Published in final edited form as:
Psychosom Med. 2011 ; 73(2): 127–133. doi:10.1097/PSY.0b013e31820433a5.

Exercise and Pharmacotherapy in Patients With Major Depression: One-Year Follow-Up of the SMILE Study

Benson M. Hoffman, PhD, **Michael A. Babyak, PhD**, **W. Edward Craighead, PhD**, **Andrew Sherwood, PhD**, **P. Murali Doraiswamy, MD**, **Michael J. Coons, MA**, and **James A. Blumenthal, PhD**
Department of Psychiatry and Behavioral Sciences (B.M.H., M.A.B., A.S., M.D., M.J.C., J.A.B.), Duke University Medical Center, Durham, North Carolina; and the Department of Psychology (W.E.C.), Emory University, Atlanta, Georgia

Abstract

Objective—To examine a 1-year follow-up of a 4-month, controlled clinical trial of exercise and antidepressant medication in patients with major depressive disorder (MDD).

Methods—In the original study, 202 sedentary adults with MDD were randomized to: a) supervised exercise; b) home-based exercise; c) sertraline; or d) placebo pill. We examined two outcomes measured at 1-year follow-up (i.e., 16 months post randomization): 1) continuous Hamilton Depression Rating Scale score; and 2) MDD status (depressed; partial remission; full remission) in 172 available participants (85% of the original cohort). Regression analyses were performed to examine the effects of treatment group assignment, as well as follow-up antidepressant medication use and self-reported exercise (Godin Leisure-Time Exercise Questionnaire), on the two outcomes.

Results—In the original study, patients receiving exercise achieved similar benefits compared with those receiving sertraline. At the time of the 1-year follow-up, rates of MDD remission increased from 46% at post treatment to 66% for participants available for follow-up. Neither initial treatment group assignment nor antidepressant medication use during the follow-up period were significant predictors of MDD remission at 1 year. However, regular exercise during the follow-up period predicted both Hamilton Depression Rating Scale scores and MDD diagnosis at 1 year. This relationship was curvilinear, with the association concentrated between 0 minute and 180 minutes of weekly exercise.

Conclusion—The effects of aerobic exercise on MDD remission seem to be similar to sertraline after 4 months of treatment; exercise during the follow-up period seems to extend the short-term benefits of exercise and may augment the benefits of antidepressant use.

Keywords

exercise; depression; remission; selective serotonin reuptake inhibitor; follow-up study

Address correspondence and reprint requests to: Benson M. Hoffman, PhD, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 3119, Durham, NC 27710. Benson.Hoffman@duke.edu.

Trial Registration: clinicaltrials.gov Identifier: NCT00331305.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site www.psychosomaticmedicine.org.

The remaining authors did not disclose any potential conflicts of interest.

INTRODUCTION

Major depressive disorder (MDD) has a lifetime prevalence of 15% to 20% (1) and is associated with significant disability, morbidity, and mortality (2). Antidepressant medication is currently the accepted treatment of choice for MDD (3). Randomized clinical trials have generally reported response rates of 30% to 45% with single-action or dual-action antidepressant monotherapy (4), and up to 67% for patients receiving augmentation with additional medications (5,6). Although MDD is likely to recur in 50% to 85% of patients initially treated with antidepressants, continued regular use of the medication during follow-up periods reduces the risk of relapse (7).

Aerobic exercise also has demonstrated antidepressant effects (8) and has been associated with rates of MDD remission that are comparable to pharmacotherapy (9,10). Although several small studies have reported significant benefits of exercise relative to placebo or no-exercise controls, most studies have significant methodological limitations, and the longer-term benefits of aerobic exercise compared with medication and pill placebo on MDD remission have not been examined. The present study reports 1-year follow-up data from the SMILE-II study (10), in which 202 participants with MDD were randomized to aerobic exercise (home-based or supervised), antidepressant medication (sertraline), or placebo pill. After 4 months of treatment, patients undergoing aerobic exercise achieved comparable benefits to those patients receiving sertraline, and both active treatments tended to show greater improvement relative to placebo controls, especially when immediate responders (n = 14) were removed from the analysis. The present report is a naturalistic study that evaluates the extent to which benefits of initial treatment assignment (exercise or sertraline) were maintained over the 1-year follow-up period and examines the relationship of subsequent exercise and the presence of depressive symptoms 1 year after the completion of treatment.

METHODS

This study was approved by the Duke University Medical Center Institutional Review Board, and all patients provided their informed consent. Participants in the original study were enrolled between October 2000 and November 2005, and 1-year follow-up data were collected between February 2002 and May 2007. All participants met the criteria for MDD (11), were 51 years old on average, scored ≥12 on the Beck Depression Inventory-II (12), were not receiving antidepressant medication or psychotherapy, and were physically inactive at the time of study enrollment.

Treatment

Participants were assigned randomly in the original study to one of four 16-week study conditions:

1. Supervised Aerobic Exercise. Participants attended three 45-minute exercise groups each week. Groups were supervised by study exercise physiologists. Participants were assigned individualized target heart rate ranges of between 70% and 85% of their heart rate reserve.
2. Home-Based Aerobic Exercise. Participants completed an initial training session with a study exercise physiologist, during which they received similar exercise prescriptions as described above, as well as two follow-up sessions after the initial month and after 2 months, to assess and encourage adherence to the exercise prescription and to problem-solve any barriers to adherence.

3. Sertraline. Participants received sertraline (Zoloft), a selective serotonin reuptake inhibitor. Participants met with a staff psychiatrist at the time of randomization and at weeks 2, 4, 8, 12, and 16. Treatment was initiated at 50 mg and titrated until a well-tolerated therapeutic dosage was achieved, up to 200 mg.

4. Placebo Pill. As with the sertraline condition, participants met with a staff psychiatrist for six visits, and treatment was titrated up to 200 mg. Both participants and study staff were blinded to the pill condition.

At the conclusion of treatment, pill participants were unblinded, and participants received feedback about their changes in depressive symptoms post treatment. All participants were presented options to receive an exercise prescription, a consultation with the study psychiatrist for medication, or both. Participants could also elect to discontinue treatment or to seek treatment elsewhere. During the 1-year naturalistic follow-up period, participants were free to choose their own treatment(s), or they could elect to discontinue all therapy. Follow-up assessments occurred at 1 year post treatment (i.e., 16 months post randomization).

Measures

Depression Assessment—To assess depression, we used the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Axis I Disorders, Depression Module (SCID) (13) to diagnose depression and the Hamilton Depression Rating Scale (HAM-D) (14,15) to quantify the severity of depressive symptoms. The SCID (13) is a commonly used semistructured interview, which assesses current and lifetime diagnoses of Axis I disorders. First et al. (13) reported that typical interrater κ scores range from 0.70 to 1.00. The17-item structured HAM-D (14,15) quantifies the severity of depressive symptoms and also permits classification (i.e., depressed versus nondepressed). The interrater reliability coefficient for the HAM-D was 0.98 (16).

At baseline, the SCID was used to diagnose MDD and to differentiate between single-episode MDD and recurrent MDD, and the HAM-D was used to determine MDD severity. The SCID and HAM-D were also administered at post treatment and 1 year after treatment completion. The baseline SCID covered lifetime depressive episodes, whereas the 1-year follow-up covered the interval from the time of treatment completion (i.e., 4 months) to 1 year. The SCID and HAM-D were used to classify participants as being in full remission (i.e., symptoms no longer satisfied MDD criteria and HAM-D score of ≤8), partial remission (i.e., no longer satisfied MDD criteria and HAM-D between 8 and 15), or depressed (i.e., satisfied MDD criteria or HAM-D score of ≥15). These criteria have been established (17), and we modeled this categorization after that used in other studies (18).

Exercise Behavior—Participants completed the Godin Leisure-Time Exercise Questionnaire (Godin) (19). Respondents indicated the number of occasions per week, and the number of minutes per occasion, that they engaged in mild, moderate, and strenuous exercise. This measure was scored by summing the number of minutes of moderate and strenuous exercise, consistent with the intensity of the exercise prescription provided to study participants. The authors (20) reported that typical 2-week interrater reliability coefficients (r) range from .62 to .81. Godin scores have been validated against objective measures of exercise participation (e.g., activity monitors; $r = .45$) (21) as well as various measures of physical fitness (20). In the original validation study (19), discriminant function analysis by maximal oxygen consumption (VO_2 max) yielded a correct two-way classification of 69%.

Posttreatment Antidepressant Treatment—Participants were interviewed about their current use of antidepressant medications or herbal remedies (e.g., name of medication, length of use), as well as their participation in psychotherapy, for the purposes of treating depression.

Perceived Social Support Scale (PSSS)—The PSSS (22) is a 12-item self-report questionnaire that assesses perceptions of social support. Participants are asked to respond to each question, using a 5-point Likert scale that ranges from 1 ("Very strongly disagree") to 7 ("Very strongly agree"). The PSSS has been observed to be internally consistent ($\alpha = 0.88$) and reliable (2–3 month test-retest reliability coefficient = .85).

Statistical Analyses

We examined two outcomes measured 1 year after treatment: 1) the continuous HAM-D score; and 2) the ordinal, three-level (depressed; partial remission; full remission) outcome of MDD classification. We used the general linear model for the HAM-D score outcome and ordinal logistic regression for the ordinal diagnostic outcome. In a first set of models, we estimated the unadjusted association between the original trial treatment assignment and each of the two outcomes. In a second set of analyses, we examined the association between the continuous Godin score and the two outcomes, adjusted for age, gender, ethnicity, HAM-D score at 16 weeks, number of prior MDD episodes, antidepressant medication use, and perceived social support (PSSS score). We allowed the association between the Godin score and the depression outcomes to be nonlinear, using a flexible curve-fitting algorithm (23). Because using complete cases only may bias regression estimates, we also performed a parallel set of the above analyses on the entire 202 cases, using multiple imputation employing the aregImpute function in Harrell's rms package in R (available at http://cran.r-project.org).

RESULTS

Of 202 randomized participants, 172 (85%) provided 1-year follow-up data, including 48 (91%) of home-based exercise, 43 (84%) of supervised exercise, 41 (84%) of sertraline, and 40 (82%) of placebo pill. Figure 1 shows the flow of participants from recruitment through the 1-year follow-up assessment.

Participants who were available for 1-year follow-up assessment were more likely to have completed the original 4-month intervention, compared with participants who were not (87% versus 60%; $p = .0002$). Otherwise, available participants were comparable to unavailable participants in age, gender, ethnicity, baseline depression severity, MDD diagnosis, and perceived social support (Table 1).

Treatment Group and Depression Outcomes 1 Year After Treatment

Of the participants who were available at the 1-year follow-up assessment, 76 (46%) had been classified as "treatment remitters" (i.e., fully remitted) at the conclusion of the original 4-month study treatment, including 19 (41%) in home-based exercise, 22 (54%) in supervised exercise, 21 (51%) in the sertraline condition, and 14 (38%) in the placebo pill condition. One year later, 113 (66%) were fully remitted, including 32 (67%) of the home-based exercise group, 29 (67%) of the supervised exercise group, 26 (63%) of the sertraline group, and 26 (65%) of the placebo group (Table 2). The unadjusted regression models revealed no effect of treatment on either HAM-D continuous scores ($p = .73$) or MDD remission status ($p = .96$) at 1- year follow-up.

Exercise, Antidepressants, and Depressive Symptoms 1 Year After Treatment

Almost half of the sample reported scores of 0 (i.e., no exercise) on the Godin at the 1-year follow-up. Among those who reported either moderate or vigorous exercise, the median time of exercise per week was 103 minutes (interquartile range, 60–178). In addition, 36% of participants reported using antidepressant medications, including 49% of those initially randomized to sertraline, 32% of those assigned to exercise, and 33% of the placebo pill group ($p = .27$). The most commonly used antidepressants included sertraline ($n = 21$), bupropion ($n = 13$), escitalopram ($n = 9$), and venlafaxine ($n = 8$); 21 participants reported that they were both taking an antidepressant and exercising at the time of follow-up.

Results of the general linear model revealed that the associations of age, ethnicity, and antidepressant medication with HAM-D at 1-year follow-up were not significant (Supplemental Digital Content 1, available at http://links.lww.com/PSYMED/A19). The results further demonstrated that the Godin score was related to the continuous HAM-D score 1-year after treatment in a curvilinear fashion ($p = .01$), with a negative slope from 0 minute to about 180 minutes per week of exercise, flattening after about 180 minutes (Fig. 2*a*). The expected difference in HAM-D score between a person who reported 180 minutes of exercise and a person who reported 0 minute of exercise was a decrement of 3.1 points (95% confidence interval [CI] = −5.1, −1.2). In addition to Godin scores, social support also was associated with lower HAM-D scores at 1-year follow-up, with every 2-point increase in social support associated with a 1.4 decrease in HAM-D scores (95% CI = −2.5, −0.2, $p = .01$). The number of previous depressive episodes also was related to HAM-D such that every additional MDD episode was associated with a 0.8 increase in HAM-D score at the time of follow-up (95% CI = 0.2, 1.4, $p = .01$). Similarly, HAM-D scores immediately after treatment were associated with higher HAM-D scores at 1 year, with each 5-point increase associated with a 1.2-point increase at the time of follow-up (95% CI = 0.5, 1.8, $p < .001$). Being male was associated with 1.1 decrease in HAM-D scores at follow-up, but this estimate did not reach conventional significance levels (95% CI = −2.8, 0.06, $p = .20$). Results of the same model using multiple imputation differed very little from those above, with age, ethnicity, and antidepressant medication being only trivially related to the HAM-D at time of follow-up. The estimate for the Godin also was similar, with only slightly wider CIs: the expected difference in HAM-D score between a person who reported 180 minutes of exercise and a person who reported 0 minute of exercise being a reduction of 3.1 points (95% CI = −5.3, −0.95, $p = .02$). The estimates also were similar for social support (b = −1.4, 95% CI = −2.9, 0.1, $p = .07$); the number of prior MDD episodes (b = 0.9, 95% CI = 0.2, 1.6, $p = .01$); and the HAM-D score at 16 weeks (b= 1.1, 95% CI = 0.4, 1.7, $p < .001$).

The results of the ordinal logistic regression revealed that age, ethnicity, and antidepressant medication were not related to improved diagnosis (Supplemental Digital Content 2, available at http://links.lww.com/PSYMED/A20). Furthermore, the Godin score was related to diagnostic outcome (full remission; partial remission or MDD) 1 year after treatment in a curvilinear fashion. Comparing a person who reported 180 minutes per week of exercise with a person who reported 0 minute of exercise revealed that the odds ratio (OR) for being improved by one diagnostic category was 2.9 (95% CI = 1.1, 7.3), although the test of the association across the entire range of the Godin scores was marginally nonsignificant ($p = .06$) (Fig. 2*b*). In addition to the Godin scores, male gender was associated with higher likelihood of improvement (OR = 2.7, 95% CI = 1.1, 6.8, $p = .03$), as was the PSSS (OR for a 2-point increase = 1.8, 95% CI = 1.0, 3.0, $p = .050$), whereas a higher number of prior MDD episodes (OR for each additional episode = 0.7, 95% CI = 0.55, 0.96), and higher HAM-D scores immediately after treatment (OR for a 5-point increase = 0.7, 95% CI = 0.55, 0.96, $p = .02$) were associated with lower likelihood of improvement. Again, the results of the model using multiple imputation to manage missing cases were very similar to the above, with the effect sizes for age, ethnicity, and antidepressant use negligible, and the

effects of the remaining variables (using the same scaling as above) as follows: minutes of exercise, OR = 2.8 (95% CI = 1.2, 6.9, $p = .06$); social support, OR = 1.6 (95% CI = 0.9, 2.8, $p = .11$); the number of prior MDD episodes, OR = 0.7 (95% CI = 0.65, 0.9, $p = .02$); the HAM-D score at 16 weeks, OR = 0.7 (95% CI = 0.6, 1.0, $p = .02$); male gender, OR = 2.4 (95% CI = 1.0, 5.5, $p = .046$).

Exploratory Analyses

In response to a request from an anonymous reviewer, we examined the differential effects of posttreatment exercise and sertraline use on "subtypes" of depression through a series of post hoc analyses. We first considered the effects of posttreatment exercise and sertraline on the score for the six-item Maier-Philipp HAM-D subscale of "core" depressive symptoms (24) and also a seven-item somatization and somatic anxiety HAM-D subscale (25). These analyses demonstrated a slightly weaker association between exercise and core depressive symptoms compared with exercise and the full HAM-D, with an expected difference between 0 minute and 180 minutes of exercise of about 1.4 points on the core subscale (unstandardized coefficient = −1.4, 95% CI = −2.5, −0.2). The standard deviation (SD) of the core subscale at 1-year follow-up was 3.1; therefore, this effect represents about a 0.45-SD difference, compared with about a 0.5 SD for the full HAM-D. For the somatization and somatic anxiety subscales, the effect of exercise was more similar to the full HAM-D, with an expected difference between 0 minute and 180 minutes of exercise of about 2 points on the somatic scale (unstandardized coefficient = −1.2, 95% CI = −2.0, −0.0.2); the SD for the somatization subscale at 1-year follow-up was 2.4; therefore, the standardized effect was almost exactly 0.5 SD, or about the same size as that of the HAM-D. We also found an exercise by baseline anxiety interaction such that the magnitude of the association between exercise and full HAMD score depended on the level of anxiety the participants reported at the time of study entry (Supplemental Digital Content 3, available at http://links.lww.com/PSYMED/A21). Specifically, the effects of exercise during the 1-year naturalistic follow-up period were most pronounced for those participants who were most anxious at baseline. This finding held for both depression outcomes, the full HAM-D score ($p = .03$), and for the depression diagnostic categories ($p = 04$). For example, for a participant with a State-Trait Anxiety Inventory score of 45 at the time of study entry, the expected difference between 0 minute and 180 minutes of exercise was about −2 points on the full HAM-D, compared with an expected difference of −4.6 points for a participant with an anxiety score of 55.

Finally, we also conducted a series of post hoc analyses in which we examined baseline predictors of exercise during the naturalistic follow-up period. For these analyses, we compared exercisers (i.e., Godin score at 1 year >0; 51% of the follow-up sample) to nonexercisers (i.e., Godin score at 1 year = 0; 49% of the follow-up sample). Exercisers were slightly younger (50 years versus 53 years, $t = 2.75$, $p = .007$) and had higher levels of perceived social support (4.5 versus 4, $t = −2.56$, $p = .01$), compared with nonexercisers. Similarly, greater self-reported minutes of exercise per week was associated with younger age (Spearman $r = −.20$, $p = .01$) and higher levels of baseline perceived social support (Spearman $r = .19$, $p = .01$). However, exercisers were similar to nonexercisers in education (16 years versus 15 years, $p = .11$), body mass index (30 versus 31, $p = .40$), depression severity (HAM-D 16 versus 17, $p = .24$), anxiety severity (State-Trait Anxiety Inventory 48 versus 49, $p = .74$), marital status (percent married: 45% versus 37%, $p = .09$) and treatment group assignment (percent originally assigned to an exercise condition: 62% versus 44%, $p = .09$).

DISCUSSION

Among this sample of clinically depressed, sedentary, middle-aged, and older adults, 46% were fully remitted at the end of the original 4-month study treatment, and 66% were fully

remitted 1 year after the end of treatment. In the original study, patients receiving exercise or sertraline achieved comparable benefits, which tended to be greater compared with placebo controls (10). When a small subgroup of "early responders" (those 14 individuals who showed a ≥50% reduction in HAM-D score after only 1 week of treatment) were eliminated from the analysis, the contrast between active treatments and placebo controls went from 0.06 to 0.02. In contrast, initial treatment group assignment did not predict depressive symptoms at 1- year follow-up. However, self-reported exercise during the follow-up period was associated with lower depression scores and greater likelihood of improved depressive status at the time of follow-up, after adjusting for age, race, gender, prior history of MDD, and use of antidepressant medication at 1 year. We found a linear, inverse association between exercise level and depressive symptom severity between 0 minute and about 180 minutes per week of exercise, with a weaker association after 180 minutes, suggesting that the antidepressive benefit of moderate-to-vigorous exercise may diminish after an average of about 3 hours per week. The expected difference in HAM-D score between a person who reported 180 minutes of exercise and a person who reported 0 minute of exercise was 3.1 points, which is considered to be a clinically meaningful difference (26).

To our knowledge, only four previous studies (27–30) of exercise training reported follow-up data of depressive symptoms, each with important methodological limitation, including small sample sizes (28,29), imprecise diagnosis of depression (29), high drop-out rates (28,30), or brief exercise interventions that failed to produce improvements in aerobic capacity (28). Only one study examined the association between continued exercise participation during the follow-up period and longer-term outcomes (27), and no study included a placebo control in the study design.

The observed association of posttreatment exercise and reduced depressive symptoms at the time of follow-up in the present study confirms the findings from our previous exercise trial in which patients who exercised over a 6-month follow-up period were 50% less likely to relapse (27). Furthermore, the positive effects of posttreatment exercise did not vary by treatment group assignment, suggesting that exercise may be effective in maintaining treatment gains from an aerobic exercise intervention and may be an effective adjunctive treatment for patients who receive pharmacotherapy. However, it should be noted that, because of the naturalistic study design of the follow-up assessments, it cannot be determined if physical activity caused people to be less depressed or whether reduced depression caused people to be less sedentary and more likely to exercise.

Our exploratory analyses suggest that exercise may be particularly beneficial for depressed participants with elevated levels of anxiety. Younger participants and participants with greater perceived social support also may be more likely to sustain an exercise regimen over time.

The absence of an association between antidepressant use at the time of follow-up and MDD remission was unexpected, as other studies (7) have reported that antidepressant use is associated with reduced risk for relapse. It is possible that participants in the present study who were depressed at the time of follow-up were more likely to be treatment resistant but were, nevertheless, motivated to use antidepressant medications in an effort to reduce their depressive symptoms.

Missing data are a study limitation, as 15% of our initial cohort were not available for follow-up, which may have biased these results. However, the statistical models that were estimated using imputed missing follow-up data yielded very similar results to models using completers-only data, mitigating this concern at least to some extent. Nevertheless, as with all nonrandomized studies, the general possibility of unmeasured confounders always exists.

Acknowledgments

This study was supported, in part, by Grant MH 49679 (J.A.B.) from the National Institutes of Health and Grant M01-RR-30 from the General Clinical Research Center Program, National Center for Research Resources, National Institutes of Health (Principal Investigator: James A. Blumenthal). Medication and matched placebo pills were provided by a grant from Pfizer Pharmaceuticals, Inc.

Dr. Craighead receives support from the National Institutes of Health for his research, owns stock in NovaDel Pharma, and receives book royalties from John Wiley & Sons. He is an officer of Hugarheill enf, an Icelandic nonprofit company dedicated to the prevention of depression. Dr. Murali Doraiswamy has received research grants (through Duke) and honoraria from several pharmaceutical companies, and he owns stock in EnergyInside.

We thank Patrick J. Smith and Chavalla Harris for their assistance with data collection, as well as to our SMILE Study participants.

Glossary

MDD	major depressive disorder
HAM-D	Hamilton Depression Rating Scale
SCID	Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Axis I Disorders
PSSS	Perceived Social Support Scale

References

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Waters 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. [PubMed: 15939837]
2. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Uston B. Depression, chronic disease, and decrements in health: results from the World Health Survey. Lancet. 2007; 370:851–8. [PubMed: 17826170]
3. Hollon SD, Thase ME, Markowitz JC. Treatment and prevention of depression. Psychol Sci Public Interest. 2002; 3:39–77.
4. Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. Efficacy and tolerability of venlafaxine compared with selective serotonin re-uptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry. 2002; 180:396–404. [PubMed: 11983635]
5. Rush AJ, Trivendi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006; 163:1905–17. [PubMed: 17074942]
6. Trivendi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, Ritz L, Nierenberg AA, Lebowitz BD, Biggs MM, Luther JF, Shores-Wilson K, Rush AJ. for the STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. N Engl J Med. 2006; 354:1243–52. [PubMed: 16554526]
7. Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP. Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. Arch Gen Psychiatry. 2005; 62:417–22. [PubMed: 15809409]
8. Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. Exercise for depression. Cochrane Database Syst Rev. 2009; 3:CD004366. [PubMed: 19588354]
9. 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. [PubMed: 10547175]
10. Blumenthal JA, Babyak MA, Doraiswamy MP, Watkins L, Hoffman B, Barbour KA, Herman S, Craighead E, Brosse AH, Waugh R, Hinderliter A, Sherwood A. Exercise and pharmacotherapy in

the treatment of major depressive disorder. Psychosom Med. 2007; 69:587–96. [PubMed: 17846259]

11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision. 4. Washington, DC: American Psychiatric Association; 2004.
12. Beck, A.; Steer, R.; Brown, G. BDI-II Manual. San Antonio, TX: Psychological Corporation; 1996.
13. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I), Research Version (SCID-I/P). New York: Biometrics Research; 2002.
14. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56–62. [PubMed: 14399272]
15. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry. 1988; 45:742–7. [PubMed: 3395203]
16. Blumenthal JA, Sherwood A, Babyak M, Doraiswamy PM, Hoffman BM. Response to letters to the editor. Psychosom Med. 2008; 70:263–5.
17. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry. 1991; 48:851–5. [PubMed: 1929776]
18. Kocsis JH, Gelenberg AJ, Rothbaum BO, Klein DN, Trivedi MH, Manber R, Keller MB, Leon AC, Wisniewski SR, Arnow BA, Markowitz JC, Thase ME. REVAMP Investigators. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression. Arch Gen Psychiatry. 2009; 66:1178–88. [PubMed: 19884606]
19. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci. 1985; 10:141–6. [PubMed: 4053261]
20. Godin G, Shephard RJ. Godin leisure-time exercise questionnaire. Med Sci Sports Exerc. 1997; 29:S36–8.
21. Miller DJ, Freedson PS, Kline GM. Comparison of activity levels using Caltrac accelerometer and five questionnaires. Med Sci Sports Exerc. 1994; 26:376–82. [PubMed: 8183104]
22. Blumenthal JA, Burg MM, Barefoot J, Williams RB, Haney T, Zimet G. Social support, Type A behavior, and coronary artery disease. Psychosom Med. 1987; 49:331–40. [PubMed: 3615762]
23. Stone, CJ.; Koo, CY. Proceedings of the Statistical Computing Section ASA. Washington, DC: American Statistical Association; 1985. Additive splines in statistics.
24. Maier W, Philipp M. Improving the assessment of severity of depressive states: a reduction of the Hamilton Depression Scale. Pharmacopsychiatry. 1985; 18:114–5.
25. Entsuah R, Shaffer M, Zhang J. A critical examination of the sensitivity of unidimensional subscales derived from the Hamilton Depression Rating Scale to antidepressant drug effects. J Psychiatr Res. 2002; 36:437–48. [PubMed: 12393314]
26. National Institute for Clinical Excellence. Depression: Management of Depression in Primary and Secondary Care. London, England: National Institute for Clinical Excellence; 2004.
27. Babyak M, Blumenthal JA, Herman S, Khatri P, Doraiswamy M, Moore K, Craighead WE, Baldewicz TT, Krishnan KR. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom Med. 2000; 62:633–8. [PubMed: 11020092]
28. Doyne EJ, Ossip-Klein DJ, Bowman ED, Osborn KM, McDogall-Wilson IB, Neimeyer RA. Running versus weight lifting in the treatment of depression. J Consult Clin Psychol. 1987; 55:748–54. [PubMed: 3454786]
29. Fremont J, Wilcoxon Craighead L. Aerobic exercise and cognitive therapy in the treatment of dysphoric moods. Cognit Ther Res. 1987; 11:241–51.
30. Klein MH, Greist JH, Gurman RA, Neimeyer RA, Lesser DP, Bushnell NJ. A comparative outcome study of group psychotherapy vs. exercise treatments for depression. Int J Ment Health. 1985; 13:148–77.

Clinical Implications

Although aerobic exercise has been shown to be an effective short-term treatment for MDD in patient volunteers, the beneficial effects of exercise, like those of antidepressant medications, may dissipate after the intervention is discontinued. However, regardless of the initial treatment strategy (i.e., exercise or medication), it is possible that depressed patients may be able to benefit from ongoing exercise participation.

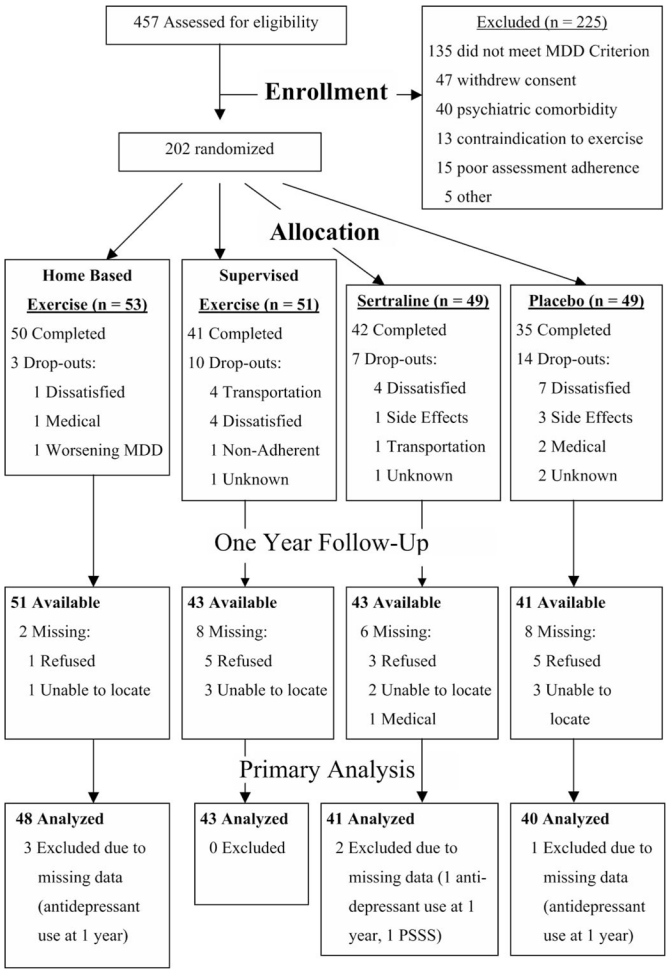

Figure 1.
Flowchart from participant recruitment through the 1-year posttreatment follow-up assessment. *MDD* = major depressive disorder; *PSSS* = Perceived Social Support Scale.

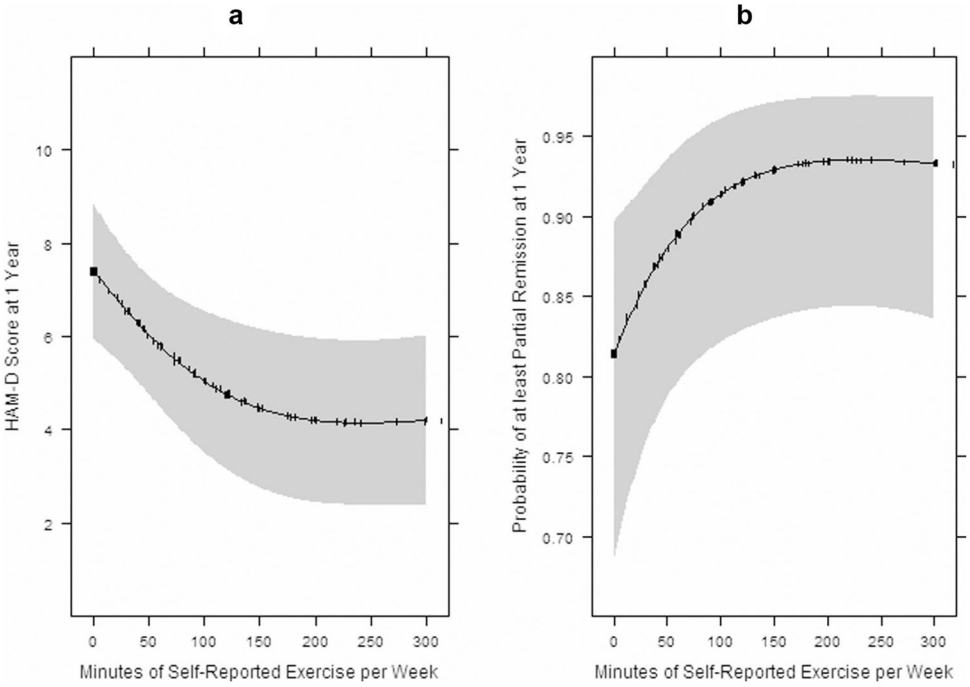

Figure 2.

Association between self-reported exercise during follow-up and depressive status at 1 year. *Panel a* displays the association between self-reported exercise and the predicted Hamilton Depression Rating Scale (*HAM-D*) score at 1 year. *Panel b* shows the association between self-reported exercise and the predicted probability of being at least partially remitted at 1 year. Estimates are for a typical study participant (age 51 years, white, female, not on antidepressant medication during follow-up, one prior major depressive episode, HAM-D score of 8 at 16 weeks, perceived social support score of 4.5). The expected difference in HAM-D score between a person reporting 180 minutes of exercise and a person reporting 0 minute of exercise was a decrement of 3.1 points (95% confidence interval = −5.1, −1.2). The adjusted odds of being in an improved category of depressive status for a person reporting exercising 180 minutes per week are about three times greater compared with a person reporting 0 minute of exercise.

TABLE 1

Participant Characteristics by Availability at 1-Year Follow-Up

	Available at 1-Yr Follow-Up (*n* = 172)	**Missing at 1-Yr Follow-Up (*n* = 30)**	***p***
Age in years, mean (SD)	51.7 (7.7)	51.9 (7.3)	.90
Gender, male, *n* (%)	46 (26.7)	3 (10.0)	.06
Ethnicity, white, *n* (%)	119 (69.2)	19 (63.3)	.52
Baseline HAM-D <18, *n* (%)	89 (51.7)	13 (43.3)	.39
MDD diagnosis = single episode (versus recurrent), *n* (%)	61 (35.5)	8 (26.7)	.41
Baseline Perceived Social Support Scale, mean (SD)	4.3 (1.3)	4.1 (1.2)	.44
Completed study treatment (versus withdrew), *n* (%)	150 (87.2)	18 (60.0)	<.001

SD = standard deviation; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder.

Table 2

MDD Remission and Posttreatment Activities

	Home-Based Exercise (*n* = 48)	Supervised Exercise (*n* = 43)	Sertraline (*n* = 41)	Placebo (*n* = 40)	Total (*n* = 172)
1-Year MDD status, *n* (%)					
Depressed	7 (15)	9 (21)	9 (22)	5 (13)	30 (17)
Partial remission	9 (19)	5 (12)	6 (15)	9 (23)	26 (17)
Full remission	32 (67)	29 (67)	26 (63)	26 (65)	113 (66)
Number who reported no exercise, *n* (%)	19 (40)	20 (47)	23 (56)	26 (65)	88 (51)
Exercise minutes/week among those reporting exercise, median (IQR)	90 (60–120)	100 (60–175)	110 (55–220)	143 (120–233)	103 (60–178)
Antidepressant, *n* (%)	16 (33)	13 (30)	20 (49)	13 (33)	62 (36)
Talk therapy, *n* (%)	7 (15)	7 (16)	8 (18)	8 (20)	30 (17)
Antidepressant herbal supplements, *n* (%)	1 (2)	1 (2)	0 (0)	4 (10)	6 (3)

MDD = major depressive disorder; IQR = interquartile range.