

Exercise and Pharmacotherapy in the Treatment of Major Depressive Disorder

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Objective: To assess whether patients receiving aerobic exercise training performed either at home or in a supervised group setting achieve reductions in depression comparable to standard antidepressant medication (sertraline) and greater reductions in depression compared to placebo controls. **Methods:** Between October 2000 and November 2005, we performed a prospective, randomized controlled trial (SMILE study) with allocation concealment and blinded outcome assessment in a tertiary care teaching hospital. A total of 202 adults (153 women; 49 men) diagnosed with major depression were assigned randomly to one of four conditions: supervised exercise in a group setting; home-based exercise; antidepressant medication (sertraline, 50–200 mg daily); or placebo pill for 16 weeks. Patients underwent the structured clinical interview for depression and completed the Hamilton Depression Rating Scale (HAM-D). **Results:** After 4 months of treatment, 41% of the participants achieved remission, defined as no longer meeting the criteria for major depressive disorder (MDD) and a HAM-D score of <8. Patients receiving active treatments tended to have higher remission rates than the placebo controls: supervised exercise = 45%; home-based exercise = 40%; medication = 47%; placebo = 31% ($p = .057$). All treatment groups had lower HAM-D scores after treatment; scores for the active treatment groups were not significantly different from the placebo group ($p = .23$). **Conclusions:** The efficacy of exercise in patients seems generally comparable with patients receiving antidepressant medication and both tend to be better than the placebo in patients with MDD. Placebo response rates were high, suggesting that a considerable portion of the therapeutic response is determined by patient expectations, ongoing symptom monitoring, attention, and other nonspecific factors. **Key words:** depression, exercise, antidepressant medication, selective serotonin reuptake inhibitors.

BDI = Beck Depression Inventory; **CI** = confidence interval; **HAM-D** = Hamilton Depression Rating Scale; **ITT** = intention-to-treat; **MDD** = major depressive disorder; **SD** = standard deviation; **SSRIs** = selective serotonin reuptake inhibitors; **TSH** = thyroid stimulating hormone.

INTRODUCTION

Major depressive disorder (MDD) is a significant health problem with a lifetime prevalence of 15% to 20% (1). MDD is associated with significant morbidity, mortality, disability, and suffering for patients and their families (2,3), and ranks fourth among the leading causes of disability-adjusted life-years worldwide (4). Projections for the year 2020 indicate that MDD will be second only to coronary heart disease as a cause of illness burden worldwide (5). Because no single treatment is effective for everyone (6,7), there has been great interest in the development and evaluation of alternative therapies for MDD. Physical exercise is one such therapy that has

received considerable attention (8). A number of studies have shown that aerobic exercise and resistance training may reduce self-reported depressive symptoms in nonclinical populations (9–12) and in patients diagnosed with MDD (13–20). However, as noted in previous reviews (8,21–24), many exercise studies have had a variety of methodological limitations, including a lack of randomized designs, failure to assess adequately and document cardiopulmonary training effects, unblinding of assessors, confounding of exercise with psychotherapy, and inclusion of participants classified as “depressed” solely by self-reports of symptom severity rather than by clinical interviews. In a meta-analysis evaluating 11 randomized controlled trials, Lawlor and Hopker (21) argued that because of these methodological shortcomings, “the effectiveness of exercise in reducing symptoms of depression cannot be determined because of a lack of good quality research on clinical populations with adequate follow up.”

A previous study from our research group demonstrated that exercise was equally effective as antidepressant medication in reducing depressive symptoms in 156 older patients with MDD (13,25). However, because we did not include a no-treatment or placebo control group, we could not rule out the possibility that the treatment benefits were due to the nonspecific effects of staff attention and support that accompany involvement in a research study, or alternatively, to the phenomenon of regression to the mean. In developing the current study protocol to address this issue, the question was raised whether the information provided by a placebo control condition is of significant scientific value to offset the possible negative consequences of providing a “treatment” known to be of limited effectiveness. This ethical and scientific dilemma has been a concern of our research team from the earliest stages of protocol development. In our earlier study (13), the expectation was that an adequate assessment of the efficacy of exercise therapy could be obtained through comparison with a

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standard medication of proven efficacy. Subsequent critical reaction to our findings, however, demonstrated the methodological weaknesses of this approach. Although we were able to show equivalent rates of therapeutic response for exercise and antidepressant medication, experienced clinicians and researchers viewed our results with skepticism because the data did not permit exclusion of placebo response as accounting for the findings. This view is understandable, insofar as MDD is a condition known to have a high and variable rate of placebo responsiveness, making it essential that any innovative treatment be proven superior in effectiveness to placebo. As a result of these considerations, we decided to incorporate a placebo pill condition into the present design. Coupled with this decision, however, was an approach to safeguard the patients' well-being by establishing the eligibility criteria that would minimize their risk of participation, closely monitoring patient symptoms and developing a plan for removing patients from the trial if necessary. Our protocol was approved by the National Institutes of Health Review Panel as well as our local Institutional Review Board.

In addition to the control group issue, because patients in our prior study exercised in a supervised group, it is possible that social support from other patients may have contributed to the observed reductions in depression. This issue also was a challenge in developing the study design for our current protocol. Although we considered a "social support" control condition, this intervention presumably also would be less effective, which raised the same ethical issues presented by a drug-placebo condition. We elected to control for the effects of social support by comparing home-based exercise with supervised, group-based exercise. The exercise prescriptions were identical, and the only difference between the groups was the setting in which the exercise occurred.

A final issue that we considered in the development of the design of the present study concerns the established treatment with which exercise would be compared. Antidepressant medications, and specifically selective serotonin reuptake inhibitors (SSRIs), are common first-line therapies. As in our prior study, we selected sertraline (Zoloft, Pfizer) as the standard treatment for purposes of comparison because of its widespread usage and proven efficacy, tolerability, and low toxicity (26). Remission, defined by the absence of MDD diagnosis and significant reduction in depressive symptomatology (i.e., HAM-D score of <8) (27), was identified as the goal of treatment (2,28); a better prognosis and higher levels of daily functioning accompany remission as compared with the simple reduction of symptom severity (29,30). Thus, the present study compared the effects of supervised group exercise, home-based individual exercise, and an established antidepressant medication (sertraline) with placebo in a relatively large sample of middle-aged and older adults diagnosed with MDD.

METHODS

This study was a randomized, parallel group, 16-week, placebo-controlled trial of exercise (group-supervised and individual home-based), and sertraline treatment for MDD.

Participants

Outpatients were initially screened using the 21-item Beck Depression Inventory II (BDI) (31). Participants obtaining a BDI score of ≥ 12 and subsequently meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for MDD (32) were recruited between October 2000 and November 2005 through television, radio, and newspaper advertisements. Eligibility criteria included age ≥ 40 years, presence of MDD, sedentary (i.e., no current involvement in regular exercise), and no current psychiatric treatment. Exclusion criteria included the presence of another primary psychiatric diagnosis, such as a history of bipolar disorder or psychosis; medical comorbidities that would preclude participation in the trial (e.g., significant musculoskeletal difficulties); current use of antidepressants or other psychotropic medications; dietary supplements or herbal therapies with purported psychoactive indications; current active alcohol or drug abuse or dependence; and active suicidal intent. All participants provided written informed consent and the protocol was approved by the Institutional Review Board at Duke University Medical Center.

Assessment Procedures

Medical Screening

Before entry into the study, patients underwent a physical examination by a study physician. Blood pressure was measured by standard sphygmomanometry in sitting and standing positions. Patients were also given blood tests including routine electrolytes, pregnancy and liver function tests, blood count, and thyroid stimulating hormone (TSH). If a patient was found to have any significant medical condition that would contraindicate safe participation in this study, he/she was excluded from participation in the study.

Depression Assessment

All potential patients were evaluated using the structured clinical interview for depression (33) to diagnose MDD and the 17-item Hamilton Depression Rating Scale (HAM-D) (34) to assess MDD severity at baseline and after 16 weeks. Assessments were performed by licensed clinical psychologists blinded to the treatment condition. To ensure patient safety and monitor symptom severity and suicidality, a trained research assistant administered the BDI by telephone weekly for the first 4 weeks and biweekly for the subsequent 12 weeks.

Exercise Testing

Graded treadmill exercise testing was conducted before treatment and at the conclusion of treatment to document the patients' fitness levels and establish an exercise training prescription for those patients subsequently randomized to exercise. Patients exercised to exhaustion or other standard end points (e.g., chest pain, decreasing blood pressure, complex premature ventricular contractions, progressive ST-segment depression) under continuous electrocardiographic monitoring using the Duke-Wake Forest protocol in which workloads are increased at a rate of 1 metabolic equivalent per minute (35). Expired air was collected by mouthpiece for quantification of minute ventilation, oxygen consumption (VO_2), and carbon dioxide production (SensorMedics Metabolic Cart; Model 2900; Yorba Linda, California). Samples were collected at 20-second intervals, and peak values were determined from an average obtained during the last 60 seconds.

Treatment

Participants were assigned randomly in equal proportions to supervised aerobic exercise ($n = 51$), home-based aerobic exercise ($n = 53$), sertraline ($n = 49$), or placebo ($n = 49$). Randomization was performed centrally by computer with conditional randomization (stratified by age, gender, and depression severity); patients were provided with sealed envelopes containing their group assignment.

Patients in the supervised aerobic exercise condition attended three supervised group exercise sessions per week for 16 weeks. Based on maximum heart rate achieved during the treadmill test, these patients were assigned training ranges equivalent to 70% to 85% maximum heart rate reserve. Each aerobic session began with a 10-minute warm-up exercise of walking fol-

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lowed by 30 minutes of walking or jogging on a treadmill at an intensity that would maintain their heart rate within the assigned training range. The exercise session concluded with 5 minutes of cool-down exercises.

Participants in a home-based exercise program received the same exercise prescription but exercised at home on their own with minimal contact from the study staff. Patients received an initial home visit to establish their exercise training routine and they received instruction about monitoring their exercise heart rates accurately. Home-based exercisers received subsequent visits from an exercise physiologist after 1 month and 2 months, and telephone calls at weeks 1 to 4 and biweekly thereafter until the end of the trial. Up to two additional home visits were permitted if the patients reported difficulty adhering to the exercise prescription. Three times during each exercise session, the participants in both exercise conditions monitored and recorded their heart rates via radial pulses, along with ratings of perceived exertion. Each week, home-based exercisers returned their exercise logs, documenting exercise duration, intensity (heart rates), and ratings of perceived exertion.

Participants in the “pill” conditions were given the SSRIs, sertraline, or matching placebo provided by Pfizer Inc. (New York, NY) by the treating psychiatrist (PMD). Medications were provided once daily; the dosage depended on the clinical response, but usually each patient received a starting dosage at 50 mg (one pill) of drug or placebo and received increasing dosages to 200 mg (four pills)—contingent on therapeutic response and presence of side effects. The treating psychiatrist was blinded to pill condition and used supportive measures to help manage medication side effects. In cases of severe side effects or patient discomfort, the psychiatrist could decrease the medication dosage at any time during the study. For insomnia, use of a hypnotic (zolpidem) was limited to no more than four doses during treatment. Patients were seen at the time of randomization and at weeks 2, 4, 8, 12, and 16.

The treatment team and outcome assessors were unaware of the patients’ treatment assignments, and only the research pharmacist was aware of which patients were assigned to sertraline or placebo. The principal investigator and study coordinator, who were not involved in the assessments or delivery of the interventions, were aware of whether patients were in pill or exercise conditions. Pfizer provided sertraline tablets and placebo pills for use in this research study, but they had no other role in the study design, data acquisition, data analysis, or preparation of this manuscript.

Statistical Analysis

Treatment effects were evaluated using generalized linear models with maximum likelihood estimation available in PROC GENMOD in SAS 9.1 (SAS Institute, Cary, North Carolina). Our primary end point was remission, defined as no DSM diagnosis of MDD and a HAM-D score of <8, and also as a continuous severity score on the HAM-D. Treatment group, age, gender, race (Caucasian versus non-Caucasian), pretreatment HAM-D score, and number of prior episodes of MDD were selected a priori as covariables. In the generalized linear model, the binomial error distribution was assumed for the binary outcome, and Gaussian errors were assumed for the HAM-D outcome.

Prior antidepressant drug trials have shown a high rate of placebo response (36,37), which often takes the form of a clinically significant response (>50% reduction in symptoms) during the first week of treatment. For this reason, we performed an exploratory analysis in which we examined the subset of patients who did not show this early response. (In the present report, the term “early responder” and not “placebo responder” is used to describe patients in any treatment group—active as well as placebo—who exhibited a >50% reduction in self-reported BDI scores within the first week after initiating treatment). Treatment effects for the primary depression outcomes were estimated using three planned contrasts: all active treatment versus placebo; the two exercise groups versus medication; and home-based versus supervised exercise.

Analyses followed the intent-to-treat (ITT) principle (38), using the last observation carried forward method. We also evaluated the extent to which models met assumptions, including nonadditivity, linearity, outlying data points, and the distribution of residuals. With respect to statistical power, assuming a recovery rate of 30% in the placebo group and a two-side test at $\alpha = 0.05$, we estimated that with the sample size (assuming ITT), for any given group comparison, we would have a power of about 0.80 to detect a

difference of 0.30 in the proportion of patients classified as recovered using the criteria of no DSM-IV diagnosis and a HAM-D score of <8. For the HAM-D, the power was 0.80 to detect about a 4-point difference (i.e., a little over a half standard deviation (SD)) between any two groups.

RESULTS

We screened 457 patients; 135 did not meet the criteria for MDD, 47 withdrew consent, 40 had an excluding psychiatric comorbidity, and 33 were ruled out for other reasons, leaving 202 participants available for randomization. Figure 1 shows the patient flow from initial recruitment screening to posttreatment assessment and analysis.

Patient Characteristics

The four treatment groups had similar demographic and clinical characteristics. The mean age of participants was 53 years, the majority being Caucasian and female (Table 1). The treatment groups were similar with respect to history of MDD, age, gender, and ethnicity. The mean \pm standard deviation (SD) HAM-D score for the sample was 17 ± 5 ; most patients were considered mild to moderately depressed (HAM-D score of <23); 40% of the sample had a history of recurrent depression.

Adherence and Treatment Fidelity

Adherence to medication treatment was evaluated by pill count. The mean dose of medication prescribed over the course of the study was similar for the sertraline and placebo groups (mean = 2.3 pills for both groups). There were seven (14.3%) dropouts in the sertraline (s) condition and 14 (28.6%) dropouts in the placebo (p) condition. Reasons for dropout included dissatisfaction with group assignment (2s, 1p), adverse effects of medication (1s, 3p), logistical difficulties in attending treatment (1s), dissatisfaction with progress in treatment (2s, 5p), dissatisfaction with treatment program (1p), development of a new medical condition (2p), and unknown reasons due to difficulties contacting patients (1s, 3p).

Patients met with a study psychiatrist for six visits including a baseline visit to initiate therapy, four planned medication visits to adjust dosage at weeks 2, 4, 8, and 12, and a final visit at week 16 to transition patients for further treatment if needed. Eighty-three per cent of patients in the medication condition attended six visits compared with 72% of patients in the placebo group ($p = .481$). Seven patients (3p, 4s) had an additional (i.e., seventh) visit with the study psychiatrist to address issues related to side effects. Pill patients attended an average of 5.30 ± 1.7 psychiatric visits; there was no statistically significant difference in attendance between patients receiving sertraline (5.53 ± 1.4) and patients receiving placebo (5.06 ± 1.9 ; $p = .16$).

We employed a 5-point Likert “Treatment Belief” rating scale ranging from 1 (I am very sure I am on placebo) to 5 (I am very sure I am on the active medication) to assess the patients’ beliefs about which pill they were receiving. At the end of treatment, 52% of patients receiving sertraline thought that they had received the active drug, 38% were “unsure,” and only 10% thought they were on placebo. In contrast, 37% of patients receiving the placebo thought that they had re-

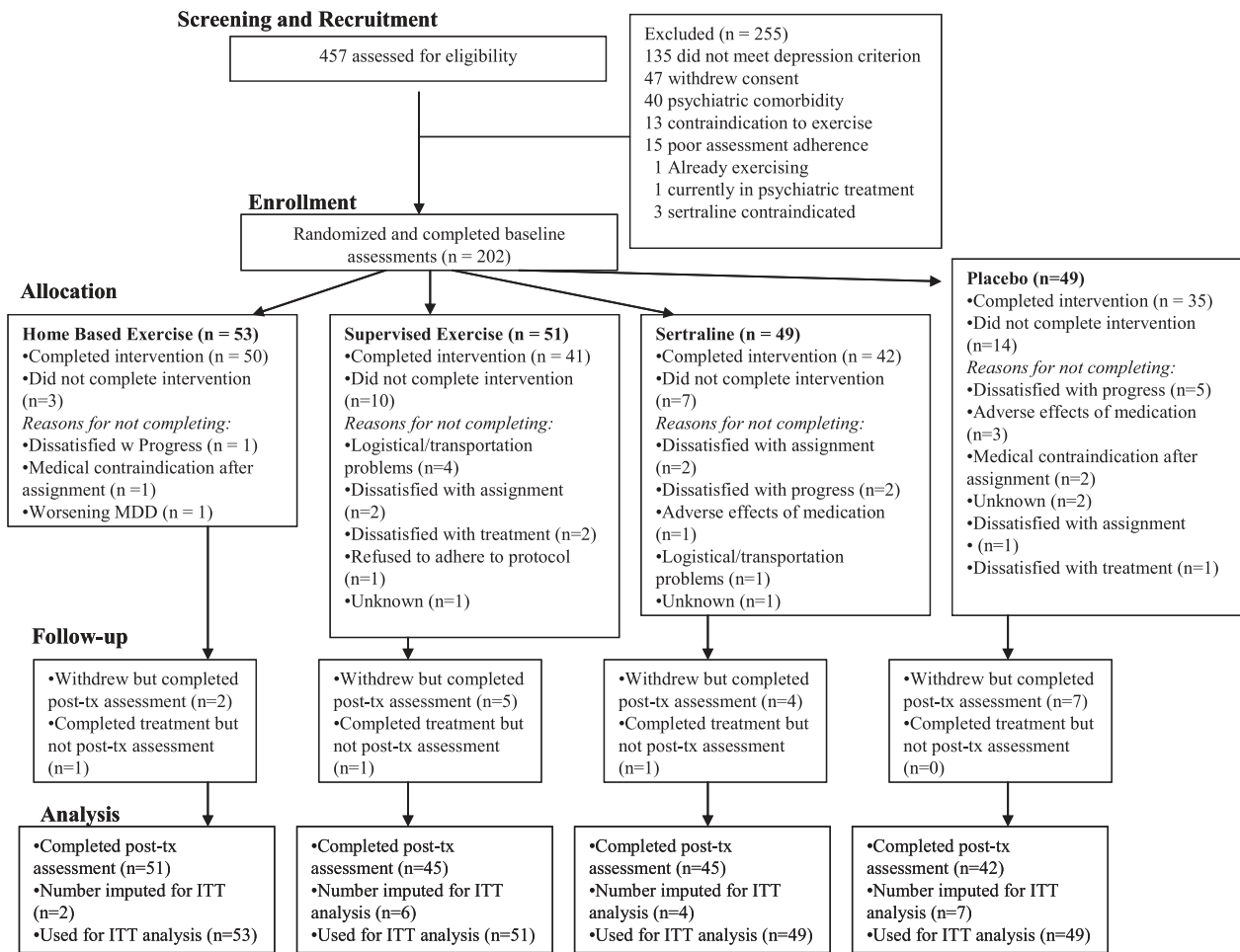


Figure 1. Flowchart of participant recruitment and retention throughout the study. MDD = major depressive disorder; ITT = intention-to-treat.

TABLE 1. Background Characteristics at Study Entry

Variable	Home, n = 53	Supervised, n = 51	Medication, n = 49	Placebo, n = 49	Entire Cohort, n = 202
Age, years (mean ± SD)	53 ± 8	52 ± 7	52 ± 8	52 ± 8	52 ± 8
Male, n (%)	14 (26)	12 (25)	12 (25)	11 (23)	49 (24)
White, n (%)	35 (66)	36 (71)	35 (71)	31 (63)	137 (68)
African-American, n (%)	14 (26)	12 (24)	12 (25)	14 (28)	52 (26)
Hispanic, n (%)	2 (4)	2 (4)	0 (0)	0 (0)	4 (2)
Native American, n (%)	1 (2)	1 (0)	1 (2)	0 (0)	2 (1)
Other ethnicity, n (%)	1 (2)	1 (2)	1 (2)	4 (8)	7 (3)
College, n (%)	49 (92)	46 (90)	44 (90)	44 (90)	183 (91)
No prior MDD, n (%)	17 (32)	16 (31)	17 (35)	20 (41)	70 (35)
>1 MDD episode, n (%)	21 (40)	22 (43)	21 (42)	20 (41)	84 (42)
HAM-D, mean ± SD	17 ± 5	16 ± 4	16 ± 4	17 ± 4	17 ± 4
BDI, mean ± SD	31 ± 9	30 ± 8	30 ± 8	31 ± 8	31 ± 8
Systolic BP, mean ± SD	123 ± 16	121 ± 16	126 ± 19	128 ± 18	124 ± 17
Diastolic BP, mean ± SD	78 ± 10	78 ± 9	81 ± 10	80 ± 9	79 ± 9
Hypertension, n (%)	11 (21)	16 (34)	14 (29)	14 (30)	55 (27)
Diabetes, n (%)	4 (8)	3 (6)	3 (6)	4 (9)	14 (7)
Body mass index (kg/m ²), mean ± SD	30 ± 6.8	28 ± 6.6	30 ± 7.9	31 ± 7.6	30 ± 7.3
History of or current smoking, n (%)	28 (55)	21 (43)	19 (41)	22 (47)	90 (45)
Current smoking, n (%)	8 (15)	7 (14)	9 (19)	8 (17)	32 (16)
Alcohol: ≥3 alcoholic drinks per week, n (%)	4 (8)	3 (6)	3 (6)	5 (10)	15 (7)

SD = standard deviation; MDD = major depressive disorder; HAM-D = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory; BP = blood pressure.

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ceived the active medication, 27% thought they were receiving the placebo, and 36% were “unsure.”

Self-reported exercise frequency was greater for patients in the home-based exercise condition (median = 40; interquartile range = 29–48 sessions) compared with patient attendance in the supervised exercise condition (median = 37; interquartile range = 15–41 sessions). This difference can be partially attributed to differential dropout rates, with only 3 (6%) dropouts in home exercise and 10 (20%) dropouts from supervised exercise ($p = .002$). Because the participants were not considered dropouts unless they discontinued exercise for the remaining duration of the study, it was easier for patients in the home-based exercise to remain in the study by maintaining minimal involvement in the exercise program. If data from exercise dropouts are excluded, the attendance rates were comparable for home-based (93.9%) and supervised (82.9%) exercise; 68% of home exercisers completed at least 75% of the 48 scheduled sessions compared with 67% of supervised exercisers ($p = .892$). Reasons for 13 exercise dropouts (home-based = h; supervised = s) included development of medical contraindication (1h), worsening MDD (1h), logistical difficulties in attending treatment (4s), dissatisfaction with progress in treatment (1h, 2s), dissatisfaction with treatment program (2s), noncompliance (1s), and an unknown reason due to difficulty contacting the patient (1s).

All patients monitored their radial pulses manually to document adherence to their exercise prescriptions. Polar monitors (Polar Electro Incorporated, Woodbury, New York) were also used to verify self-reported heart rates among home exercisers by objectively measuring heart rates in a random sample of 26 home exercisers over 1 to 4 months of monitoring. Polar-derived exercise heart rate recordings and self-reported heart rates were highly correlated ($r = .97$; $p < .001$). During exercise sessions, home-based exercisers achieved or exceeded their prescribed heart rates 65% of the time, whereas supervised exercisers were at or above their target heart rates 77% of the time ($p < .01$).

Changes in Aerobic Capacity After Treatment

Figure 2 shows the mean posttreatment aerobic capacity and exercise treadmill test duration for each of the treatment groups, adjusting for pretreatment levels. The exercise groups displayed significantly higher levels of aerobic capacity (peak VO_2) compared with placebo and medication pill conditions ($p < .0001$). Differences in aerobic capacity were also noted between exercise treatment conditions, with supervised exercise participants achieving higher levels of posttreatment aerobic capacity than did home-based exercisers. Similarly, patients in the two exercise conditions exhibited greater treadmill times compared with patients who received pills ($p < .0001$), with supervised exercisers attaining longer treadmill times than those patients who exercised at home ($p < .0001$). Participants in home-based exercise showed an improvement of 3.5% in peak VO_2 and 7.5% in treadmill time; supervised exercise improved by 8.3% in peak VO_2 and 18.8% in treadmill time; the medication group showed a 0.8% decrease in

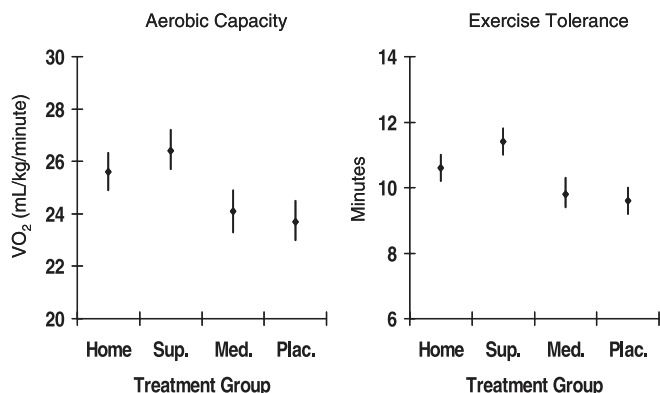


Figure 2. Mean aerobic capacity and exercise tolerance after 16 weeks of treatment, adjusting for pretreatment levels of outcome variable, age, gender, race, and past major depressive disorder. Participants in the exercise conditions showed greater aerobic capacity (left panel) and exercise tolerance (right panel) compared with patients in the medication or placebo conditions. Error bars represent 95% confidence limits. Planned contrasts for aerobic capacity were as follows: all exercise versus placebo, $p = .0001$; medication versus placebo, $p = .420$; all exercise versus medication, $p = .0001$. For exercise tolerance, the contrast results were: all exercise versus placebo, $p = .0001$; medication versus placebo, $p = .410$; all exercise versus medication, $p = .0001$. VO_2 = oxygen consumption; Sup = supervised exercise; Med = medication; Plac = placebo.

peak VO_2 and 3.9% improvement in treadmill time; and the placebo group declined by 4% in peak VO_2 and 2.3% in treadmill time.

Depression Outcomes

Our primary end point was remission of MDD, defined as no longer meeting the criteria for MDD and achieving a HAM-D rating of < 8 (27). Figure 3 (left panel) displays the predicted probabilities of having no depression diagnosis after treatment for each group, adjusted for age, gender, race,

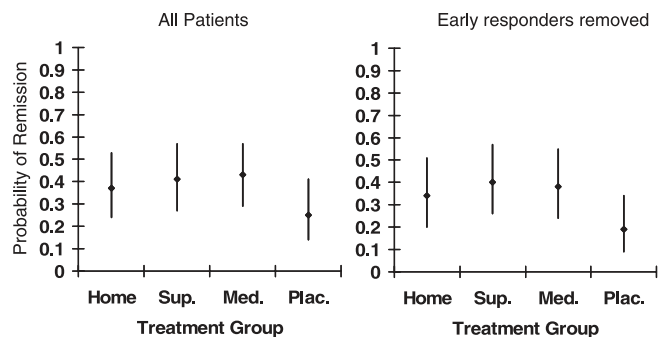


Figure 3. Predicted probability of remission, defined as no major depressive disorder diagnosis and Hamilton Depression Rating Scale (HAM-D) score of < 8 after treatment, using intention-to-treat (left panel) and limited to patients who did not exhibit an early response ($n = 183$) (right panel). Early responders are defined as patients with $> 50\%$ reduction from baseline in Beck Depression Inventory scores after the first week of treatment. Probability estimates are for a patient with the most typical profile in the study: age 52 years, female, Caucasian, one prior major depressive episode, and a baseline HAM-D score of 17. Error bars represent 95% confidence limits. Planned contrasts using intention-to-treat yielded the following test results: all active treatment versus placebo, $p = .057$; all exercise versus medication, $p = .636$; supervised exercise versus home exercise, $p = .666$. After removing early responders, the contrast results were: all active treatment versus placebo, $p = .022$; all exercise versus medication, $p = .879$; supervised exercise versus home exercise, $p = .519$. Sup = supervised exercise; Med = medication; Plac = placebo.

number of prior MDD episodes, and pretreatment HAM-D scores. Planned contrasts demonstrated that home-based exercise, supervised exercise, and medication tended to achieve higher remission rates compared with placebo ($p = .057$); there were no statistically significant differences between the exercise groups and antidepressant medication or between home-based and supervised exercise. The unadjusted remission rates were: supervised exercise = 45%; home-based exercise = 40%; medication = 47%; and placebo = 31%. The adjusted odds ratio for remission comparing active treatment with placebo was 2.0 (95% CI = 0.97, 4.2).

Previous trials have documented a high placebo response rate in which participants exhibit significant and rapid (<1 week) symptomatic improvement to placebo treatment (39). Rather than using a placebo run-in, which we considered to be too costly and burdensome to patients, we performed an exploratory examination of our data and observed that 14 patients (7%) exhibited a >50% reduction in BDI scores after the first week of treatment: five (9%) patients in home exercise; one (2%) patient in supervised exercise; four (8%) patients received medication; and four (8%) patients received placebo. Five patients failed to complete the interim BDI assessments at week 1 and data from week 2 were used; five patients failed to complete the BDI at weeks 1 and 2 and could therefore not be defined with respect to early response and therefore were excluded from this analysis. When we limited our analysis to the 183 patients who did not show an early response, contrasts from the general linear model demonstrated that all active treatment groups had higher remission rates compared with placebo ($p = .022$); the differences between the exercise groups and medication ($p = .879$) and the differences between the two exercise groups from each other ($p = .519$) were not statistically significant. The adjusted odds ratio for remission comparing active treatment with placebo was 2.6 (95% confidence interval (CI) = 1.1, 5.8). The unadjusted rates of remission were: supervised exercise (46%); home-based exercise (38%); medication (44%); and placebo controls (26%). There was no difference among the remission rates of the active treatments (Figure 3, right panel).

Continuous HAM-D depression scores served as a second primary end point. All groups showed a clinically and statistically significant decline ($p < .0001$) in HAM-D scores from baseline to 16 weeks: supervised exercise: -7.2 (SD = 6.9); home-based exercise: -7.1 (SD = 6.9); medication: -6.1 (SD = 6.7); placebo: -6.1 (SD = 7.3). Although the observed posttreatment HAM-D scores in the active treatments were lower than those in placebo, the difference did not reach statistical significance ($p = .231$) (Figure 4, left panel). After limiting the sample to those who did not show an early response and adjusting for age, gender, race, number of prior MDD episodes, and pretreatment HAM-D scores, the HAM-D scores for exercise and medication treatments tended to be lower than the placebo ($p = .123$). There were no differences between the exercise groups and medication ($p = .514$) or between the two exercise groups (Figure 4, right panel) ($p = .510$).

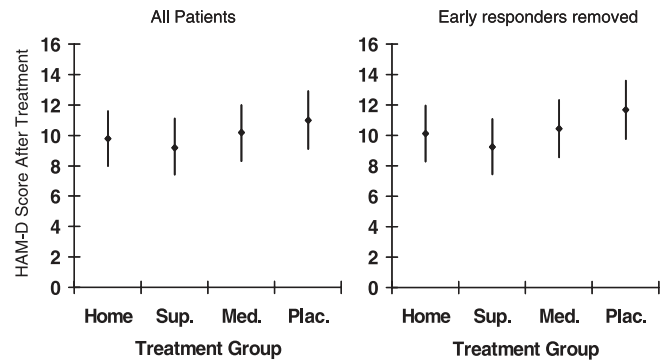


Figure 4. Hamilton Depression Rating Scale (HAM-D) scores after 16 weeks of treatment using intention-to-treat analysis (left panel) and limited to patients who did not exhibit an early response ($n = 183$) (right panel). Probability estimates are for a patient with the most typical profile in the study: age 52 years, female, Caucasian, one prior major depressive episode, and a baseline HAM-D score of 17. Error bars represent 95% confidence limits. Planned contrasts for the HAM-D using intention-to-treat analysis yielded the following test results: all active treatment versus placebo, $p = .231$; all exercise versus medication, $p = .574$; supervised exercise versus home exercise, $p = .624$. After removing early responders, the contrast results were: all active treatment versus placebo, $p = .123$; all exercise versus medication, $p = .514$; supervised exercise versus home exercise, $p = .510$. Sup = supervised exercise; Med = medication; Plac = placebo.

The treatment by depression severity interaction was not significant, suggesting that the treatments affected mildly and more severely depressed patients in a similar fashion. Examination of the 78 patients who obtained baseline HAM-D scores of ≥ 18 demonstrated that the remission rates showed a similar pattern as observed in the full sample: home-based exercise = 30%, $n = 6/20$; supervised exercise = 44%, $n = 8/18$; medication = 39%, $n = 7/18$; and placebo = 27%, $n = 6/22$ ($p = .51$). A similar pattern was observed for the HAM-D scores at posttreatment adjusting for pretreatment scores: home-based exercise ($n = 20$) = 12.3; supervised exercise ($n = 18$) = 9.8; medication ($n = 18$) = 11.8; and placebo ($n = 22$) = 12.9 ($p = .45$).

Side Effects

Untoward effects of each treatment were examined by obtaining patient ratings on a 36-item somatic symptom checklist (e.g., headaches, dizziness, gas, constipation, thirst, muscle pain, and soreness), on which symptoms were rated on a 5-point Likert scale ranging from 0 (never) to 4 (almost always). Calculations were obtained from the number of participants who reported that a symptom had worsened after treatment. Few patients reported a worsening of symptoms. Among the 36 side effects assessed, only one showed a statistically significant group difference ($p = .03$): 31% patients receiving sertraline reported worse posttreatment diarrhea and loose stools compared with 21% in home-based exercise, 10% in supervised exercise, and 12% in the placebo group.

DISCUSSION

These results confirm and extend previous findings that exercise is comparable to antidepressant medication in the

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treatment of patients with MDD. In our previous study (13), 56% of patients receiving sertraline and 47% assigned to supervised exercise were in remission after 4 months of treatment and all patients achieved significant and comparable reductions in depressive symptoms. That study, however, did not include a placebo control group, in the absence of which it could not be affirmed that the observed improvement was due to exercise or medication and not to nonspecific factors such as time, staff attention, or positive expectations. Klein (40) argued cogently that when comparing nonpharmacologic interventions to antidepressant medications, investigators must include a pill-placebo to assure that the patient sample studied is one that is responsive to medication beyond the effects of a placebo. This perspective maintains that it is not adequate merely to compare a new intervention to a Food and Drug Administration-approved and widely utilized antidepressant (e.g., sertraline), but that all such trials must include a pill-placebo condition. Walsh and Sysko (41) made similar arguments and concluded that studies evaluating new treatments lack scientific credibility if there is no placebo and the only evidence for treatment efficacy is a response that is statistically indistinguishable from the response to an established medication. Therefore, we considered it essential to include a placebo condition in our study design.

In the current study, both exercise and medication achieved higher remission rates compared with placebo; 45% of MDD patients undergoing supervised exercise, 40% undergoing home-based exercise, and 47% receiving medication were in remission after 16 weeks of treatment, compared with only 31% receiving placebo. These remission rates are considered to be clinically meaningful, especially because HAM-D scores of <8 are associated with low relapse rates (42). The odds ratio for patients receiving either medication or exercise compared with placebo was 0.50, which represents a 50% reduction in the odds of remaining depressed after 16 weeks. The remission rates that were observed in the present study compare favorably with other randomized placebo controlled psychopharmacology trials in patients with MDD, which are typically 35% to 40% (43–45). Fourteen (7%) patients exhibited an “early response” defined as a $\geq 50\%$ reduction in self-reported (BDI) depressive symptoms after only the first week of treatment. When these early responders were removed from the analysis, the differences between active treatments and placebo became more pronounced: 46% of patients in supervised exercise, 38% in home-based exercise, and 44% receiving sertraline were in remission after 4 months, compared with only 26% of the placebo controls.

Although placebo response rates in treatment studies of MDD are highly variable, the 31% placebo response rate observed in the present study is consistent with previous studies that have reported placebo response rates ranging from 30% to 50% (46–48). Our finding of no difference in HAM-D scores in patients receiving sertraline and placebo also is consistent with results of other randomized control trials such as the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) (49) and the St. John’s Wort trial (50),

which found that reductions in depressive symptoms were comparable when analyzing data from all patients randomized to placebo and sertraline conditions.

Our overall findings are generally consistent with several meta-analytic reviews that suggested that exercise may be an effective treatment for depression (22–24). However, as noted by Lawlor and Hopker (21), the methodological limitations of prior studies have made it impossible to definitively conclude that exercise is efficacious for treating MDD. Our findings also do not provide conclusive evidence for the value of exercise. To our knowledge, the present study is the first to compare the independent effects of exercise and medication to a placebo control group. However, the effect size (defined as the mean group difference divided by the pooled sample SD before treatment) for the HAM-D outcome was rather modest—comparing all active treatment versus placebo, the treatment effect was about 0.20 using ITT and 0.30 after eliminating early responders. One reason for the low effect size relative to other studies may be due to the fact that we used a placebo group rather than a wait list control group. Because expectations for improvement are greater among patients receiving placebo compared with wait list controls, the difference between active treatments and control conditions is likely to be smaller in studies in which there are credible no-treatment control conditions. In addition, the close surveillance and support of placebo participants may have provided additional therapeutic benefit, further reducing differences between the active treatments and placebo controls.

Another factor contributing to the modest effect size in the present study was our use of ITT as our primary analytic approach. We used the last observation carried forward method to derive outcome effects from patients who drop out prematurely and do not undergo follow-up assessments. Although this approach is a widely used method of analysis, differential dropout rates can affect the results. Assuming that there is a general tendency for depressed patients to feel progressively better over the course of treatment, this improvement would be minimized when posttreatment levels of depressive symptoms are represented by observations taken at earlier points (51). The fact that the dropout rate for supervised exercise (20%) was greater than that for home-based exercise (6%) or sertraline (7%) makes it more difficult to compare the relative effectiveness of the treatment groups in this study.

Another question we addressed in the present study was whether the beneficial effects of exercise observed in our previous study could have been attributable to the social stimulation and support provided by the group setting of the exercise intervention. Would the same benefit be observed if patients engaged in the exercise regimen individually at home? A small, randomized, controlled trial (14) recently demonstrated that exercise was associated with reduced depressive symptoms independent of group support. However, this conclusion is weakened by the fact that only 53 of 80 patients actually completed the 12-week trial, including 5 of 13 no-treatment controls. The present sample included 202

patients with MDD, and all randomized patients were included in the primary ITT analyses. Our findings showed that there was no difference in remission rates between patients who exercised in a supervised group setting and those who exercised on their own. Although the two groups showed similar rates of compliance with the exercise prescription, the supervised exercisers tended to push themselves more consistently into the target heart rate range, which probably accounts for why this group performed better than the home exercisers on end-of-study assessments of aerobic fitness. The present findings suggest that, for this patient population, supervised exercise yields better outcomes than home exercise with respect to physical conditioning, but that both seem equally effective in achieving remission of clinical depression. Some studies (52,53), but not all (54), have reported that supervised exercise training results in larger improvements in functional capacity compared with home-based exercise, and that greater energy expenditure is associated with larger reductions in depressive symptoms (14). It should be noted, however, that our study was not powered to detect the relatively small differences in depressive symptoms that we observed between the two exercise conditions; it is therefore not possible to be certain that home-based exercise is comparable with supervised exercise in reducing depressive symptoms. Even with greater power, however, it is not clear that such differences would be clinically meaningful.

The mechanisms responsible for exercise-related improvements in depression are not known. Although our data suggest that social support was not necessarily critical to the therapeutic benefit of exercise, a number of psychological factors have been proposed to explain the effect that exercise has on depressed mood including increased self-efficacy, a sense of mastery, positive thoughts, distraction from negative thoughts, and enhanced self-concept. A number of biologic pathways also have been suggested including increased central norepinephrine neurotransmission (55–57), alterations in the hypothalamo-pituitary-adrenocortical axis (58), and increased secretion of amine metabolites as well as serotonin synthesis and metabolism (59–62).

It also should be emphasized that the intent of our study was not to determine if exercise is superior to sertraline. It is more difficult to distinguish between active therapies than it is to find a difference between active therapies and placebo. To reliably detect the small differences in depression as measured by the HAM-D or BDI scores, it is estimated that at a minimum of 300 patients per arm is required (63). Although our sample of 202 patients with MDD is, to our knowledge, the largest single site exercise study of MDD yet conducted, it also is important to recognize that our study was underpowered to detect small differences between the active treatment groups. Our initial power analysis determined that we had enough power to detect just over a half SD ($d = 0.55$) difference with 50 patients per cell, which translates into about a 4-point difference on the HAM-D (depending on the estimate of the variance of the scores). However, we observed only a little over a 1-point difference between active treatment

and placebo on the HAM-D. If we assume that this is a reasonable estimate of the population treatment effect, we would have required 950 patients to detect a statistically significant difference, and a 1-point difference is not clinically meaningful.

Because participants in this study represent patient volunteers, it is difficult to determine the extent to which these findings may generalize to typical outpatients seeking treatment for MDD. Zimmerman et al. (64) estimated that only one in seven patients seen in an outpatient clinical setting would be eligible to participate in pharmacological clinical trials, suggesting that the response rate could be lower for patients seeking treatment in outpatient psychiatric settings than those observed in clinical trials. Also, patients who are actively suicidal or who have severe MDD are ineligible for most placebo-controlled trials in which a subgroup of individuals essentially receive “no treatment” for several months. Our sample consisted primarily of patients with mild depression; only 39% of our sample had moderate-severe depression (HAM-D scores of ≥ 18), which may limit the generalizability of our findings. However, the more severely depressed patients in our study showed the same pattern of results as their less depressed counterparts, suggesting that exercise may be beneficial to patients with moderately severe depression as well as mild depression. Finally, we note that most of the participants in the present study enrolled with the hope that they would receive exercise treatment for their depression. It is unknown to what extent this willingness to engage in exercise therapy is shared by the general population of outpatients with MDD. Thus, although these results are promising and suggest that patients receptive to exercise therapy can achieve significant symptomatic relief comparable to established medical therapies, the clinical application of exercise therapy and the long-term benefits of exercise need to be studied further.

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REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* 2005;62:593–602.
2. Agency for Health Care Policy and Research. Depression in primary care. Vol 1. Detection and diagnosis. Rockville, MD: Department of Health and Human Services; 1993. UH CPR publication number 93-0550.
3. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet* 1997;349:1436–42.
4. Insel TR, Charney DS. Research on major depression. *JAMA* 2003;289:3167–8.
5. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020. Global burden of disease study. *Lancet* 1997;349:1498–504.
6. Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, Quitkin FM, Wisniewski S, Lavori PW, Rosenbaum JF, Kupfer DJ.

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- Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. *Psychiatr Clin North Am* 2003;26:457–94.
- Agency for Health Care Policy and Research. Depression in primary care. Vol 2. Treatment of major depression. Rockville, MD: Department of Health and Human Services; 1993. UHCPR publication number 93-0551.
 - Brosse AL, Sheets ES, Lett HS, Blumenthal JA. Exercise and the treatment of clinical depression in adults: recent findings and future directions. *Sports Med* 2002;32:741–60.
 - Blumenthal JA, Emery CF, Madden DJ, George LK, Coleman RE, Riddle MW, McKee DC, Reasoner J, Williams RS. Cardiovascular and behavioral effects of aerobic exercise training in healthy older men and women. *J Gerontol* 1989;44:M147–57.
 - DiLorenzo TM, Bargman EP, Stucky-Ropp R, Brassington GS, Frensch PA, LaFontaine T. Long-term effects of aerobic exercise on psychological outcomes. *Prev Med* 1999;28:75–85.
 - Roth DL, Holmes DS. Influence of aerobic exercise training and relaxation training on physical and psychological health following stressful life events. *Psychosom Med* 1987;49:355–65.
 - King AC, Taylor CB, Haskell WL. Effects of differing intensities and formats of 12 months of exercise training on psychological outcomes in older adults. *Health Psych* 1993;12:292–300.
 - Blumenthal JA, Babyak MA, Moore KA, Craighead WE, Herman S, Khatri P, Waugh R, Napolitano MA, Forman LM, Appelbaum M, Doraiswamy PM, Krishnan KR. Effects of exercise training on older patients with major depression. *Arch Intern Med* 1999;159:2349–56.
 - Dunn AL, Trivedi MH, Kempert JB, Clark CG, Chambliss OH. Exercise treatment for depression: efficacy and dose response. *Am J Prev Med* 2005;28:1–8.
 - Singh NA, Stavrinou TM, Scarbek Y, Galambos G, Liber CL, Fiatarone Singh M. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *J Gerontol Med Sci* 2005;60A:768–76.
 - Martinsen EW, Medhus A, Sandvik L. Effects of aerobic exercise on depression: a controlled study. *BMJ* 1985;291:109.
 - Klein MH, Greist JH, Gurman AS, Neiberger DP. A comparative outcome study of group psychotherapy vs. exercise treatments for depression. *Int J Mental Health* 1985;13:148–76.
 - Veale D, Le Fevre K, Pantelis C, de Souza V, Mann A, Sargeant A. Aerobic exercise in the adjunctive treatment of depression: a randomized controlled trial. *J R Soc Med* 1992;85:541–4.
 - McNeil JK, LeBlanc EM, Joyner M. The effect of exercise on depressive symptoms in the moderately depressed elderly. *Psych Aging* 1991;6:487–8.
 - Singh NA, Clements KM, Singh MA. The efficacy of exercise as a long-term antidepressant in elderly subjects: a randomized, controlled trial. *J Gerontol A Bio Sci Med Sci* 2001;56:M497–504.
 - Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomized controlled trials. *BMJ* 2001;322:763–6.
 - North TC, McCullagh P, Tran ZV. Effect of exercise on depression. *Exerc Sport Sci Rev* 1990;18:379–415.
 - Craft LL, Landers DM. The effects of exercise on clinical depression and depression resulting from mental illness: a meta-regression analysis. *J Sport Ex Psych* 1998;20:339–57.
 - Stathopoulou G, Powers MB, Berry AC, Smits JAJ, Otto MW. Exercise interventions for mental health: a quantitative and qualitative review. *Clin Psychol Sci Pract* 2006;13:179–93.
 - Babyak M, Blumenthal JA, Herman S, Khatri P, Doraiswamy M, Moore K, Craighead WE, Baldevicz TT, Krishnan KR. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med* 2000;62:633–8.
 - Alexopoulos GS, Katz IR, Reynolds CF III, Carpenter D, Docherty JP, Ross RW. Pharmacotherapy of depressive disorders in older patients: a summary of the expert consensus guidelines. *J Psychiatr Pract* 2001;7:361–76.
 - Ballinger JC. Clinical guidelines for establishing remission in patients with depression and anxiety. *J Clin Psychiatry* 1999;60(Suppl 22):29–34.
 - American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry* 2000;157(Suppl 14):1–45.
 - Judd LL, Paulus MP, Zeller P. The role of residual subthreshold depressive symptoms in early episode relapse in unipolar major depressive disorder. *Arch Gen Psychiatry* 1999;56:764–5.
 - Miller IW, Keitner GI, Schatzberg AF, Klein DN, Thase ME, Rush AJ, Markowitz JC, Schlager DS, Kornstein SG, Davis SM, Harrison WM, Keller MB. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. *J Clin Psychiatry* 1998;59:608–19.
 - Beck AT, Sheer RA, Brown GK. Beck depression inventory manual. 2nd ed. San Antonio, Texas: Psychological Corporation; 1996.
 - Diagnostic and statistical manual of mental disorders. 4th ed. DSM-IV. Washington, DC: American Psychiatric Association; 2000.
 - First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV Axis I Disorders (SCID-I), clinician version. Washington, DC: American Psychiatric Press; 1995.
 - Williams JB. A structured interview guide for the Hamilton depression rating scale. *Arch Gen Psychiatry* 1988;45:742–7.
 - Blumenthal JA, Rejeski WJ, Walsh-Riddle M, Emery CF, Miller H, Roark S, Ribisl PM, Morris PB, Brubaker P, Williams RS. Comparison of high- and low-intensity exercise training early after acute myocardial infarction. *Am J Cardiol* 1988;61:26–30.
 - Khan A, Khan S, Brown WA. Are placebo controls necessary to test new antidepressants and anxiolytics? *Int J Neuropsychopharmacology* 2002;5:193–7.
 - Taylor WD, Doraiswamy PM. A systematic review of the antidepressant placebo-controlled trials for geriatric depression: limitations of current data and directions for the future. *Neuropsychopharmacology* 2004;29:2285–99.
 - Fisher LD, Dixon DO, Herson J, Frankowski RK, Hearon MS, Pearce KE. Intention to treat in clinical trials. In: Pearce KE, editor. Statistical issues in drug research and development. New York: Marcel Dekker; 1990.
 - Khan A, Cohen S, Dager S, Avery DH, Dunner DL. Onset of response in relation to outcome in depressed outpatients with placebo and imipramine. *J Affect Disord* 1989;17:33–8.
 - Klein DF. Preventing hung juries about therapy studies. *J Consult Clin Psych* 1996;4:81–7.
 - Walsh BT, Sysko R. Placebo control groups in trials of major depressive disorder among older patients. *J Clin Psychopharm* 2005;25(Suppl 1):S29–33.
 - Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med* 1995;25:1171–80.
 - Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M, STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006;163:28–40.
 - Arroll B, Macgillivray S, Ogston S, Reid I, Sullivan F, Williams B, Crombie I. Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *Ann Fam Med* 2005;3:449–56.
 - Roose SP, Sackeim HA, Krishnan KR, Pollock BG, Alexopoulos G, Lavretsky H, Katz IR, Hakkaraian H, Old-Old Depression Study Group. Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo controlled trial. *Am J Psychiatry* 2004;161:2050–9.
 - Trivedi MH, Rush H. Does a placebo run-in or a placebo treatment cell affect the efficacy of antidepressant medications? *Neuropsychopharmacology* 1994;11:33–43.
 - Brown WA. Placebo as a treatment for depression. *Neuropsychopharmacology* 1994;10:265–69.
 - Kahn A, Kolts RL, Rapaport MH, Krishnan KRR, Brodhead AE, Brown WA. Magnitude of placebo response and drug-placebo differences across psychiatric disorders. *Psychol Med* 2005;35:743–9.
 - Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT, Krishnan KR, van Zyl LT, Swenson JR, Finkel MS, Landau C, Shapiro PA, Pepine CJ, Mardekian J, Harrison WM, Barton D, McIvor M, Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002;288:701–9.
 - Hypericum Depression Trial Study Group. Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA* 2002;287:1807–14.

51. Thase ME. Studying new antidepressants: if there were a light at the end of the tunnel, could we see it? *J Clin Psychiatry* 2002;63(Suppl 2):24–8.
52. Dunn AL, Garcia ME, Marcus BH, Kampert JB, Kohl, HW, Blair SN. Six month physical activity and fitness changes in project active, a randomized trial. *Med Sci Sports Exer* 1998;30:1076–83.
53. Kodis J, Smith KM, Arthur HM, Daniels C, Suskin N, McKelvie RS. Changes in exercise capacity and lipids after clinic versus home-based aerobic training in coronary artery bypass graft surgery patients. *J Cardiopul Rehab* 2001;21:31–6.
54. King AC, Haskell WL, Taylor CB, Kraemer HC, DeBusk RF. Group- vs. home-based exercise training in healthy older men and women: a community-based trial. *JAMA* 1991;266:1535–42.
55. Rubin RT. Pharmacoenocrinology of major depression. *Eur Arch Psychiatry Neurol Sci* 1989;238:259–67.
56. Sothman MS, Ismail AH. Relationships between urinary catecholamine metabolites, particularly MHPG, and selected personality and physical fitness characteristics in normal subjects. *Psychosom Med* 1984;46:523.
57. Sothmann MS, Ismail AH. Factor analytic derivation of the MHPG/NM ratio: implications for studying the link between physical fitness and depression. *Biol Psychiatry* 1985;20:570–83.
58. Droste SK, Gesing A, Ulbricht S, Muller MB, Linthorst AC, Reul JM. Effects of long-term voluntary exercise on the mouse hypothalamic-pituitary-adrenocortical axis. *Endocrinology* 2003;114(7):3012–23.
59. Dishman RK, Renner KJ, Youngstedt SD, Reigle TG, Bunnell BN, Burke KA, Yoo HS, Mougey EH, Meyerhoff JL. Activity wheel running reduces escape latency and alters brain monoamine levels after footshock. *Brain Res Bull* 1997;42:399–406.
60. Dunn AL, Dishman RK. Exercise and the neurobiology of depression. *Exerc Sport Sci Rev* 1991;19:41–98.
61. Esler M, Jennings G, Lambert G, Meredith I, Home M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. *Physiol Rev* 1990;70:963–85.
62. Ransford CP. A role for amines in the antidepressant effect of exercise: a review. *Med Sci Sports Exerc* 1982;14:1–10.
63. Thase ME. Comparing the methods used to compare antidepressants. *Psychopharmacol Bull* 2002;36(Suppl 1), Suppl 1–17, quiz Suppl 18–9.
64. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry* 2002;159:469–73.