Exercise Treatment for Major Depression: Maintenance of Therapeutic Benefit at 10 Months

MICHAEL BABYAK, PHD, JAMES A. BLUMENTHAL, PHD, STEVE HERMAN, PHD, PARINDA KHATRI, PHD, MURALI DORAISWAMY, MD, KATHLEEN MOORE, PHD, W. EDWARD CRAIGHEAD, PHD, TERI T. BALDEWICZ, PHD, AND K. RANGA KRISHNAN, MD

Objective: The purpose of this study was to assess the status of 156 adult volunteers with major depressive disorder (MDD) 6 months after completion of a study in which they were randomly assigned to a 4-month course of aerobic exercise, sertraline therapy, or a combination of exercise and sertraline. **Methods:** The presence and severity of depression were assessed by clinical interview using the Diagnostic Interview Schedule and the Hamilton Rating Scale for Depression (HRSD) and by self-report using the Beck Depression Inventory. Assessments were performed at baseline, after 4 months of treatment, and 6 months after treatment was concluded (ie, after 10 months). **Results:** After 4 months patients in all three groups exhibited significant improvement; the proportion of remitted participants (ie, those who no longer met diagnostic criteria for MDD and had an HRSD score <8) was comparable across the three treatment conditions. After 10 months, however, remitted subjects in the exercise group had significantly lower relapse rates ($p = .01$) than subjects in the medication group. Exercising on one's own during the follow-up period was associated with a reduced probability of depression diagnosis at the end of that period (odds ratio = 0.49, $p = .0009$). **Conclusions:** Among individuals with MDD, exercise therapy is feasible and is associated with significant therapeutic benefit, especially if exercise is continued over time. **Key words:** depression, exercise, aging.

BDI = Beck Depression Inventory; DIS = Diagnostic Interview Schedule; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; HRSD = Hamilton Rating Scale for Depression; MDD = major depressive disorder; OR = odds ratio; SMILE = Standard Medical Intervention and Long-Term Exercise (study).

Aerobic exercise has been prescribed for the treatment of a wide range of medical disorders, including cardiovascular disease (1, 2), hyperlipidemia (3), osteoarthritis (4), fibromyalgia (5), and diabetes (6). In addition, exercise may have a number of psychological benefits (7, 8), and it has been suggested as a potential treatment for a variety of psychiatric conditions, especially depression (9, 10). Epidemiological studies have shown an inverse relation between physical activity and mental health (11, 12). It has been shown, for example, that physical activity is inversely related to depressive symptoms (12, 13) and that individuals who increased their activity over time were at no greater risk for depression than individuals who had been physically active all along (14). Moreover, individuals who had been physically active in the past but who became inactive were 1.5 times more likely to become depressed than those who consistently maintained a high level of physical activity.

Interventional studies also have provided evidence of the value of aerobic exercise in reducing depression (15–19). Martinsen et al. (18, 19), for example, found that depressed patients who underwent exercise training reported significant reductions in depressive symptoms compared with patients receiving occupational therapy. However, these findings are not conclusive because patients also were receiving concomitant psychotherapy and more than half were taking antidepressant medication.

Recently we demonstrated that the efficacy of 16 weeks of aerobic exercise training was comparable to that of standard pharmacotherapy (20). In that study (the Standard Medical Intervention and Long-term Exercise, or SMILE, study), 156 patients with MDD were randomly assigned to exercise training, pharmacotherapy (sertraline), or a combination of exercise and medication. After 16 weeks of treatment, patients in all three groups exhibited significant reductions in depressive symptoms. Although patients tended to respond more quickly in the medication group, there were no clinically or statistically significant group differences after 16 weeks. Questions remained, however, about whether patients would continue to exercise on their own after termination of the treatment period and what impact exercise therapy would have on depression over an extended follow-up period. This is an important issue, because current treatment guidelines recommend continuous therapy for 6 months or longer to reduce the risk of recurrence or relapse (21). The present study reports 6-month follow-up data on participants previously enrolled in SMILE.

From the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC.

Address reprint requests to: James A. Blumenthal, PhD, Department of Psychiatry and Behavioral Sciences, Box 3119, Duke University Medical Center, Durham, NC 27710. Email: blume003@mc.duke.edu

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METHODS

Participants

Participants were volunteers aged 50 years and older who met DSM-IV criteria for MDD (22) and scored at least 13 on the HRSD (23) at study entry. In addition, participants also met the following criteria: 1) not currently taking antidepressant medication; 2) not currently using other medications that would preclude their being randomly assigned to either medication or exercise conditions (eg, quinidine or metoprolol); 3) no current problem with alcohol or substance dependence; 4) no medical contraindications to exercise (eg, significant orthopedic problems or cardiopulmonary disease that would prevent regular aerobic exercise); 5) no primary axis I psychiatric diagnosis other than major depression (eg, bipolar disorder or psychosis); 6) not imminently suicidal; 7) not currently in psychotherapy that was initiated within the past year; and 8) not already participating in regular aerobic exercise. Additional details of recruitment and selection criteria were reported by Blumenthal et al. (20).

Depression Measures

Diagnostic Interview Schedule. Patients were interviewed by a clinical psychologist using the depression-relevant sections of the DIS (24). Subjects were considered to meet DSM-IV criteria for MDD if they exhibited either persistent depressed mood or loss of interest or pleasure plus the following additional symptoms: sleep disturbance, weight loss or change in appetite, psychomotor retardation or agitation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, impaired cognition or concentration, or recurrent thoughts of death, for a total of at least 5 symptoms.

Hamilton Rating Scale for Depression. The HRSD (23) is a 17-item clinical rating scale that was used to evaluate eligibility for the study as well as treatment outcome. To evaluate interrater reliability, 10 randomly selected interviews were independently rated by two clinicians. The intraclass correlation for the two raters was 0.96.

Beck Depression Inventory. The BDI (25) is a 21-item self-report questionnaire consisting of symptoms and attitudes relating to depression. The items are summed in a total score; higher numbers indicate greater depression with a range of 0 to 63.

Interventions

On completion of the baseline assessment, participants were randomly assigned to one of three treatments: 1) exercise 2), medication, or 3) combined exercise and medication.

Exercise. Subjects in this group attended three supervised exercise sessions per week for 16 consecutive weeks. Participants were assigned training ranges equivalent to 70% to 85% of heart rate reserve (26), which was calculated from the maximum heart rate achieved during a treadmill test. Each aerobic session began with a 10-minute warmup period, followed by 30 minutes of continuous cycle ergometry or brisk walking/jogging at an intensity that would maintain heart rate within the assigned training range. The exercise session concluded with 5 minutes of cooldown exercises. Heart rate (radial pulse) and perceived exertion were monitored and recorded three times during each exercise session by a trained exercise physiologist.

Medication. Subjects in this group received sertraline (Zoloft), a selective serotonin-reuptake inhibitor. This medication was selected because of its documented efficacy and favorable side effect profile for the elderly (27). Medication management was provided by a staff psychiatrist, who met with each patient at the beginning of the study and during weeks 2, 6, 10, 14, and 16. At these meetings, the psychiatrist evaluated treatment response and side effects and titrated the dosage accordingly. Treatment was initiated with 50 mg and titrated until a well-tolerated therapeutic dosage was achieved up to 200 mg. An effort was made to follow standard "usual care" guidelines for medication management, with the exception that a change to a different antidepressant was not permitted during the course of the study.

Combined Exercise and Medication. Subjects in the combination group received concurrently the same medication and exercise regimens described above.

Follow-Up Assessments

Depression evaluations using the DIS, HRSD, and BDI were conducted at baseline, immediately after the 4-month treatment period, and 6 months after treatment ended (ie, 10 months after study entry). All evaluations were conducted in the hospital clinic, with the exception of that for one participant who could not return to the laboratory for the 6-month evaluation and was instead interviewed by telephone.

Criteria developed by the MacArthur Foundation Research Network were used to classify therapeutic response (28). Subjects were classified as being in *full remission* if they no longer met criteria for MDD and had an HRSD score <8 after 4 months of treatment. Subjects were considered *recovered* if they if they continued to remain in full remission for >6 months (ie, at the 6-month follow-up visit). A classification of *partial recovery* was used to designate subjects who did not meet criteria for MDD but still exhibited significant depressive symptoms as reflected by an HRSD score >7 but <15. Subjects were considered to have *relapsed* if they were initially considered in remission after 4 months of treatment but were found at the 6-month follow-up visit to meet DSM-IV criteria for MDD or to have an HRSD score of ≥ 15.

At the outset of the 6-month follow-up evaluation, and before the current level of depression was assessed, participants were asked about the nature and extent of any therapeutic activity engaged in during the follow-up period, including use of antidepressants or any form of psychotherapy. Subjects were then questioned about the extent of their participation in regular exercise activity during the 6 months since the treatment phase ended. Inquiry was directed at three forms of exercise: aerobic exercise, weight training, and vigorous leisure-time activity. In each instance subjects were asked how many times per week, if at all, they engaged in that particular type of exercise and the usual duration (in minutes) of sessions.

RESULTS

Summary of Findings After 4 Months of Treatment

Outcomes immediately after 4 months of treatment are reported in detail elsewhere (20). Briefly, intention-to-treat analyses showed that the groups had similar remission rates with respect to presence or absence of current MDD ($p = .67$): 60.4% of patients in the exercise group, 65.5% in the medication group, and 68.8% in the combined group no longer met DSM-IV criteria for MDD. When the additional criterion of an HRSD score <8 was added to the classification scheme, the rates of remission were again comparable for the three groups ($p = .58$). Finally, after adjust-

ments for initial levels of depression were made, the groups still did not differ on HRSD (p = .39) or BDI (p = .40) scores immediately after completion of treatment.

Findings After 10 Months (6-Month Follow-Up Visit)

Follow-up assessments were available on 133 (85.6%) of the original 156 enrolled patients. Twenty of the 23 patients who initially dropped out of treatment before completion of the treatment program were not available for follow-up. Three additional patients who completed the 4-month assessment (one in each group) declined to participate in the 6-month follow-up. There were no group differences in the lost-to-follow-up rate for each treatment group (exercise: N = 9, 17%; medication: N = 6, 13%; combination: N = 8, 15%; p = .89).

Depression at 10 Months. When all participants available at follow-up were considered and adjustments were made for corresponding BDI scores at 4 months, self-reported depressive symptoms (ie, BDI scores) did not vary among persons initially assigned to the exercise (mean ± SE = 8.9±0.77), medication (11.0 ± 0.81), or combined exercise and medication (10.6 ± 0.75) groups (p = .13). However, when interviewer ratings in which the presence of MDD was defined as the presence of DSM-IV diagnosis or an HRSD score >7 were used, it was found that participants in the exercise group exhibited lower rates of depression (30%) than participants in the medication (52%) and combined groups (55%) (p = .028).

Status of Remitted Subjects. A more detailed analysis of depression rates at the 6-month follow-up visit was conducted among the 83 patients who had been assessed as being in remission at the end of the 4-month treatment period. At the 6-month follow-up visit, participants were categorized as recovered (no DSM-IV diagnosis of MDD and an HRSD score <8 for >6 months), partially recovered (no DSM-IV diagnosis of MDD and an HRSD score >7 but <15), or relapsed (presence of DSM-IV diagnosis of MDD regardless of HRSD score or an HRSD score ≥15) (28). To assess the relation between treatment and outcome classification, a proportional odds regression model, in which the three-level outcome (full recovery, partial recovery, or relapse) served as the dependent variable with baseline HRSD score specified as a covariate, was used. Two dummy variables carrying treatment effects, with medication as the reference group, served as predictors in the model. This analysis revealed a significant overall treatment effect ($\chi^2(2)$ = 8.30, p = .016). Specifically, participants in the exercise group were more likely than those in the medication group to be partially or fully recovered at the 6-month follow-up visit (OR = 6.10, p = .01). In contrast, patients receiving combination therapy were no more likely to be categorized as partially or fully recovered than were patients in the medication group (OR = 1.32, p = .57). In addition, only 8% of remitted patients in the exercise group had relapsed, compared with 38% in the medication group and 31% in the combination group (see Fig. 1).

Exercise Participation and Other Interventions During the Follow-up Period. At the end of the 4-month intervention, all patients were educated about MDD and were encouraged to continue with some form of treatment on their own, including exercise or medication. Although 64% of subjects in the exercise group and 66% of subjects in the combination group reported that they continued to exercise, 48% of participants in the medication group initiated an exercise program during the 6-month follow-up period (p = .17). The groups differed significantly in the number of subjects using antidepressant medication, with 40% of subjects in the combination group, 26% in the medication group, and 7% in the exercise group reporting antidepressant use during the 6-month follow-up period (p = .001). Twenty-two (16%) of the participants entered psychotherapy at the end of the 4-month intervention (medication: N = 7; combination: N = 8; exercise: N = 7; p = .99).

Multiple logistic regression analysis was used to assess the relation of exercise and medication to MDD diagnosis at 6 months. Medication use was coded as 0

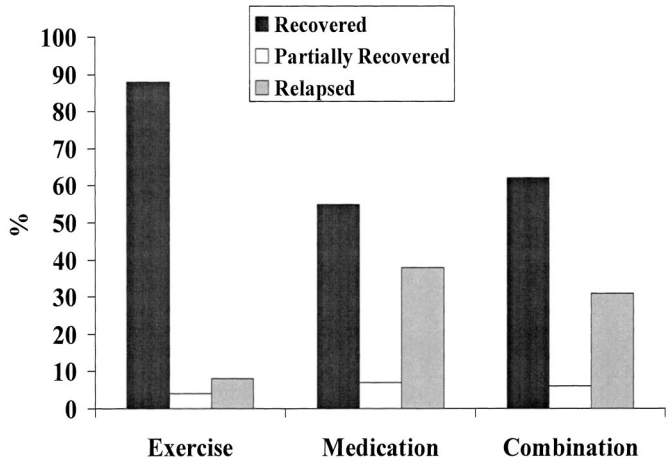

Fig. 1 Clinical status at 10 months (6 months after treatment) among patients who were remitted (N = 83) after 4 months of treatment in Exercise (N = 25), Medication (N = 29), and Combination (N = 29) groups. Compared with participants in the other conditions, those in the Exercise condition were more likely to be partially or fully recovered and were less likely to have relapsed.

or 1 (no or yes), and exercise was quantified as the number of minutes per week of aerobic exercise, scaled to increments of 1 SD (about 50 minutes). Age, gender, and baseline HRSD scores were included in the model as control variables. These analyses revealed that patients who reported that they engaged in regular aerobic exercise during the 6-month follow-up period were less likely to be classified as depressed at the end of that period (see Table 1), adjusting for depression level at study entry, age, gender, and antidepressant medication use during the follow-up period ($p < .0009$). HRSD scores at 4 months also were inversely related to minutes of exercise per week (-0.33, $p < .001$).

A further analysis was conducted using HSRD scores at 4 months as a covariate to rule out the possibility that the relationship between exercise and 10-month depressive status was confounded by the severity of depression present at the end of treatment. HRSD scores at 4 months were significant predictors of HRSD scores at 10 months (standardized OR = 2.23, $p = .002$); however, minutes of exercise per week remained a significant predictor of depressive status with little change in the effect size (standardized OR = 0.550, $p = .010$).

DISCUSSION

Results of this relatively large, single-center clinical trial indicate that exercise is a feasible therapy for patients suffering from MDD and may be at least as effective as standard pharmacotherapy. As reported previously (20), the majority of patients in all three treatment groups exhibited a clinically significant reduction in depressive symptoms at the end of 4 months of treatment. The analyses presented in this report indicate that in most instances these improvements persisted for at least 6 months after the termination of treatment. Among patients who had been assessed as being in full remission at the end of the 4-month treatment period, participants in the exercise group were less likely to relapse than participants in the two groups receiving medication. Interestingly, combining exercise with medication conferred no additional advantage over either treatment alone. In fact, the opposite was the case, at least with respect to relapse rates for patients who initially responded well to treatment. This was an unexpected finding because it was assumed that combining exercise with medication would have, if anything, an additive effect. The reasons for this are open to speculation. It was apparent that there may have been some "antimedication" sentiment among some study participants, as evidenced by expressions of disappointment when notified of their assignment to a group in which they would receive medication in addition to exercise. During treatment, several in the combined group mentioned spontaneously that the medication seemed to interfere with the beneficial effects of the exercise program. It is unclear how this would occur physiologically, and the explanation might have more to do with psychological factors. One of the positive psychological benefits of systematic exercise is the development of a sense of personal mastery and positive self-regard, which we believe is likely to play some role in the depression-reducing effects of exercise. It is conceivable that the concurrent use of medication may undermine this benefit by prioritizing an alternative, less self-confirming attribution for one's improved condition. Instead of incorporating the belief "I was dedicated and worked hard with the exercise program; it wasn't easy, but I beat this depression," patients might incorporate the belief that "I took an antidepressant and got better." The possibilities here are interesting, and future research might well focus on attitudinal and attributional factors associated with patient response to exercise therapy.

TABLE 1. Logistic Regression Predicting MDD Defined by DSM-IV and HRSD Criteria at 6 Months

Variable	Standardized OR	95% Confidence Interval	*p*
Age	1.21	0.83–1.74	.321
Female	1.05	0.73–1.54	.768
Baseline HRSD score	1.41	0.95–2.09	.093
Antidepressant (no/yes)	1.31	0.91–1.89	.152
Exercise (≈50 min/wk)	0.49	0.32–.74	.0009

Self-reported participation in exercise during the follow-up period was inversely related to the incidence of depression at 10 months. Each 50-minute increment in exercise per week was associated with a 50% decrease in the odds of being classified as depressed. Limitations of the study design prevent us from concluding that exercise *caused* depressive symptoms to be reduced at 6-month follow-up, because it is possible that patients who continued to exercise after the intervention did so because they already were less depressed at the end of the treatment period. Indeed, the significant inverse correlation we observed between posttreatment HRSD scores and weekly minutes of aerobic exercise during the follow-up period could be interpreted as showing that patients exercise if they are less depressed. We note, however, that after controlling for posttreatment depression level, the number of minutes of exercise per

week still predicted depressive status 6 months after treatment. Together these results suggest a potential reciprocal relationship between exercise and depression: Feeling less depressed may make it more likely that patients will continue to exercise, and continuing to exercise may make it less likely that the patient will suffer a return of depressive symptoms. Another possibility, which we introduced in our original report (20), is that the benefits of the exercise program may be attributable, at least in part, to the social support aspects of the exercise group setting. Such an explanation would be less likely to apply to the present findings, however, because continuation of exercise during the follow-up period generally took place in an individual, rather than a group, setting.

There are several additional limitations of the present study, the most significant of which concerns the special nature of our study population. The sample consisted of patient-volunteers who responded to advertisements seeking participants for a study of exercise therapy for depression. We presume that these participants believed exercise to be a credible treatment modality for depression and were favorably inclined toward participation. That this is the case is supported by the number of patients (48%) in the medication group who initiated an exercise program on their own after the formal treatment phase ended. In contrast, only 26% of patients in the medication group chose to continue pharmacotherapy, and only 6% of patients in the exercise group initiated pharmacotherapy. The question remains whether the impressive results of the SMILE study will be applicable to the general population of middle-aged and older patients with MDD and whether exercise "prescribed" by a clinician will be accepted and complied with to the same extent as when it is sought out and adopted on one's own.

Another issue concerns the substantial degree of "crossover" in treatment modality after completion of the 4-month period of formal therapy. The fact that almost half of the participants in the medication group switched on their own to an exercise program renders meaningful intergroup comparisons at 6-month follow-up problematic. However, the finding that self-reported exercise, independent of the original treatment group, was associated with reduced depression provides potential support for the value of exercise as a treatment for MDD. In addition, although we used the intention-to-treat principle in conducting our analyses, 15% of the original cohort were unavailable for follow-up. It is unknown how these missing data may have influenced the results, although it should be noted that most of the subjects who were not followed up at 10 months dropped out of the treatment program prematurely and virtually all were not improved at the time of their dropping out.

A final limitation concerns the lack of independent verification of posttreatment therapeutic activity (medication, psychotherapy, and exercise). During the follow-up period, participants were assessed solely by self-report, which raises the possibility of inaccuracies in these data. To have arranged for independent verification, however, would itself potentially compromise the intended naturalistic conditions for the follow-up period. For example, the use of diaries or pill counts would have conveyed expectations that could have influenced subject's behavior over the follow-up period. It is also notable that ratings of depression and of posttreatment exercise participation were made by the same interviewer (albeit blinded to initial treatment group assignment), which raises the possibility of potential bias in the data obtained. It is recommended that future studies incorporate separate, blind ratings of exercise participation to avoid this potential confounding factor.

Despite these limitations, the present findings suggest that a modest exercise program (eg, three times per week with 30 minutes at 70% of maximum heart rate reserve each time) is an effective, robust treatment for patients with major depression who are positively inclined to participate in it and that clinical benefits are particularly likely to endure among patients who adopt exercise as a regular, ongoing life activity.

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