Individualized Web-based Exercise for the Treatment of Depression – a Feasibility Study

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Abstract

Background

Due to the high prevalence of depressive disorders, it is mandatory to develop therapeutic strategies that provide universal access and require limited financial and human resources. Web-based therapeutic approaches fulfill these claims.

Objective

The purpose of this study was to assess if a supervised, individualized 8-week web-based exercise program in patients with moderate to severe depressive episodes was feasible, accepted and promising to relieve symptoms.

Methods

Twenty patients with unipolar depression were recruited and randomly assigned into two groups (1: intervention, exercise program, n=14; 2: control, treatment-as-usual, n=6). At baseline, depressive symptoms were rated via the Quick Inventory of Depressive Symptomatology (QIDS) by the patient him- or herself (QIDS-SR) and a blinded psychiatrist (QIDS-C) and performance diagnostics (lactate analysis, spiroergometry during a treadmill walking test) were conducted. Participants of the intervention group received exercise schedules once weekly with endurance and strength training instructions. Rating of depressive symptoms was repeated after 6-12 days and 8 weeks; performance diagnostics were repeated after 8 weeks, only.

Results

Severity of depression subsided significantly in the intervention group after 8 weeks (median change of QIDS-SR: -5, IQR: -2 to -10), already evident within the first 6-12 days (median change of QIDS-SR: -6, IQR: -2 to -8). During the intervention, participants conducted on average 75 minutes of endurance training (IQR: 63-98) per week or 16 (IQR: 15-21) of 19 recommended endurance units in total. In addition, 9 (IQR: 4-12) of 10 recommended strength training exercise units were conducted during the 8 weeks. Performance diagnostics revealed a significant increase of maximum output in Watt for the intervention group after 8 weeks.
Conclusions

Our individualized web-based exercise intervention in moderate to severe depression was highly accepted and led to a significant and clinically relevant improvement of depressive symptoms.

Trial registration

ClinicalTrials.gov Identifier: NCT02874833

Key Words

Depression; Exercise; Web-based intervention; E-Health
Introduction

Unipolar depression or major depressive disorder (MDD) is the worldwide leading cause of disability [1] with a lifetime prevalence of around 17% [2]. MDD is commonly treated with antidepressive medication and/or psychotherapy [3]. However, side effects of and an often sceptical attitude towards pharmacotherapy lead to poor compliance [4]. In addition, about 30-50% of patients do not respond adequately to antidepressants [5, 6]. On the other hand, personalized psychotherapy requires high personal effort, especially for highly prevalent diseases such as MDD. However, the high personnel costs of personalized psychotherapy cannot be warranted, especially in rural areas. This results in waiting periods of several months [7]. Thus, the development of easily accessible, cost-saving, ubiquitous and effective treatment strategies, well-accepted by patients, is of great importance in health politics. In this study, we exploited such an innovative form of therapy in terms of an individualized, supervised, web-based exercise therapy in patients with MDD and moderate to severe depressive symptoms. We chose this approach since physical activity is currently recommended as a safe and effective adjunctive therapy in the treatment of MDD in numerous national guidelines [8-10].

In the last years, exercise arose growing interest as a component in the treatment of depression. Evidence suggests that exercise may lead to a significant reduction in depressive symptoms, comparable to pharmacotherapy after 16 weeks [5, 11]. The latest Cochrane Review [12] reported a moderate clinical effect of exercise on depressive symptoms. However, if only those studies with high methodological quality were considered, the effects of exercise were shown to be only small to moderate, in line with the meta-analysis of randomized controlled trials by Krogh et al. [13] and by Josefsson et al. [3], who showed large overall effects but merely moderate effects, if only methodologically high quality trials were considered. In contrast, a more recent meta-analysis supports the assumption of an underestimation of exercise effects on depressive symptoms due to publication bias [14]. In sum, further more standardized studies are needed to give a robust estimate about the therapeutic effect size of exercise.

It has not yet been clarified which type, duration and intensity of exercise is most effective in depression [12], and if there are exercise-specific physiological changes that mediate antidepressive effects [15]. The specific psychological or biological mechanisms by which
physical activity may lead to positive effects on depressive symptoms are still a matter of current research. However, exercise seems to be a promising adjunctive therapy option in depression, given that there exists no specific monomodal therapy that is effective in every patient [11].

In contrast to previous exercise studies on depression [5, 16, 17], we developed an individualized web-based approach that did not schedule attendance exercise sessions. The purpose of the current study was to evaluate i.) the feasibility and ii.) the antidepressive effects of our web-based exercise program.

Methods

General information and Ethics

The multidisciplinary single center trial was a collaboration between the Department of Psychiatry and Psychotherapy and the Institute of Sports Medicine of the University Mainz. The study was designed as a feasibility study, which would be continued with higher sample sizes and under participation of multiple centers if the study provided promising outcomes. All procedures have been approved by the regional Ethical Board Mainz, Germany. Previous treatments were continued independent of study participation. In addition, measures to intensify the antidepressant therapy in case of deteriorated depressive symptoms were also not affected by study participation.

Inclusion criteria

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations
2. Sufficient computer/internet literacy to get along with our internet platform
3. Aged 20 to 65 years old, inclusive, at the time of informed consent
4. Montreal Cognitive Assessment (MoCA [18]) > 18 to exclude moderate to severe cognitive impairment
5. Apart from a clinical diagnosis of major depression or bipolar affective disorder, the subject must be in good health as determined by the Investigator, based on medical history and physical examination.
6. QIDS scores > 5
7. No change of antidepressive therapy in the four weeks before study entry
For detailed exclusion criteria, we refer to clinicaltrials.gov (NCT02874833).

Participants and Randomization

A total of 20 depressive participants were enrolled after two out of 22 patients were excluded due to myocardial inflammation and pregnancy, respectively. For randomization, numbers between 0-1 were randomly computer generated and used for the assignment to either the control (values ≤ 0.3) or intervention group (IG) (values of > 0.3). At baseline (T0), depressive symptoms were rated by the subject him- or herself and by a blinded psychiatrist (S.L. or C.K.). Thereafter, patients were subjected to performance diagnostics (lactate diagnostics, spiroergometry), which was followed by either an 8-week supervised, individualized internet-based exercise program (intervention group) or treatment as usual (control group). Within 6 to 12 days (median: 9 days) after T0, rating was repeated (T1). The final examination took place after 8 weeks including clinical rating and performance diagnostics (T2). Controls underwent all examinations, while any other form of existing therapy (e.g. antidepressive medication) was not affected (Figure 1).

![Flowchart of the study](image)

**Figure 1. Flowchart of the study.**

Intervention and internet platform

IG patients gained access to our homepage (Figure 2) and were provided with a heart rate monitor (Polar FT1; Polar Electro, Büttelborn, Germany) and 4 different types of resistance bands (Thera-Band, Akron, USA). The platform was designed user-friendly [19]. Message
function was used to send exercise schedules to the patients once weekly. After each week, motivational feedback was given to improve adherence [20, 21].

Schedules included the recommended extent of exercise with a maximum of 3 endurance and 2 strength training units per week. An additional group training session was offered biweekly by a sports therapist. At the end of each week, patients were expected to upload a protocol of their weekly activity on our platform making the protocol available to the supervisor. Based on this response, training goals were individually adapted in duration and intensity for the following week in order to keep motivation high and to prevent patients from overload and frustration.

Structure of weekly exercise

Endurance exercise recommendations were based on heart rate (baseline +1.5 mmol model [22]) with a duration of 30 to 60 minutes per unit. This has proven to be effective in the reduction of depressive symptoms [5, 17, 20]. However, as suggested by Craft and Landers [23] and in line with guidelines [24], it was necessary in some untrained or unexperienced subjects to start with a more moderate duration of 20 minutes per session and 2 units per week. Patients with a poor exercise capacity were recommended to start with walking instead of jogging. By taking these personal preferences and individual conditions into
account, we aimed at achieving high adherence [17, 20]. Adjustment and weekly progression of the endurance training was assessed by the Borg-Scale [25] (Figure 3) to keep the intensity in a moderate to vigorous range according to common guidelines and recommendations [8, 9, 20].

Figure 3. Activity protocol of one participant. Patients responded after each week by uploading the filled protocol with objective (heart rate, duration) and subjective data (Borg-Scale), allowing the supervisor to adapt the training for the following week. In this example, intensity and duration of the endurance training was recommend to be increased while intensity of the strength training was advised to be decreased.

If patients reported Borg values < 4, training intensity was moderately increased [26] in terms of an expanded duration of approximately 10 minutes per week or by recommending a higher average heart rate leading to a higher intensity. In case of fatigue or injury or if exercise was too hard (Borg > 7), intensity and duration was reduced according to the patient’s request. In this case, alternative units such as relaxing were recommended. Strength training exercises for major muscle groups were performed home-based with detailed instructions on our homepage. Progression was ensured with increased sets and repetitions or by changing the type of resistance band.

Evaluation of primary outcomes

Adherence

Adherence has been defined as attendance, lack of dropout, participation rate or the fulfillment of predefined goals [27]. IG patients dropped out if no protocol was uploaded for
more than 2 weeks. Controls dropped out, if they failed to attend the final examination at T2 [28]. The participation rate to our exercise program was defined as i.) total training units conducted during the intervention and ii.) due to the formula: training units conducted / training units recommended [11, 28]. Data was extracted from weekly protocols of the participants (Figure 2). All units, which did not count to regular, prescribed strength or endurance exercise such as hiking or relaxing, were counted as alternative units. In addition, after T2, we asked with a self-developed questionnaire for satisfaction with our program and for reasons not to meet our exercise recommendations.

Depression scales

The severity of depressive symptoms were determined by the “Quick Inventory of Depressive Symptomatology” (QIDS; clinician (QIDS-C) and self-report (QIDS-SR), [29]). Rating was conducted at baseline, at T1 within 6-12 days, and after 8 weeks. QIDS can range from scores of 0 to a maximum of 36. QIDS showed good internal consistency (Cronbach’s α = .86) and QIDS-SR16 total scores were highly correlated with IDS-SR30 (r = .96) and HAM-D24 (r = .86; [29]).

Evaluation of secondary outcomes

Self-efficacy, quality of life and habitual physical activity

The Short-Form-36 (SF-36) Quality Of Life questionnaire [30] was filled out by every patient at baseline and after 8 weeks. SF-36 items show high reliability (Cronbach’s alpha > 0.85, reliability coefficient > 0.75) and construct validity [31]. In addition, General Self-Efficacy scale (GSE, [32]) and Habitual Physical Activity (HPA; [33]) were assessed at T0 and T2.

Physiological parameters

After clinical rating and answering questionnaires, all patients performed a treadmill walking test until exhaustion to determine $VO_2$ peak and lactate threshold. Slope and velocity were increased stepwise after 3 minutes of walking at a time (for protocol see [26]). Lactate samples were drawn after every step to determine lactate threshold using the baseline +1.5 mmol model [22]. Maximum output in Watt was determined due to the formula: $9.81 \times \text{weight(kg)} \times v(m/s) \times \sin \alpha$. 
Statistical methods

For statistical analysis, we used JMP13 (SAS, Cary), SPSS 23 (IBM) and the software package R, version 3.4.2 (2017-09-28). Differences in baseline characteristics were examined with Mann-Whitney U test. The correlation of QIDS-SR and QIDS-C was calculated with Spearman’s rank correlation coefficient. Comparisons at different time points were determined with Wilcoxon signed rank test and Bonferroni correction for multiple testing. To evaluate the influence of the intervention in comparison to the control condition, an analysis of covariance (ANCOVA) was conducted for each outcome. The outcomes at T2 served as dependent variables, the ones at T0 as covariates. To exclude a violation of ANCOVA preconditions, we tested for normal distribution in the residuals of the dependant variable and for homogeneity of regression slopes by analysing the interaction term of independent variable*covariate. P-values of <.05 were considered as statistical significant.

For the explorative analysis of the trajectories of the QIDS-SR and QIDS-C measures, we fit multi-level linear models. Hereby, the number of training units at the actual number of days in the program after T0 was used as covariates, and the observations for the individuals were nested in the respective groups, i.e. intervention or control. Log-linear transformation of the response variables QIDS-SR and QIDS-C showed better model fit, hinting at an exponential decay over time.
Results

All patients included were diagnosed with major depression, none with bipolar affective disorder. Fourteen patients were assigned to the IG, while 6 patients served as controls. Table 1 outlines the clinical characteristics of the patients at baseline. Three IG patients dropped out after T1 and before T2 (15%), while all 6 controls completed the study. Dropouts were due to missing responses for more than two weeks after T1 (cf. Fig. 1). Medication did not change over the course of the study except for one IG subject in which a dosage reduction of an antidepressive drug was prescribed by the treating physician.

For the covariate analysis, missing data were dealt by using the last observation carried forward method. In the explorative multi-level analysis, missing data were omitted from the data set.

Table 1. Characteristics at baseline.

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Exercise group (n=14)</th>
<th>Controls (n=6)</th>
<th>Total (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Age in years</td>
<td>43 (14)</td>
<td>51 (12)</td>
<td>45 (14)</td>
</tr>
<tr>
<td>Height in cm</td>
<td>171 (8)</td>
<td>168 (7)</td>
<td>170 (8)</td>
</tr>
<tr>
<td>Weight in kg</td>
<td>77 (17)</td>
<td>88 (11)</td>
<td>80 (16)</td>
</tr>
<tr>
<td>BMI in kg/m²</td>
<td>26.5 (5.6)</td>
<td>31.3 (4.3)</td>
<td>27.0 (5.6)</td>
</tr>
<tr>
<td>Depression scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QIDS-SR</td>
<td>16 (3)</td>
<td>17 (4)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>QIDS-C</td>
<td>14 (3)</td>
<td>15 (1)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>MoCA</td>
<td>26 (2)</td>
<td>26 (3)</td>
<td>26 (2)</td>
</tr>
<tr>
<td>Spiroergometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂ peak in ml/min/kg</td>
<td>27.0 (7.6)</td>
<td>23.8 (5.9)</td>
<td>26.0 (7.1)</td>
</tr>
<tr>
<td>Maximum output in Watt</td>
<td>112 (37)</td>
<td>110 (55)</td>
<td>112 (42)</td>
</tr>
</tbody>
</table>

Values are total numbers (gender) or means (SD). No significant differences between the groups were observed in any characteristics at baseline.

At baseline, patients rated their depressive symptoms with a mean QIDS-SR score of 16, i.e. severe depressive symptoms, while QIDS-C was rated slightly lower with 14, representing moderate depressive symptoms [29]. QIDS-SR and QIDS-C scores were correlated with each other (r=.64, P <.001). Mean physical fitness in terms of VO₂ peak was determined at 26
ml/min/kg, which matches the predicted values of healthy subjects, adjusted for sex, age and weight [34].

**Adherence**

The dropout rate for IG was 21% (3 out of 14), while all controls completed the study. In the IG, a median of 75 (IQR: 63-98) minutes of endurance exercise was performed per week. Sixteen (IQR: 9-19) out of 19 recommended endurance units (IQR: 15-21) were completed, i.e. 84%. In addition, patients conducted 9 (IQR: 4-12) strength training units during the intervention (9 out of 10 prescribed, i.e. 90%). Four (IQR: 2-28) optional, alternative training units, such as relaxing, hiking or yoga, were furthermore executed during 8 weeks. The offer to join group training with a sports therapist was accepted by one patient, only.

Self-reported reasons for missing the prescribed training were: orthopedic problems (n=4), depressive symptoms (n=3), illness (n=3), lack of motivation (n=2) or work (n=2). Moreover, our questionnaire revealed that 9 of 11 patients did not fear any injury, all of the 11 patients saw no risk during exercise, 9 out of 11 perceived communication via our platform as “personal” and 10 of 11 patients assessed the amount of weekly training instructions as adequate.

**Effects on depressive symptoms after 8 weeks**

![Figure 4. Depression scores in QIDS-SR (left) and QIDS-C (right) at baseline (T0) and after 8 weeks (T2). Depressive symptoms significantly decreased in the IG (red) during the 8 week intervention, reflected](image-url)
in both QIDS-SR (median change: -5; interquartile range (IQR): -2 to -10; \(P = .001\)) and QIDS-C (median change: -5; IQR: -2 to -7; \(P = .02\)). However, symptom relief was not different to controls (blue).

Figure 4 outlines the scores of the depression scales QIDS-SR und QIDS-C at T0 and T2 in both groups. A reduction of depressive symptoms of \(\geq 50\%\) was shown via QIDS-SR in 5 IG patients (36\%) and QIDS-C in 3 IG patients (21\%). In comparison to the control group, ANCOVA revealed no statistically significant difference between IG and controls. However, one control showed a striking improvement of depressive symptoms from a QIDS-SR of 22 at baseline to a score of 2 at T2.

**Early antidepressive response**

![Box plots of QIDS-SR and QIDS-C scores at T0 and T1](image)

Figure 5. Depression scores in QIDS-SR (left) and QIDS-C (right) at baseline (T0) and after 6-12 days (median: 9 days; T1). Depressive symptoms in the IG (red) were significantly reduced in QIDS-SR (median change: -6; IQR: -2 to -8; \(P = .003\)) and QIDS-C (median change: -3; IQR: -2 to -6; \(P = .04\)). This early antidepressive effect approached significance compared to controls (\(P = .06\)).

Figure 5 shows depression scores of T1 after 6-12 days compared to baseline. The ANCOVA showed an estimated advantage of IG at T1 in QIDS-SR of -3.1 points (coefficient B). However, this effect was not statistically significant (\(P = .06\); \(\eta^2\) (effect size) =0.2). An early response of \(> 50\%\) reduction was observed for 5 patients (36\%) in QIDS-SR and 3 of 14 patients (21\%) in QIDS-C. A depressive symptom reduction of \(\geq 20\%\) [35] was observed for 10 patients (71\%) in QIDS-SR and for 7 patients (50\%) in QIDS-C, while only 2 out of 6 (33\%) controls showed an early response of \(\geq 20\%\) in both QIDS-SR and QIDS-C.
Self-efficacy, quality of life and habitual physical activity

Figure 6. General self-efficacy scores at T0 (baseline) and T2 after 8 weeks. ANCOVA revealed a favorable effect on GSE for the IG (red) compared to controls (blue) ($P = .02$, $\eta^2 = 0.28$).

The effect of the intervention and treatment-as-usual on GSE are shown in Figure 6. ANCOVA revealed a positive influence of the intervention on SF36 quality of life items “emotional well-being” ($P = .02$, $\eta^2 = 0.29$) and “social functioning” ($P = .04$, $\eta^2 = 0.23$), while total quality of life score ($P = .07$) and the item “mental health” ($P = .08$) showed an estimated advantage. As expected, IG showed a higher level of physical activity than controls, reflected in total HPA ($P = .007$, $\eta^2 = 0.36$) and HPA items “leisure time” ($P = .02$; $\eta^2 = 0.27$) and “sport” ($P = .001$, $\eta^2 = 0.51$).

Effects on physiological performance parameters
Figure 7: VO\textsubscript{2} peak (left) and maximum output in Watt (right) at baseline (T0) and after 8 weeks (T2). Participants in the exercise group (red) showed an improvement in VO\textsubscript{2} peak of 0.7 ml/min/kg that approached significance, while VO\textsubscript{2} peak of controls (blue) declined by 1.6 ml/min/kg. Maximum output in Watt was improved by 4% in the IG, while controls declined by 9% after 8 weeks. The difference was significant between the groups.

Figure 7 illustrates the physiological parameters in terms of VO\textsubscript{2} peak and maximum output in Watt. In comparison to the control condition, ANCOVA revealed no statistically significant influence of the intervention on VO\textsubscript{2} peak ($P = .07$) and lactate threshold ($P = .09$), but on maximum output in Watt ($P = .006$; $\eta^2=0.37$; $B=14.1$).

**Explorative multi-level analysis**

With respect to QIDS-SR, multi-level analysis showed a statistically significant effect of both, day of the measure (estimate: -0.01 on the log-linear scale, $P < .01$), number of training units (estimate: -0.07 on the log-linear scale, $P = .05$), and their interaction term (estimate: 0.001 on the log-linear scale, $P = .04$). Similar effects could be determined for QIDS-C with respect to day of measure (estimate: -0.01 on the log-linear scale, $P < .01$), and its interaction term with training units (estimate: 0.001 on the log-linear scale, $P = .05$). The latter does not show a statistically significant effect on QIDS-C ($P = .07$).

**Side Effects of the intervention**

Besides minor orthopedic problems in 4 cases, no side effects of regular exercise had been reported by the patients.
Discussion

Due to the high prevalence, high personnel expenses and therapeutic costs of MDD, it is desirable to have therapeutic strategies at hand that are both effective and provide universal access with limited financial and human resource requirements. Web-based and computerized therapeutic approaches are promising to fulfill these claims [36]. To date, the focus has been on cognitive behavioural [37, 38] or self-help [39] internet therapy. Exercise is suggested as an augmentation or alternative therapy for depressed patients [9, 12]. Here, we show for the first time that an 8-week web-based exercise intervention with individualized weekly training schedules is feasible and effective in patients with moderate to severe depressive symptoms.

IG Patients showed a significant decline of depressive symptoms after 8 weeks in both self- and clinician rating. Moreover, the intervention has led to a significant improvement in self-efficacy and the quality of life items “emotional well-being” and “social functioning”. During the 8 week intervention, patients conducted 16, i.e. 84% of recommended endurance units, and 9 (90%) strength training units, which is comparable to the adherence of previous studies with attendance or home-based exercise, i.e. exercising at home with regular contact to the supervisor [11]. Table 2 compares our results with previous randomized rater-blinded trials that investigated the effects of exercise on depression with an intention-to-treat approach.

Table 2: Comparison of the adherence of our web-based intervention with previous randomized trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>EG</th>
<th>Severity of depression</th>
<th>Duration</th>
<th>Type of exercise</th>
<th>Adherence (% conducted of prescribed units)</th>
<th>Dropouts in EG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haller et al., 2018</td>
<td>20</td>
<td>14</td>
<td>moderate to severe</td>
<td>8 weeks</td>
<td>Web-based exercise program</td>
<td>16 endurance (84%), 9 strength training (90%) units in 8 weeks</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>Blumenthal et al., 1999</td>
<td>156</td>
<td>53</td>
<td>mild to severe</td>
<td>16 weeks</td>
<td>Supervised aerobic exercise</td>
<td>43 units in 16 weeks (90%)</td>
<td>14 (26%)</td>
</tr>
<tr>
<td>Blumenthal</td>
<td>202</td>
<td>51</td>
<td>mild to severe</td>
<td>16 weeks</td>
<td>Supervised</td>
<td>37 units in 16 weeks</td>
<td>10 (20%)</td>
</tr>
</tbody>
</table>
Hal et al., 2007

<table>
<thead>
<tr>
<th>Blumenthal et al., 2007B</th>
<th>202</th>
<th>53</th>
<th>mild to moderate</th>
<th>16 weeks</th>
<th>Home-based aerobic exercise</th>
<th>40 units in 16 weeks (83%)</th>
<th>3 (6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunn et al., 2005</td>
<td>80</td>
<td>33</td>
<td>mild to moderate</td>
<td>12 weeks</td>
<td>Supervised exercise (public health dose); 3 or 5 times per week</td>
<td>71% (prescribed exercise sessions completed)</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>Hallgren et al., 2016</td>
<td>945</td>
<td>316</td>
<td>mild to moderate</td>
<td>12 weeks</td>
<td>Supervised yoga or aerobic exercise or vigorous strength training</td>
<td>12 units in 12 weeks (33%)</td>
<td>49 (16%)</td>
</tr>
</tbody>
</table>

Abbreviations: n=total number of patients; EG=Exercise group; patients randomized to exercise group.

The severity of depression in the present study was moderate to severe, i.e. higher than in previous trials that investigated the effects of exercise on depressive symptoms. Christensen et al. [28] reported that the probability of adherence in web-based therapeutic trials decreases with the severity of depression. It is thus somewhat surprising that adherence in the present study was comparable to previous ones. Our dropout rate was 21% in the IG, comparable to personalized psychotherapy [40], but probably lower than for psychotropic drugs. Up to 50% do not adhere to their antidepressant [41].

The high therapeutic adherence in our study might partially be attributed to the preferential recruitment of patients with relatively high interest in sports. Our patient sample reached the predicted VO$_2$ peak values [34], in contrast to expected lower physical fitness values in depression [42]. This suggests that the physical fitness of our participants was higher-than-average for depressive patients. Web-based exercise might therefore be a preferred therapeutic option for depressive patients that were physically active before the manifestation of their depressive disorder.

Interestingly, there has already been a significant IG response within 6-12 days after study start. QIDS-SR and QIDS-C were reduced ≥ 50% in 5 (36%) and 3 (21%) patients, respectively, while an early reduction of ≥ 20% in depressive symptoms was assessed in 10 patients (71%)
in QIDS-SR and in 7 patients (50%) in QIDS-C. This is comparable to the response rate of selective serotonin reuptake inhibitors (SSRI, 78%) within the first 14 days of treatment [35]. However, the early response rate of SSRI as described by Tadic et al. [35] is likely to be overestimated since it was evaluated under conditions of inpatient treatment which entails several putative antidepressive factors.

Since it is unlikely that exercise results in physiological adaptations within two weeks, an early improvement in depressive symptoms may rather be due to increased self-efficacy and/or further factors such as personal contact, care, motivation, ongoing monitoring and patient expectations towards a positive effect [11, 20], i.e. factors which are suggested to contribute to placebo effects. Early antidepressive effects of exercise may be mediated by these placebo effects [43] but they may also be explained by i.) disengaged higher-order functions of the prefrontal cortex to keep unhelpful emotional processes from compromising optimal motor execution (transient hypofrontality hypothesis [44]), ii.) the dual-mode theory of affective responses to exercise [45] or iii.) the opponent-process theory of emotion [46]. However, even if placebo effects were mainly responsible for the early positive effects of exercise, this would not devalue exercise as a therapeutic option since placebo effects are likely to constitute a large proportion of the response to antidepressants, too [47].

In contrast to the initial antidepressive effects, the sustained reduction in depressive symptoms after 8 weeks could be attributed to physiological adaptations triggered by exercise. Regular physical activity over several weeks might have provoked a complex interaction of psychological (e.g. increased self-efficacy) and neurobiological (e.g. increased serotonin synthesis in the brain) adaptations [21]. As the explorative multi-level analysis revealed, an exponential decay model can be expected for the treatment. Thus, both a time-function and the number of training units per time should be included in future analyses to model the trajectories of the QIDS-SR and QIDS-C variables.

Computerized cognitive behavioral therapy (cCBT) is highly accepted [48] and arises increasing interest due to its capability to deliver a potentially effective and efficient therapeutic method to large numbers of people with depression. However, independent evaluations of cCBT failed to prove relevant clinical benefits in depression [49] unless offered in an individually tailored form [50]. In this study, depressive symptoms declined by
individualized web-based exercise therapy. This therapeutic approach has thus a similar potential as individually tailored cCBT. However, in contrast to cCBT, it has the advantage of being cognitively little demanding. In our study, 40% of depressive participants showed a MoCA score of < 26, indicating mild cognitive impairment. In depression, attentional and executive functions are often affected, which limits the patients’ capability to follow the cognitive demanding instructions of cCBT. Another advantage of exercise is its positive influence on cardiovascular risk factors, the immune system, bone metabolism, and others [51], which helps to prevent somatic disorders such as cardiovascular and cerebrovascular diseases and diabetes mellitus type 2 [16] for which chronic depressive patients are more vulnerable. However, a web-based exercise program has the disadvantage that people must be motivated and physically able to perform exercise therapy. This is a particular challenge in depression since depressive people are on average physically little active [52, 53]. Thus, it is likely that individualized web-based exercise will be accepted by a subgroup of depressive patients, only. However, the acceptability can be enhanced by starting with a lesser number of exercise units (two instead of three) with individually adapted moderate intensity and by giving regular motivational feedback.

One objective of the present study was to evaluate the acceptability of individualized web-based exercise therapy and its effects on depressive symptoms. The study was thus designed as it is appropriate for a feasibility study. Hence, the sample size was rather small, especially for the control group (n=6). Furthermore, one participant in the control group showed full remission at T2 from severe depressive symptoms at study entry, entailing a probable overestimation of antidepressive effects in the control group. Thus, comparisons between the intervention and control group should be considered as little valid. Another limitation of our study is its duration of 8 weeks. Although exercise intervention led to a significant increase of maximum output in Watt, regular endurance exercise should be performed for at least 10 weeks to achieve an improvement of physiological performance parameters [20] (Table 2), especially if exercise starts moderately with in part only 2 endurance units per week as in this study.

IG participants performed on average 75 minutes of weekly endurance exercise over the 8 weeks. This only meets the minimum level of required exercise for both healthy and depressed subjects [9, 24, 54], which in combination with the short intervention may have
led to a non-significant improvement of physiological performance parameters. Nonetheless, patients also benefit from a small amount of physical activity [55].

In sum, this study proved that an individualized web-based exercise program over 8 weeks is feasible and well accepted. The exercise program also led to a significant and clinically relevant improvement of depressive symptoms in the IG. Expensive performance diagnostics are dispensable if exercise starts generally low with 2 endurance units per week of moderate intensity. Exercise recommendations for the upcoming week can then be given on the basis on performance of the last week (Figure 3) according to a strict algorithm (cf. Methods).

Moreover, the coherence between self-rated and clinician-rated depressive symptoms was high. Thus, rating by a physician is redundant. Regular motivational feedback and goal-setting – key factors to high adherence, especially in web-based settings [20, 21, 28, 39] - can also be generated by a virtual therapist. As a consequence, rating of depressive symptoms as well as exercise recommendations could be given without the involvement of a physician. If such modifications are implemented, our exercise program is suitable for full computerization.

Conclusions and Implications for Further Research

We showed for the first time, that an individualized, web-based exercise program is feasible and effective in patients with moderate to severe depression. Our program could be an option for i.) patients who do not respond to or do not want to apply pharmaceuticals or psychotherapy and ii.) patients who are motivated and physically able [23] to complete a structured exercise program over several weeks. The study also gives important implications for future randomized, fully computerized and individually tailored exercise trials in MDD.

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Conflict of interest

The authors declare that there is no conflict of interest.
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