Late-life major depression is associated with individual suffering, increases in medical morbidity and mortality,1–3 healthcare service use and costs for society.4 Available antidepressant therapies currently provide unsatisfactory results, as no more than half of those treated reach remission after a single treatment course.5 Therefore, any viable and safe strategy that can improve the efficacy of antidepressant drugs will critically contribute to the management of late-life depression.6 It has been proposed that physical exercise could improve the effectiveness of pharmacological treatments in geriatric major depression.7,8 In fact, physical exercise can counteract key biological alterations linked with depression that are only partially modified by antidepressant drug therapy.9,10 It increases levels of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), and neurogenesis, leading to improvements in neurocognitive performance;11,12 exercise also reduces pro-inflammatory cytokines and hypothalamic-pituitary-adrenal (HPA) axis activity.13,14 Moreover, physical exercise counteracts disability and social isolation,15 while improving psychological self-evaluation.13 So far, no study has tested such a hypothesis or examined whether the intensity of physical exercise influences its antidepressant effect, as it has been observed in younger adults.16 Our aim was therefore to investigate whether the combination of sertraline treatment with two types of physical exercise – higher-intensity, progressive aerobic exercise plus sertraline (S+PAE), lower-intensity, non-progressive exercise plus sertraline (S+NPE) and sertraline alone. The primary outcome was remission (a score of <10 on the Hamilton Rating Scale for Depression). This study was undertaken as part of the Safety and Efficacy of Exercise for Depression in Seniors (SEEDS) Study Group.

Background
Interventions including physical exercise may help improve the outcomes of late-life major depression, but few studies are available.

Aims
To investigate whether augmenting sertraline therapy with physical exercise leads to better outcomes of late-life major depression.

Method
Primary care patients (≥65 years) with major depression were randomised to 24 weeks of higher-intensity, progressive aerobic exercise plus sertraline (S+PAE), lower-intensity, non-progressive exercise plus sertraline (S+NPE) and sertraline alone. The primary outcome was remission (a score of <10 on the Hamilton Rating Scale for Depression).

Results
A total of 121 patients were included. At study end, 45% of participants in the sertraline group, 73% of those in the S+NPE group and 81% of those in the S+PAE group achieved remission (P = 0.001). A shorter time to remission was observed in the S+PAE group than in the sertraline-only group.

Conclusions
Physical exercise may be a safe and effective augmentation to antidepressant therapy in late-life major depression.

Declaration of interest
None.

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Randomisation and masking

Randomisation was performed after the cardiologist visit by computer with a randomised permutation blocks method (size of blocks 4), stratifying individuals according to study centre, severity of depression (Clinical Global Impression scale severity item mildly/moderately v. severely ill),21 past treatments with anti-depressant (yes v. no), age (<75 years v. ≥75 years) and gender. Each study centre coordinator was sent a personal email containing participants’ group assignments and was allowed to share this information only with the study instructors, while keeping the clinical assessor unaware of participant allocation. Also, participants were asked not to disclose to the clinical assessors the type of intervention they were receiving.

Interventions

Participants were randomly assigned to receive sertraline only (n = 42), sertraline plus supervised group non-progressive exercise (n = 37) or sertraline plus supervised group progressive aerobic exercise (n = 42).

Sertraline

Patients in the sertraline-only condition were prescribed the drug by the centre psychiatrists, with a slow titration scheme to reach the standard dosage of 50 mg within 2 weeks. The choice of sertraline was based on its safety and efficacy in elderly patients and on its low potential for pharmacological interactions.22 The prescribing dosage was decided on according to clinical response and the presence of side-effects, in accordance with routine clinical practice. For insomnia, daily use of a hypnotic (zolpidem up to 10 mg/day or lorazepam up to 2 mg/day) was allowed during the first 4 weeks of treatment and discouraged later. At each visit participants were asked to bring their medications to verify their adherence to the prescription scheme. Episodes of non-adherence, defined as not taking the prescribed dosage for at least 3 consecutive days, were recorded.

Sertraline plus non-progressive exercise

Participants in the sertraline plus non-progressive exercise (S+NPE) arm received sertraline as in the sertraline-only group. In addition they were prescribed attendance at three supervised group exercise sessions per week (60 min duration) for 24 weeks in groups of three to six participants. These sessions were designed to improve participants’ strength, balance, respiration and motor coordination, and comprised both mat work and instrumental exercises (see Appendix). Sessions were conducted using heart-rate meters as in the S+NPE arm. The training scheme was programmed to increase over the weeks, adapting to possible increases in peak heart rate, and to include brief sessions of interval training. All exercise sessions concluded with 5–10 min of cool-down cycling (see Appendix).

Statistical analysis

A post hoc power analysis showed that a sample size of 40 patients per intervention arm (120 participants) would give an 85% power to detect a 30% difference in remission rates (35% v. 65%, P <0.05) and a 92% power to detect a standardised mean difference of 0.34 in HRSD scores (P <0.05), similar to the effect yielded by a recent meta-analysis.7 We aimed at assessing the superiority of each combined intervention (S+NPE and S+PAE) compared with antidepressant drug treatment for remission rates, time to remission and other secondary outcomes. To estimate differences in the time to achieve remission we used a survival analysis with Kaplan–Meier estimates of the survival function. A Cox regression analysis was then performed to test whether results held after adjustment for demographic and clinical confounders. To analyse the patterns of change in depression scores over time we performed multilevel hierarchical growth curve analysis using repeated HRSD scores as the dependent variable (baseline, 4 weeks, 8 weeks, 12 weeks and 24 weeks), nested within individual and study centre. The linear, quadratic and cubic terms of time were
also tested as fixed parameters, along with the interaction terms with group.\textsuperscript{24} Estimation of the parameters was done using the maximum likelihood method and heterogeneous autoregressive covariance structure. Analyses were carried out in the intention-to-treat population, using the last observation carried forward (LOCF) method to impute missing data. All analyses were performed using SPSS version 15.0 on Windows 7.

Results

Eligible participants were recruited from January 2011 to June 2012. A total of 121 patients entered the study and were randomised to the three treatments: 42 in the sertraline group, 37 in the S+P group and 42 in the S+PAE group (Fig. 1). Most participants were recruited in the Bologna East centre (sertraline n = 18, S+NPE n = 17, S+PAE n = 18), smaller numbers were drawn from Bologna West (sertraline n = 11, S+NPE n = 10, S+PAE n = 9), Parma (sertraline n = 10, S+NPE n = 4, S+PAE n = 9) and Modena–Correggio (sertraline n = 3, S+NPE n = 6, S+PAE n = 6). Participants’ demographic and clinical characteristics are reported in Table 1. Their mean age was 75 years (s.d. = 6); the majority were women, most were not married and had elementary or lower educational level. The most frequent physical comorbidities were hypertension (64%), musculoskeletal problems (61%), metabolic–endocrinological disorders (40%) and conditions relating to eye, ear, nose and throat (39%). The median HRSD score for the whole sample was 18 (interquartile range (IQR) 18–22), indicating mild to moderate severity of depressive symptoms; most participants had already been treated with antidepressant drugs at some point in their lives – more than 80% with a selective serotonin reuptake inhibitor (SSRI).

Attrition, safety and adherence

A few people withdrew from the study; six from the sertraline only arm, five from the S+NPE arm and four from the S+PAE arm (14%, 14% and 10% respectively; \(\chi^2 = 0.50, \text{d.f.} = 2, P = 0.78\)). Reasons for withdrawing were unwillingness to remain in the study (n = 10), new medical problems (n = 4) and the need for higher level of care for depression (n = 1). Common mild side-effects attributable to the medication included nausea, diarrhoea and insomnia and were rare. Two people left the study because of incidents correlated with physical exercise (one in the S+NPE group and one in the S+PAE group), one for ankle distortion and the other for worsening of musculoskeletal pain. The majority of participants attended assessment visits, with no significant between-group difference (sertraline 79%, S+NPE 78%, S+PAE 81%; \(\chi^2 = 0.10, \text{d.f.} = 2, P = 0.95\)). All participants received 50 mg of sertraline at entry. By the study end 43% of those in the sertraline-only group had their dosage increased by the study psychiatrists, as opposed to 22% in the S+NPE group and 17% in the S+PAE group (\(\chi^2 = 8.121, \text{d.f.} = 2, P = 0.02\); pairwise comparisons \(P < 0.05\)). The rate of non-adherence to sertraline treatment tended to be higher in those in the drug-only arm (26%) than in the combined interventions (S+PAE 7%, S+NPE 16%; \(\chi^2 = 5.53, \text{d.f.} = 2, P = 0.06\)). Attendance at exercise sessions was high (70% for 72 total sessions) and similar in the two exercise groups (S+PAE median 54 sessions, IQR 44–64; S+NPE median 51 sessions, IQR 38–58; Mann–Whitney \(z = 2.167, P = 0.14\), with a tendency to decrease over the follow-up period.

Remission of depression

Remission rates were higher in the S+P and S+NPE groups than in the sertraline-only group: at week 4, rates were 36%, 40% and 7% respectively (\(P = 0.001\)). At week 8, rates were 60%, 49% and 40% (\(P = 0.22\)) and at week 12 they were 83%, 54% and 45% (\(P = 0.001\)). By the study end, remission was achieved by 45% of participants in the sertraline group, 73% of those in the S+NPE group and 81% of those in the S+PAE group (\(P = 0.001\)). Figure 2 reports survival curves for the three intervention groups; in Kaplan–Meier analyses time to remission was significantly different between groups (log rank \(\chi^2 = 12.6, \text{d.f.} = 2, P = 0.002\); this was driven by a shorter time to remission...
in the S+PAE group (9.3 weeks, 95% CI 7.4–11.2) than in the sertraline group (14.8 weeks, 95% CI 12.2–17.4), whereas the time to remission was intermediate for the S+NPE group (12.0 weeks, 95% CI 9.2–14.8). Compared with participants in the drug-only group, those in the S+PAE group had a twofold hazard ratio for an earlier remission; this value survived after adjusting for various study contextual and clinical factors (Table 2). Furthermore, the hazard ratio for the S+NPE group also became statistically significant with a similar value (1.91) when the same factors were taken into account.

Changes in depressive symptoms

There were greater decreases in HRSD scores in the two exercise groups compared with the drug-only group (Table 3, Fig. 3). The overall time course of HRSD scores was best predicted by a third-order polynomial of time, and by the interactions of intervention group (S+NPE vs. sertraline and S+PAE vs. sertraline) with time (Table 4). This model’s fitness showed significant improvements over models including only the linear and quadratic terms of time (both 2LL decreases \(445\), d.f. = 3, \(P < 0.01\)), whereas adjusting for the control variables did not lead to further improvement in the model fitness. There was no significant association between the baseline severity of depression and the rate of decrease over time (rho: \(P = 0.15\)). Last, the percentage of participants rated as ‘very much improved’ or ‘much improved’ on the CGI (scores 1 and 2) at the study end was significantly higher in the S+PAE group (71%) and in the S+NPE group (60%) than in the sertraline-only group (43%; \(\chi^2 = 7.09\), d.f. = 2, \(P = 0.03\)).

Changes in aerobic capacity

Only 73 participants had their aerobic capacity assessed at both baseline and 24 weeks (25 in the S+NPE group, 34 in the S+PAE group and 14 in the sertraline group). Peak \(VO_2\) was on average stable among participants in the S+NPE group (−0.22%; IQR −14.5 to −12.9), whereas those in the S+PAE group showed a median improvement of 4.7% (IQR −10.3 to 16.8) and those in the sertraline-only group a decrease (−2.5%, IQR −18.6 to −5.9). However, after adjusting for baseline peak aerobic capacity, intervention group did not predict aerobic capacity at 24 weeks (S+NPE group \(P = 0.22\), S+PAE group \(P = 0.32\)), whereas the number of sessions attended in both groups did (\(P = 0.03\)).
A significantly higher proportion of sedentary older people with major depression achieved remission with sertraline plus a 24-week exercise programme compared with those treated with sertraline alone. Both the exercise protocols were associated with earlier and higher remission rates, which were evident after only 4 weeks of treatment. The beneficial effect of physical exercise was independent of the severity and chronicity of depression, of participants’ demographic characteristics and of physical comorbidities. Overall, a high degree of adherence to the interventions was observed in a frail population group that had not been sufficiently studied in this regard. These findings are particularly significant for clinical practice, since late-life depression is often associated with poor or slow responses to first-line pharmacotherapy, and with physical inactivity.

Other research
To our knowledge this study is the first to examine the efficacy of structured physical exercise interventions in the antidepressant treatment of older adults with major depression. Our findings are consistent with research suggesting that exercise could exert antidepressant properties in adults with subthreshold or fully fledged clinical depression. In older patients, most commonly with non-major depression, a few studies have shown that physical exercise (group- or home-based, strength training or mixed aerobic and strength training, mostly three times per week) was effective in reducing depressive symptoms, with small to moderate effects. Several factors may account for this difference:

### Table 2 Time to remission from depression: effect of sertraline v. integrated treatments

<table>
<thead>
<tr>
<th>Predictor</th>
<th>B (s.e.)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S+NPE</td>
<td>0.51 (0.27)</td>
<td>1.68</td>
<td>0.98–2.88</td>
</tr>
<tr>
<td>S+PAE</td>
<td>0.75 (0.26)</td>
<td>2.12**</td>
<td>1.27–3.54</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S+NPE</td>
<td>0.65 (0.29)</td>
<td>1.91*</td>
<td>1.08–3.39</td>
</tr>
<tr>
<td>S+PAE</td>
<td>0.72 (0.29)</td>
<td>2.04*</td>
<td>1.17–3.58</td>
</tr>
</tbody>
</table>

#### Clinical factors
- Age
  - <0.01 (0.02) | 1.00 | 0.97–1.04 |
- Gender, male
  - −0.11 (0.24) | 0.90 | 0.56–1.44 |
- CIRS comorbidity score
  - −0.39 (0.55) | 0.68 | 0.23–1.99 |
- Baseline HRSD score
  - −0.06 (0.04) | 0.95 | 0.87–1.03 |
- Number of previous episodes of depression
  - −0.05 (0.24) | 0.95 | 0.60–1.51 |
- Prior treatment with antidepressants
  - −0.07 (0.26) | 0.94 | 0.56–1.56 |

#### Medication
- Dosage of sertraline
  - 0.52 (0.39) | 0.59 | 0.28–1.27 |
- Non-adherence to sertraline
  - −0.22 (0.14) | 0.80 | 0.61–1.04 |

**CIRS, Cumulative Illness Rating Scale; HR, hazard ratio; HRSD, Hamilton Rating Scale for Depression; S+NPE, sertraline plus non-progressive exercise; S+PAE, sertraline plus progressive aerobic exercise.**

* Cox regression models: remission in the sertraline-only intervention arm is the reference category.
+ Unadjusted model; \( \chi^2 = 8.9, \) d.f. = 2, \( P = 0.01. \)
+ Adjusted model; \( \chi^2 = 34.8, \) d.f. = 13, \( P = 0.001. \)

* \( P < 0.05; ** P < 0.01. \)

### Table 3 Severity of depression

<table>
<thead>
<tr>
<th>Assessment</th>
<th>HRSD total score: mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sertraline group ( n=42 )</td>
</tr>
<tr>
<td>Baseline</td>
<td>20.4 (3.4)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>15.8 (4.4)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>12.8 (5.0)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>11.7 (5.0)</td>
</tr>
<tr>
<td>24 weeks</td>
<td>11.7 (5.9)</td>
</tr>
</tbody>
</table>

**HRSD, Hamilton Rating Scale for Depression; S+NPE, sertraline plus non-progressive exercise; S+PAE, sertraline plus progressive aerobic exercise.**
these include the use of an antidepressant drug, social support due to exercising in groups, more intense exercise protocols and a longer duration of the interventions. More recently another study has found that a low-intensity, low-frequency tai chi plus meditation protocol in combination with escitalopram therapy was more effective than health education meetings plus escitalopram among older volunteers with depression from the community. In contrast, a recent large trial failed to demonstrate significant reductions of depressive symptoms associated with physical exercise (two sessions per week) among very old people living in care homes. This inconsistency might be due to differences in sample characteristics (participants were more physically and cognitively impaired and only half had clinical depression in the latter study), assessment instrument (Geriatric Depression Scale), a lower frequency, intensity and adherence to the physical exercise protocol and lower antidepressant use (30% of participants). Taken together, these findings suggest that physical exercise might need to be provided along with an antidepressant, or at least be scheduled with sufficient frequency and/or intensity to exert significant antidepressant effects. In our study both protocols followed the recommendations set by guidelines for physical exercise in elderly people, but differed in that the S+PAE intervention was characterised by increasing energy expenditure, whereas the S+NPE group exercises were aimed at improving participants’ balance and strength. After adjusting for confounders, the outcomes of depression were similar in the two groups. Unlike others, we did not observe significant improvement in aerobic capacity in the exercise groups compared with the sertraline-only group, or between the two exercise groups. However, only a small number of participants (n=73) were assessed for aerobic capacity both at baseline and after 24 weeks, so the statistical power may have not been sufficient to detect the effect of exercise on the aerobic capacity. Further analyses and larger studies should clarify whether different types of physical activity might elicit specific mechanisms of antidepressant action in elderly patients for example, among younger adults aerobic training but not strength exercise seems associated with increases of BDNF.

**Study limitations**

This study has some limitations that need to be taken into account. We did not include an active comparator, such as social support or health education group meetings, as an augmentation strategy to sertraline. Hence, we cannot rule out that part of the additional antidepressive efficacy provided by physical exercise was related to social support rather than to exercise itself. However, this choice was undertaken for several reasons: first, our aim was to assess the added benefit of exercise to SSRI therapy, since SSRIs are commonly used by primary care physicians and the low efficacy of these drugs leaves many patients with continuing symptoms. Second, physical exercise was already shown to be more effective than comparators such as social group programmes. Third, patients might have been less likely to engage in non-therapeutic activities with such a high frequency.

**Clinical implications**

Our findings provide the clinician with a rationale for adopting physical exercise as a potential tool in the management of late-life major depression; it is noteworthy that nearly three-quarters of the patients who received physical exercise as an add-on to sertraline therapy reached remission within the study period – well beyond those who received sertraline alone. Also, remission was faster than is commonly observed for antidepressant therapy.

**Table 4** Growth curve model for the changes in depressive symptoms with time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>b</th>
<th>s.e.</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>19.87</td>
<td>0.45</td>
<td>18.99 to 20.75</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Time 2</td>
<td>−2.36</td>
<td>0.16</td>
<td>−2.67 to −2.06</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Time 3</td>
<td>0.17</td>
<td>0.02</td>
<td>0.13 to 0.20</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>S+NPE</td>
<td>−0.03</td>
<td>0.05</td>
<td>−0.04 to −0.03</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>S+NPE*Time</td>
<td>−0.22</td>
<td>0.45</td>
<td>−1.10 to 0.66</td>
<td>0.621</td>
</tr>
<tr>
<td>S+NPE*Time 2</td>
<td>−0.46</td>
<td>0.16</td>
<td>−0.77 to −0.16</td>
<td>0.003**</td>
</tr>
<tr>
<td>S+NPE*Time 3</td>
<td>0.06</td>
<td>0.02</td>
<td>0.01 to 0.09</td>
<td>0.007**</td>
</tr>
<tr>
<td>S+PAE</td>
<td>−0.36</td>
<td>0.43</td>
<td>−1.21 to 0.49</td>
<td>0.399</td>
</tr>
<tr>
<td>S+PAE*Time</td>
<td>−0.44</td>
<td>0.15</td>
<td>−0.74 to −0.15</td>
<td>0.003**</td>
</tr>
<tr>
<td>S+PAE*Time 2</td>
<td>0.04</td>
<td>0.02</td>
<td>0.003 to 0.08</td>
<td>0.033*</td>
</tr>
<tr>
<td>S+PAE*Time 3</td>
<td>−0.01</td>
<td>0.05</td>
<td>−0.002 to 0.0004</td>
<td>0.060</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variance intercept</td>
<td>8.69</td>
<td>1.57</td>
<td>6.10 to 12.37</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Variance time</td>
<td>0.03</td>
<td>0.01</td>
<td>0.02 to 0.04</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>ARH rho</td>
<td>−0.20</td>
<td>0.14</td>
<td>−0.45 to 0.08</td>
<td>0.147</td>
</tr>
</tbody>
</table>

ARH, autoregressive heterogeneous covariance structure; S+NPE, sertraline plus non-progressive exercise; S+PAE, sertraline plus progressive aerobic exercise

a. Sertraline-only group is the reference category.

*P<0.05, **P<0.01
treatment in elderly patients. Participants were representative of the sedentary patients with late-life major depression who are usually encountered in primary care: the vast majority had been sedentary patients with late-life major depression who are often failure to respond to antidepressant therapy. Adding exercise to the regimen of older patients with depression, effective than antidepressant drug therapy alone in older adults with major depression who are sedentary. Clinicians may consider adding exercise to the regimen of older patients with depression, people who often fail to respond to antidepressant therapy.

Protocol for the progressive aerobic exercise intervention

Each session of the protocol consisted of a 10 min warm-up: breathing exercises, slow cycling. This was followed by cycling at an intensity that would maintain the heart rate within the assigned target heart-rate range. Target heart rate was defined by percentage of the peak heart rate (PHR) as measured during the maximum oxygen uptake test. All exercise sessions concluded with 5–10 min of cool-down cycling.

Cycling sessions

First period (weeks 0–4): exercise bike, cycling at 60–70% of PHR, 30–40 min
Second period (weeks 5–8): treadmill exercise at 70–80% of PHR, 40–50 min
Third period (weeks 9–12): five interval training sessions of 5 min at 85% of PHR or 40 min of continuous treadmill at 70% of PHR
Fourth period (weeks 13–24): five interval training sessions of 6 min at 85% of PHR, or 40 min of continuous treadmill at 70% of PHR

Appendix

Protocol for the non-progressive exercise intervention

Each session of the protocol consisted of:

10 min warm-up: walking, strengthening exercises, quiet calisthenics
2 repetitions of 10 min each: mat work: stretching, calisthenics, breathing exercises

References


Authenticity

David Brunskill

Four components determine the degree of authenticity: awareness that we all have good and bad aspects; unbiased processing of both these aspects that should be accepted; behaviour congruent with the true self; and relational orientation in which there is honesty/honest disclosure that allows others to see us as we really are. Striving for a high degree of authenticity can seem a lofty aim (think Maslow’s pyramid) because to achieve it, one’s core self must first be identified, then accepted and finally, allowed to live and be. Perhaps the psychological prize of healthy functioning and life satisfaction is worth an inevitable struggle?
Physical exercise for late-life major depression
Access the most recent version at DOI: 10.1192/bjp.bp.114.150516

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