	.76

Note. AE group = aerobic exercise group, ST group = stretching (placebo) group, NI group = control (no intervention) group.

* 2 patients in the AE group, 2 patients in the ST group and 1 patients in the NI group received hypnotics drugs in addition to antidepressant medication ($\chi^2=0.29$, $p=.87$).

[a] Standard starting dosage for SSRIs is 20–50 mg/day for paroxetine, and 20–80 mg/day for fluoxetine.

[b] Standard starting dosage for milnacipran is 50–100 mg/day.

[c] Standard starting dosage for bupropion is 100–200 mg/day.

the hospital restricted to these activities and were also supervised by the first author. As was the case for the AE intervention, participants who missed > 2 training sessions were considered as non-completers, and the format of delivery was mostly individual (only 4 of the 85 stretching sessions included 2 patients).

Finally, participants in the control (NI) group received no intervention other than prescribed medication.

Assessment of depressive symptoms was performed the day before and the day after each treatment period of 10 days.

2.3. Depression measure

The self-report Beck Depression Inventory (BDI-II, Beck et al., 1996) was used to assess the magnitude of change (total score) in depressive symptoms and clinical response to interventions. It was preferred over other commonly used measures of depression (e.g., the Hamilton Depression Rating Scale) that have to be administered by a health care professional. The BDI-II has 21 items evaluating symptoms and attitudes related to MDD in the past week. It includes items such as sadness, self-dislike, and suicidal ideation. This instrument has been shown to be a valid and reliable measure of depression severity and is widely used in studies examining the antidepressant properties of exercise (Chu et al., 2009).

2.4. Statistical analysis

First, the changes in depression scores from baseline to final assessment were examined through a mixed-design analysis of variance (ANOVA) with one within-subject variable (testing time) and one between-subject variable (groups). Follow-up Bonferroni corrected paired sample *t*-tests were conducted to determine the presence of significant differences for the mean comparisons of interest.

The magnitude of pre- to post-intervention changes in depression scores was then compared between groups using a one-way analysis of variance (ANOVA). Follow-up independent sample *t*-tests using Bonferroni correction for multiple comparisons were conducted to determine the presence of significant differences for the mean comparisons of interest, and comparative effect sizes (Cohen's *d*) were calculated.

These analyses were performed using an intent-to-treat (ITT) approach in which all patients with baseline measures were included in analyses, even if they missed more than two training sessions. Missing data were imputed using the average change in depression score from baseline to post-intervention in the control group. When drop-out rates are less than 20% (which is the case in our study), this method keeps statistical power at higher levels compared to the last-observation-carried-forward method (Armijo-Olivo et al., 2009).

Independent-samples *t*-tests were also performed to assess whether there were any baseline differences between completers and non-completers. For all analyses, we used Statistica version 8.0 (Statsoft France, Maisons-Alfort), and a *p*-value less than or equal to .05 was considered to indicate statistical significance.

3. Results

3.1. Participants' characteristics at baseline, compliance, and adverse events

As illustrated in Table 1, there were no baseline differences between groups in terms of depressive symptoms as measured by the BDI-II.

One of the 14 (7.1%) participants in the AE group, and two of the 11 (18.2%) participants in the ST group failed to attend the required number of ≥ 8 training sessions. In addition, one patient in the NI group completed the final assessment of depression three days later than specified in the protocol. Thus they were considered as "non-completers". BDI-II scores did not differ between completers and non-completers at baseline, $t(33)=-1.52$, $p=.138$. Fig. 1 shows the progression of participants through the trial.

Adverse events in the AE group included transient muscular/joint soreness ($n=3$), headache ($n=1$), and fatigue ($n=2$). However, all of these participants continued the exercise program for the full length of the study.

3.2. Pre-to-post intervention changes in depression

A significant group × time interaction was observed, $F(2, 31)=6.15$, $p=.006$, partial eta squared = 0.28. Follow-up *t*-tests comparisons revealed that when compared to baseline mean scores, both the aerobic exercise (mean [SD] = 18.92 [6.11] *vs* 36.14 [5.87], $p<.001$) and the stretching interventions (mean [SD] = 28.43 [7.46] *vs* 37.82 [8.26], $p=.011$) yielded significant improvements. On the other hand, the depression scores remained unchanged in the control group (mean [SD] = 29.29 [12.57] *vs* 35.70 [6.73], $p=.313$).

3.3. Between-group comparison of changes in depression scores

The ANOVA showed a significant group effect $F(2, 32)=5.41$, $p=.009$, partial eta squared = 0.25. Follow-up *t*-tests comparisons indicated that the reduction in depressive symptoms was larger in

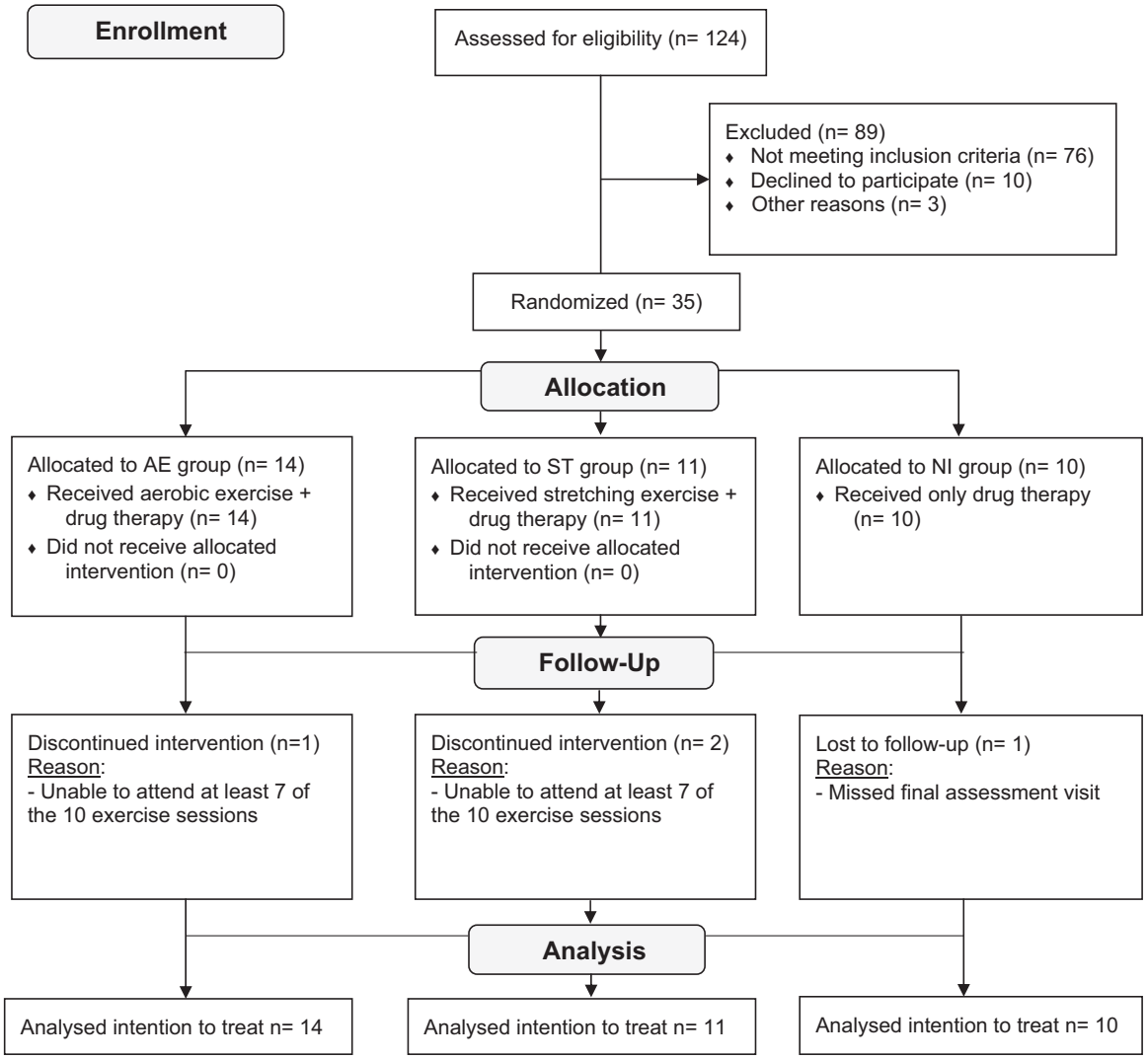

Fig. 1. Flowchart of study participants through the trial. AE=aerobic exercise, ST=stretching, NI=no intervention.

the aerobic exercise group compared to the control group (mean [SD]=−17.22 [6.49] *vs* −6.41 [10.00], p=.012) and marginally larger than for the stretching group (mean [SD]=−17.22 [6.49] *vs* −9.39 [9.02], p=.082). There was no statistically significant difference between the stretching and the control groups (p=1.000).

The effect size comparing the aerobic to the control group was large (Cohen's d=−1.39), as was the effect size comparing the aerobic to the stretching group (Cohen's d=−1.06). On the other hand, the effect size comparing stretching to no-intervention was near zero (Cohen's d=−0.33).

A clinical response (reduction of baseline BDI-II score by 50% or more) was observed in 8 patients in the aerobic-exercise group (57.1%), 1 patient in the ST group (9.1%), and 1 patient in the NI group (10.0%; Chi-2=9.27, p=.01).

Fig. 2 shows pre- and post-intervention depression mean scores in each group.

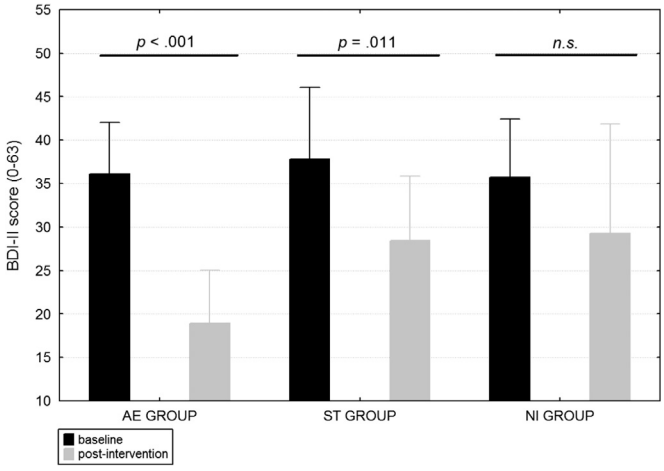

Fig. 2. Observed mean depression scores before and after add-on interventions (aerobic exercise or stretching) or drugs only. Error bars represent standard deviations. AE Group=endurance-training group, ST Group=stretching group, NI Group=control (no intervention) group. BDI-II indicates Beck Depression Inventory.

4. Discussion

Our results indicate that a short endurance training intervention can lead to a substantial reduction of depressive symptoms in hospitalized patients with severe depression, with more than 50% of exercisers achieving a more than 50% reduction in their BDI-II score. We found an average depression score decrease of 47.6% in the AE group (*vs* 24.8% in the ST group and 18.0% in the NI group). Many biologically-based reasons can account for why aerobic exercise reduced depression more than stretching or antidepressants

alone. One of these suggests that endurance training may relieve depression due to physiological changes that result in hippocampal neurogenesis (Ernst et al., 2006). According to Ernst and colleagues, there are several mechanisms by which endurance training facilitates this neurogenesis. For instance, aerobic exercise increases tryptophan hydroxylase (Chaouloff et al., 1989), which is necessary for serotonin synthesis, while Brezun and Daszuta (2000) linked serotonin to neurogenesis, and decreases in serotonin with decreased neurogenesis in adult rats. Similarly, brain-derived neurotrophic factor (BDNF) increases during aerobic exercise (Cotman and Berchtold, 2002) and has been linked to neuronal development and survival (Wozniak, 1993). Interestingly, as highlighted above, when aerobic exercise is combined with antidepressants, BDNF levels increase in two days compared with two weeks with antidepressants alone (Russo-Neustadt et al., 2001).

In the present study the amount of change in depression in the AE group falls between values obtained by Knubben et al. (2007) and Schuch et al. (2011) who respectively reported an average decrease in depression score of 36% and 68% in exercising patients. However, the study by Knubben included patients with various diagnoses and had no control (drugs-only) group, and no placebo-activity group was included in Schuch et al. In addition, both studies included participants treated with non-pharmacological therapies (sleep deprivation in the study by Knubben, electroconvulsive therapy in the study by Schuch). Finally, some participants had been receiving medication for several months, while others had just begun their treatment.

To our knowledge, the present study is the first RCT that specifically focused on inpatients who started antidepressant medication less than two weeks before study entry. This is of particular interest in view of the fact that 4–6 weeks are usually required to observe the full therapeutic effects of antidepressant drugs. Consequently, by standardizing the length of medication use to less than two weeks in all of our participants at the time of study entry, we minimized the confounding effect of pharmacotherapy. We did not eliminate it entirely, however, as some authors have reported moderate improvement in depressive symptoms after only two weeks of antidepressant medication (van Calker et al., 2009). The effect of pharmacotherapy can be determined here (release of symptoms in the control group = 18.0%) and subtracted from the average reduction in depression in the AE group to obtain the net effect of aerobic exercise.

A common criticism to using exercise in the treatment of patients with MDD is that sufficient adherence to the intervention is not possible. But interestingly, only one patient withdrew from the endurance training intervention in the present study. This corresponds exactly to the adherence rate documented in the RCT conducted by Knubben et al. (2007), and is almost identical to that observed in Schuch et al. (2011; no withdrawal). Likewise, our data on adverse events suggest that endurance training was an acceptable treatment for depressed inpatients, with few side effects.

In addition to its theoretical contribution, this study presents a number of practical implications. First, given the relatively high non-response rates during the first weeks of antidepressant medication use, physicians are in need of effective alternative therapeutic strategies for reducing depressive symptoms in a short time. Our findings indicate that endurance-training could conceivably be one of these options. Second, it has been established that individuals with MDD are especially vulnerable to even mild stressors (Hammen, 2005). Hospitalization in a psychiatric unit has been demonstrated to be a stressful experience for a number of reasons including separation from family members, boredom/inactivity, or being in the company of other acutely ill people (Maccallum and Robertson, 1999). According to Hammen (2005), exposure to a greater number of stressors may lead to huge negative emotional consequences in individual with depressive disorders, which may interfere with treatment success. A study from White et al. (2009) highlighted the effectiveness of endurance training for attenuating negative affect and increasing positive affect in individuals with elevated symptoms of depression. Given this, further support is offered for implementing supervised exercise as an add-on therapy in hospitalized patients with severe MDD.

A first important limitation that should be considered when interpreting the results is the lack of blinding of study participants to interventions. However, this was not possible in view of the nature of intervention (exercise). In addition, the possible risk of bias was minimized by comparing the antidepressant effect of "true" exercise (endurance-training) with that of "sham" exercise (stretching). A second limitation is that no individual information on dosage of antidepressant drugs was available. Bernard and Carayol (2015) recently suggested a dose-dependent interaction between exercise and antidepressant drugs through multiple direct (e.g., biological synergism/antagonism) and indirect mechanisms (e.g., deteriorated health status affecting exercise capabilities in patients receiving higher antidepressant doses). Third, this study was a short-term (10 days) RCT with no follow-up. Therefore, no conclusion can be drawn about the duration of the antidepressant effect of exercise reported here. The meta-analysis by Lawlor and Hopker (2001) suggested that the benefits of exercise do not persist beyond the end of intervention. Moreover, it may be that the sudden interruption of the exercise program resulted in a rebound effect with an increase in depressive symptoms. A fourth limitation of our study is that participants in the AE and ST groups exercised under close supervision (in order to standardize and control exercise intensity or movement execution), which resulted in a lengthy interaction time between patients from these groups and the first author. This was not the case with patients in the control group. This difference in personal contact with the investigator in the three groups may have influenced results. Finally, because patients in the AE group exercised outdoors and those in the ST group exercised indoors, daylight exposure could explain or partly explain our findings. That being said, Pinchasov et al. (2000) showed that one week of bright light exposure reduced the intensity of depressive symptoms by a lesser extent than one week of indoor cycling in non-seasonal depressed inpatients.

In summary, this study demonstrates that a short endurance-training program substantially improved depressive symptoms in hospitalized patients with severe MDD in their first three weeks of pharmacotherapy. Future research is needed to determine the duration of the antidepressant response to exercise, and its interactive effects with antidepressant medication at different levels of antidepressant dosages.

References

Adams, S.M., Miller, K.E., Zylstra, R.G., 2008. Pharmacologic management of adult depression. Am. Fam. Physician 77, 785–792.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington DC, text revised.

Armijo-Olivo, S., Warren, S., Magee, D., 2009. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research A. Rev. Phys. Ther. Rev. 14, 36–49.

Beck, A.T., Steer, R.A., Brown, K., 1996. Beck Depression Inventory, second ed. Hartcourt Brace, San Antonio, TX.

Bernard, P., Carayol, M., 2015. A commentary on the importance of controlling for medication use within trials on the effects of exercise on depression and anxiety. Ment. Health Phys. Act. 9, 10–15.

Brezun, J.M., Daszuta, A., 2000. Serotonin may stimulate granule cell proliferation in the adult hippocampus, as observed in rats grafted with foetal raphe neurons. Eur. J. Neurosci. 12, 391–396.

Chaouloff, F., Laude, D., Elghozi, J.L., 1989. Physical exercise: Evidence for differential consequences of tryptophan on 5-HT synthesis and metabolism in central

serotoninergic cell bodies and terminals. J. Neural Transm. 78, 121–130.
Chu, I.H., Buckworth, J., Kirby, T.E., Emery, C.F., 2009. Effect of exercise intensity on depressive symptoms in women. Ment. Health Phys. Act. 2, 37–43.
Cooney, G.M., Dwan, K., Greig, C.A., Lawlor, D.A., Rimer, J., Waugh, F.R., et al., 2013. Exercise for depression. Cochrane Database Syst. Rev. 9, 1–160, Art. No.: CD004366.
Cotman, C.W., Berchtold, M.C., 2002. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci. 25, 295–301.
Ernst, C., Olson, A.K., Pinel, J.P.J., Lam, R.W., Christie, B.R., 2006. Antidepressant effect of exercise: evidence for an adult-neurogenesis hypothesis. J. Psychiatry Neurosci. 31, 84–92.
Faul, F., Erdfelder, E., Lang, A.G., Buchner, A., 2007. G*POWER 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39, 175–191.
Hammen, C., 2005. Stress and depression. Ann. Rev. Clin. Psychol. 1, 293–319.
Josefsson, T., Lindwall, M., Archer, T., 2014. Physical exercise intervention in depressive disorders: meta-analysis and systematic review. Scand. J. Med. Sci. Sport. 24, 259–272.
Knubben, K., Reischies, F.M., Adli, M., Schlattmann, P., Bauer, M., Dimeo, F., 2007. A randomized controlled study on the effects of a short-term endurance training programme in patients with major depression. Br. J. Sport. Med. 41, 29–33.
Krogh, J., Nordentoft, M., Sterne, J.A.C., Lawlor, D.A., 2011. The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials. J. Clin. Psychiatry 72, 529–538.
Lawlor, D.A., Hopker, S.W., 2001. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomized controlled trials. BMJ 322, 763–767.
Maccallum, E.J., Robertson, A.E., 1999. The life of a new long-stay patient: a reflexive experience. J. Psychiatr. Ment. Health Nurs. 6, 339–414.
Mead, G.E., Morley, W., Campbell, P., Greig, C.A., McMurdo, M., Lawlor, D.A., 2009. Exercise for depression. Cochrane Database Syst. Rev. 3, 1–102, Art. No.: CD004366.
Perraton, L.G., Kumar, S., Machotka, Z., 2010. Exercise parameters in the treatment of clinical depression: a systematic review of randomized controlled trials. J. Eval. Clin. Pr. 16, 597–604.
Pinchasov, B.B., Shurgaja, A.M., Grischin, O.V., Putilov, A.A., 2000. Mood and energy regulation in seasonal and non-seasonal depression before and after midday treatment with physical exercise or bright light. Psychiatry Res. 94, 29–42.
Rethorst, C.D., Wipfli, B.M., Landers, D.M., 2009. The antidepressant effects of exercise: a meta-analysis of randomized trials. Sports Med. 39, 491–511.
Rimer, J., Dwan, K., Lawlor, D.A., Greig, C.A., McMurdo, M., Morley, W. et al., 2012. Cochrane Database Syst. Rev., vol. 7, Art. No.: CD004366.
Russo-Neustadt, A., Ha, T., Ramirez, R., Kesslak, J.P., 2001. Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. Behav. Brain Res. 120, 87–95.
Schuch, F.B., Vasconcelos-Moreno, M.P., Borowski, C., Fleck, M.P., 2011. Exercise and severe depression: preliminary results of an add-on study. J. Affect. Disord. 133, 615–618.
Stathopoulou, G., Power, M.B., Berry, A.C., Smits, J.A.J., 2006. Exercise interventions for mental health: a quantitative and qualitative review. Clin. Psychol.: Sci. Pract. 13, 179–193.
van Calker, D., Zobel, I., Dykierek, P., Deimel, C.M., Kech, S., Lieb, K., et al., 2009. Time course of response to antidepressants: predictive value of early improvement and effect of additional psychotherapy. J. Aff. Disord. 114, 243–253.
White, K., Kendrick, T., Yardley, L., 2009. Change in self-esteem, self-efficacy, and the mood dimensions of depression as potential mediators of physical activity and depression relationship: exploring the temporal relation of change. Ment. Health Phys. Act. 2, 44–52.
Wozniak, W., 1993. Brain-derived neurotrophic factor (BDNF): role in neural development and survival. Folia Morphol. 52, 173–181.