The DOSE study: a clinical trial to examine efficacy and dose response of exercise as treatment for depression

Andrea L. Dunn, Ph.D.\textsuperscript{a,*}, Madhukar H. Trivedi, M.D.\textsuperscript{b}, James B. Kampert, Ph.D.\textsuperscript{a}, Camillia G. Clark, Ph.D.\textsuperscript{c}, Heather O. Chambliss, Ph.D.\textsuperscript{a}

\textsuperscript{a}The Cooper Institute, Dallas, Texas, USA
\textsuperscript{b}The University of Texas Southwestern Medical Center, Dallas, Texas, USA
\textsuperscript{c}Alberta Children’s Hospital, Calgary, Alberta, Canada

Manuscript received October 22, 2001; manuscript accepted May 28, 2002

Abstract

The Depression Outcomes Study of Exercise (DOSE) was a randomized clinical trial to determine whether exercise is an efficacious treatment for mild to moderate major depressive disorder (MDD) in adults ages 20 to 45 years. The specific hypotheses under investigation were (1) active exercise is an efficacious monotherapy for mild to moderate levels of MDD, and (2) there is a dose-response relation between the exercise amount and reduction in depressive symptoms. The primary outcome measure was the Hamilton Rating Scale for Depression (HRSD) collected weekly over 12 weeks. Secondary outcome measures were the Inventory of Depressive Symptoms (clinician and self-report), HRSD scores at 24 weeks, cardiorespiratory fitness, self-efficacy, and quality of life. Eighty men and women who were diagnosed with a Structured Clinical Interview for Depression and who had mild (HRSD 12–16) to moderate (HRSD 17–25) MDD were randomized to one of five doses of exercise: 7.0 kcal/kg/week in 3 days/week; 7.0 kcal/kg/week in 5 days/week; 17.5 kcal/kg/week in 3 days/week; 17.5 kcal/kg/week in 5 days/week; or 3 days/week of stretching and flexibility exercises for 15 to 20 min/session. Participants exercised under supervision in our laboratory over the course of 12 weeks. Symptoms of depression were measured weekly by trained clinical raters blinded to the participant’s treatment assignment. The design of the study restricted participant characteristics to mild to moderate MDD and controlled exercise features to permit the evaluation of exercise as a sole treatment for depression. This study is the first to examine dose-response effects of exercise in participants diagnosed with MDD. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Major depressive disorder; Exercise; Dose response; Randomized clinical trial

* Corresponding author: Andrea L. Dunn, Ph.D., Senior Associate Director, Division of Research, The Cooper Institute, 12330 Preston Road, Dallas, TX 75230. Tel.: +1-972-341-3242; Fax: +1-972-341-3225.
E-mail address: adunn@cooperinst.org

0197-2456/02/$—see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0197-2456(02)00226-X
Background and aims

Depression is a prevalent illness (17% lifetime prevalence) [1] with a high cost to society (estimated $44 billion/year) [2] and to the quality of life of the individual [3,4]. The Global Burden of Disease study [5] found that in developed nations unipolar major depression ranks second behind ischemic heart disease in lost years of healthy life due to premature death or disability. Current estimates indicate that only 25% of adults suffering from depression seek treatment despite major advances in effective pharmacological and psychotherapeutic treatments. The goal for persons seeking depression treatment set by Healthy People 2000 was 35% [6] and 50% for 2010 [7]. Social stigma and distrust of the medical regimens used to treat depression are major reasons that individuals will not seek treatment even when these individuals acknowledge psychological symptoms [8]. The lack of use of effective pharmacological or cognitive-behavioral therapies demonstrates the need for acceptable treatments for individuals with depression.

Engaging in regular exercise does not carry a stigma, is relatively low cost, and can be done outside standard medical settings. In addition, exercise may be a more acceptable treatment for some (e.g., pregnant women or adolescents) because of its relative safety and lack of side effects compared to antidepressant drug treatments. Exercise can be safely prescribed and monitored in many of these individuals. Although risks are associated with exercise, these are low, especially in younger people where the prevalence of depression is high. The cost-benefit ratio clearly favors an exercise alternative [9].

One major limitation is that exercise has not met established efficacy standards [10] despite a number of epidemiological and experimental studies demonstrating a reduction in depressive symptoms with exercise. Several clinical studies [11–14] and a recent meta-analysis [15] have shown exercise to be comparable to psychotherapy. More recently Blumenthal et al. [16] conducted a randomized clinical trial comparing the effects of group exercise, antidepressant medication, and group exercise in combination with antidepressant medication in older adults with mild to moderate major depressive disorder (MDD) over a 16-week acute phase study. The major finding from this study was that all treatments were efficacious in reducing symptoms of depression. While this study adequately diagnosed depression and measured treatment effects, the fact that the exercise was done in a group rather than an individual setting still leaves a question of whether social support could influence outcomes. Moreover, the study was conducted in only older subjects, limiting the generalizability of results. Therefore, it is important to further examine the effects of exercise in depressed subjects of different age groups and to isolate exercise effects from social support. It is also important to quantify the amount of exercise needed to reduce depressive symptoms so that recommendations for exercise prescription can be developed for the purpose of treating depression. The Depression Outcomes Study of Exercise (DOSE) is the first dose-response study of exercise as a monotherapy for the treatment of mild to moderate MDD in young to middle-aged adults.

Specific objectives

There were two major objectives of the DOSE study. The first was to determine the efficacy of aerobic exercise as a sole treatment of mild to moderate MDD in participants randomized to exercise compared with an “equal contact” exercise placebo control group over a
12-week acute phase treatment. The second objective was to determine the dose-response relation between different amounts and frequencies of aerobic exercise with the reduction of depressive symptoms. We hypothesized that the active exercise compared with the exercise placebo would be efficacious after 12 weeks for mild to moderate levels of MDD using established treatment standards of recovery (50% reduction in Hamilton Rating Scale for Depression [HRSD]) or remission (HRSD≤7) [17]. We further hypothesized there would be a dose-response relation between the exercise amount and alleviation of depressive symptoms.

In addition to the major objectives, minor objectives included (1) examining the role of fitness changes (possible biological markers) in relation to symptom reduction, (2) documenting depressive symptoms during an additional 12-week follow-up period and its relation to exercise adherence, and (3) examining changes in determinants of exercise through the 12-week acute phase and 12-week continuation phase treatment for active treatment groups.

**Participant selection criteria**

We recruited men and women between the ages of 20 to 45 years with mild to moderate MDD. The HRSD score for mild depression is 12 to 16 and for moderate depression 17 to 25 [17]. The choice of age group was made for both scientific and practical reasons. The scientific literature suggests that MDD usually begins when individuals are 20 to 30 years of age, although it can begin at any age [18]. Also, visit rates to psychiatrists are the highest for the 20- to 40-year age group, and the predominant reason for seeking help in this age range is MDD [19]. Individuals in this age range can also safely exercise at any of the levels specified in the study design without extensive exercise testing and medical examinations [20]. Budget limitations precluded older adults due to the added burden of medical clearance. All selection criteria for the DOSE study are shown in Table 1.

**Methods of patient evaluation**

*Primary outcomes*

The HRSD-17 (17 items) is a clinician-rated measure designed to assess the severity of depression by assessing both the intensity and frequency of depressive symptoms. This is the most widely used measure of depression severity for clinical trials research. One review published in 1996 reported it was used in 500 published studies over a 10-year period [21], using the Cronbach α=0.88 for internal consistency. Others have found the HRSD to be correlated with psychiatrists’ global rating (r=0.89). It also has concurrent validity with other measures of depression ranging from r=0.67 for the Inventory of Depressive Symptomatology (IDS) to r=0.75 for the Beck Depression Inventory [22]. Efficacy of treatment effects are determined by a treatment response defined as a 50% reduction in depressive symptoms as measured by the HRSD or by remission of depressive symptoms defined as an HRSD≤7 [17]. Research assistants were trained and certified to conduct all HRSD assessments. Certification was established after training using a co-rating method. Interrater reliability was established as a co-rating within two points of the HRSD total score and within