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# Exercise and the Treatment of Clinical Depression in Adults

## Recent Findings and Future Directions

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## Abstract

This article critically reviews the evidence that exercise is effective in treating depression in adults. Depression is recognised as a mood state, clinical syndrome and psychiatric condition, and traditional methods for assessing depression (e.g. standard interviews, questionnaires) are described. In order to place exercise therapy into context, more established methods for treating clinical depression are discussed. Observational (e.g. cross-sectional and correlational) and interventional studies of exercise are reviewed in healthy adults, those with comorbid medical conditions, and patients with major depression. Potential mechanisms by which exercise may reduce depression are described, and directions for future research in the area are suggested. The available evidence provides considerable support for the value of exercise in reducing depressive symptoms in both healthy and clinical populations. However, many studies have significant methodological limitations. Thus, more data from carefully conducted clinical trials are needed before exercise can be recommended as an alternative to more traditional, empirically validated pharmacological and behavioural therapies.

Although the relationship between physical activity and mood has long been recognised,[1] the use of exercise training as a treatment for clinical depression has been the focus of rigourous study only recently. In this review, we first define depression and present an overview of its assessment, epidemiology and treatment. Empirical investigations of the relationship between depression and exercise are then reviewed, with an emphasis on randomised, controlled trials with clinically depressed participants. Hypothesised mechanisms of action and practical considerations regarding exercise adherence are considered briefly. We conclude with a discussion of future directions for the study of exercise as a treatment for clinical depression.

### 1. Depression

The term 'depression' is used variously to describe a dysphoric mood state, a syndrome comprised of a cluster of symptoms, or a clinical disorder. Transient dysphoria is virtually ubiquitous and generally is not the focus of clinical attention. Depressive symptoms (e.g. sadness, fatigue and disturbed sleep) can occur in the context of a variety of medical conditions (e.g. stroke, congestive heart failure) and may not warrant a separate psychiatric diagnosis. This review is focused on the use of ex-

ercise as a treatment for the clinical disorder of depression.

### 1.1 Diagnostic Criteria

In the US, the most commonly used nomenclature for classifying psychiatric disorders is the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[2] The DSM-IV criteria for major depressive disorder (MDD) are presented in table I. These criteria are very similar to those of other commonly used diagnostic criteria [e.g. Research Diagnostic Criteria (RDC),[3] International Classification of Diseases (ICD)].[4]

The DSM-IV describes several other mood disorders from which MDD should be distinguished. Dysthymic disorder is a mild, but chronic depression, lasting at least 2 years but usually much longer. People with dysthymia may subsequently develop an episode of MDD (frequently termed 'double depression'). Bipolar disorder (manic depression) is characterised by one or more episodes of mania (bipolar I) or hypomania (bipolar II) – periods of abnormally elevated, expansive or irritable mood accompanied by symptoms such as inflated self-esteem, decreased need for sleep, pressure to keep talking, flight of ideas, distractibility and impulsivity. In mania, the symptoms persist for at least 1 week (or require hospitalisation) and cause marked functional impairment; hypomania need only persist for 4 days and is not sufficiently severe to require hospitalisation or cause significant impairment in functioning. A majority of people with bipolar disorder also experience periods of depression. Depressive affect also may be part of simple bereavement ('uncomplicated grief') or an adjustment disorder (when an individual does not meet criteria for a mood or anxiety disorder, but has clinically significant symptoms that developed in response to an identifiable stressor).

### 1.2 Assessment

The gold standard for assessing MDD and distinguishing it from related mood disorders is a clinical interview performed by a trained clinician.

**Table I.** Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive episode[2]

| | |
|---|---|
| A | Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure |
| | (1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful). Note: In children and adolescents, can be irritable mood |
| | (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others) |
| | (3) significant bodyweight loss when not dieting or bodyweight gain (e.g. a change of more than 5% of bodyweight in a month), or decrease or increase in appetite nearly every day |
| | (4) insomnia or hypersomnia nearly every day |
| | (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) |
| | (6) fatigue or loss of energy nearly every day |
| | (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) |
| | (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) |
| | (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide |
| B | The symptoms do not meet criteria for a mixed episode |
| C | The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning |
| D | The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism) |
| E | The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation |

The Structured Clinical Interview for DSM-IV Disorders (SCID)[5] and the Schedule for Affective Disorders and Schizophrenia (SADS)[6] are commonly used semi-structured interviews. The Diagnostic Interview Schedule (DIS)[7] and its successor, the Composite International Diagnostic Interview (CIDI),[8] are fully structured interviews designed to be administered by lay interviewers with mini-

mal training, and were developed for use in large-scale epidemiological studies.

It is commonly recognised that depression exists on a continuum, such that a purely categorical approach to assessing depression risks the loss of much information. A number of scales exist – both clinician-rated and self-report – designed to quantify the severity of depression. For clinician-rated scales, a clinician (e.g. psychologist, psychiatrist) rates the severity of a number of symptoms, usually based on both observation and interview of the patient. Commonly used clinician-rated scales are the Hamilton Rating Scale for Depression (HRSD)[9] and the Montgomery Asberg Depression Rating Scale (MADRS).[10] Self-report questionnaires generally consist of a series of written questions with multiple-choice responses that patients complete on their own. Examples include the Beck Depression Inventory (BDI),[11,12] the Center for Epidemiological Studies Depression Scale (CES-D),[13] the Symptom Checklist 90 (SCL-90),[14] and the Zung Self-Rating Depression Scale.[15] Due to the ease and low cost of administration, questionnaires are frequently used in large-scale community-based studies. However, these instruments tend not to be sensitive enough to distinguish cases of MDD from those with symptoms that are not due to a depressive disorder. For example, in a study using the CES-D, only 36% of those identified as depressed based on the recommended cut-off score of 16 met diagnostic criteria for MDD on interview.[16] Thus, these scales are efficient and provide an index of symptom severity, but should not be considered a substitute for the diagnosis of MDD via clinical interview.

### 1.3 Epidemiology

Estimates of the lifetime prevalence of MDD in community-based adult samples vary considerably across studies, ranging from 3.3% in Seoul[17] to 17.1% in the US.[18] One-year prevalence estimates range from 5 to 10.3%.[18,19] These differences may be explained to a large extent by methodological differences, such as the diagnostic system used to define MDD, the diagnostic interview employed, and the age and gender composition of the study sample.[20]

Although the symptoms of MDD need to persist for only 2 weeks for a formal diagnosis, most episodes last longer if left untreated, with the average episode lasting 6 to 8 months.[21,22] Furthermore, MDD tends to be episodic – a majority of people who recover from an episode of MDD will have a recurrence of the disorder (unpublished observations).

The debilitating effects and enormous cost of MDD for both individuals and society have been well documented. For example, in the Epidemiologic Catchment Area (ECA) study, MDD and dysthymia were associated with increased use of general medical services, increased use of emergency departments for emotional problems, impaired physical and emotional health, lost time at work, and increased rates of attempted suicide.[23] The Medical Outcomes Study (MOS) similarly found that individuals with either MDD or sub-clinical depressive symptoms reported decreased well-being and functioning when compared with those with no chronic health problems, and similar or worse functioning than that of patients with major chronic medical diseases such as diabetes mellitus, hypertension and arthritis.[24] For the year 1990, the economic burden of depression in the US (including direct treatment costs, mortality costs of depression-related suicide, and indirect costs associated with depression in the workplace) was estimated at $US43.7 billion.[25] Thus, MDD is a prevalent, recurrent disorder associated with high rates of morbidity and significant economic costs.

### 1.4 Depression and Comorbid Medical Conditions

Medical illness – especially when chronic and/or life threatening – is a psychological stressor in itself and may serve to trigger MDD. In addition, many medical treatments (e.g. antihypertensive medications, corticosteroids) can induce depressive symptoms. It is not surprising, then, that depression is more prevalent in medical patients than in healthy controls. A review of the literature[26]

suggested that approximately 6% of ambulatory primary care patients and 11% of medical inpatients have major depression, compared with a point-prevalence of 3% in the general population.

The presence of depression may have important prognostic implications for medical patients. For example, in a study[27] of 222 patients hospitalised for myocardial infarction (MI), the presence of MDD multiplied the risk of mortality over the first 6 months by a factor of 3 to 4, even after controlling for indicators of disease severity (e.g. previous MI). Similarly, in a study[28] of 331 patients hospitalised for congestive heart failure, MDD was associated with increased mortality and rehospitalisation at 3-month and 1-year follow-up; however, these relationships were somewhat attenuated when risk factors such as age and ejection fraction were considered. In patients with diabetes mellitus, depression has been associated with poorer glycaemic control,[29] poorer physical and mental functioning,[30] and increased healthcare costs.[30] In the MOS,[24] the effects of depressive symptoms and chronic medical conditions on functioning were additive; for example, the combination of advanced coronary artery disease and depressive symptoms was associated with roughly twice the reduction in social functioning associated with either condition alone. Finally, a recent meta-analytic review concluded that, across a number of medical illnesses, depression is associated with decreased adherence to the treatment regimen.[31] Thus, there is ample evidence that depression increases morbidity and mortality in medically ill patients.

Despite its prevalence and possible prognostic implications, depression is often under recognised and under treated in the medically ill.[32] For the clinician, it may be difficult to distinguish symptoms of depression from symptoms of medical illness, or the depressive symptoms may be seen as a normal reaction to the stress of being ill. This is unfortunate given that there are a number of treatments for MDD that may alleviate the patient's suffering, improve adherence to medical treatment,[33] and reduce healthcare costs.[34,35]

### 1.5 Established Treatments

There exist a number of empirically validated somatic and nonpharmacological therapies for MDD. Antidepressant medications were first marketed in the 1950s when imipramine (a tricyclic) and iproniazid (a monoamine oxidase inhibitor) were introduced. Another class of antidepressants – the selective serotonin reuptake inhibitors (SSRIs) – became available when fluoxetine was introduced in 1988. Given the more favourable adverse effect profile and the fact that they are far safer in overdose, prescribing physicians currently tend to use SSRIs as first-line antidepressants.

Other somatic therapies that have been shown to be effective in some studies[36-41] include electroconvulsive therapy (ECT), light therapy, and herbal supplements. ECT involves the application of a brief electrical current to the skull to induce a generalised seizure. It has been shown to be more effective than antidepressant medications for the acute treatment of severe depression, but there is a high risk of relapse in the year following ECT if patients are not maintained on antidepressant medication, and ECT is generally not recommended for depressions of mild to moderate severity.[36] Light therapy (phototherapy) involves exposure to artificial light with very little ultraviolet light. It has been shown to be effective in reducing winter depressive symptoms in patients with a seasonal pattern of recurrence.[37] St. John's wort (Hypericum perforatum) is an herbal remedy that has enjoyed increased popularity over the past decade. Randomised controlled trials have found that St. John's wort performs better than placebo for mild to moderate severity MDD, but there is insufficient evidence to determine the relative efficacy of St. John's wort compared with standard antidepressant medications.[38,39] Dietary supplements such as S-adenosyl-L-methionine (SAMe) and chromium are also being marketed as antidepressant agents, although empirical support is quite limited at this time.[40,41]

Empirically validated short-term psychotherapies include behaviour therapy,[42] cognitive therapy,[43] and interpersonal psychotherapy.[44] Craighead

and colleagues[45] provided a brief description of these therapies and a review of the randomised clinical trials investigating their effectiveness. Briefly, these psychotherapies have consistently been shown to be as effective as pharmacotherapy in the short-term treatment of mild-moderate severity MDD, and may also be effective for severe MDD.

Despite the widespread success of somatic and nonpharmacologic therapies in randomised, placebo-controlled trials, it is important to note that a significant minority (30 to 40%) of depressed patients do not respond favourably to the first treatment they receive. Furthermore, a high percentage of patients who do recover experience a relapse or recurrence of MDD upon discontinuing treatment (unpublished observations).[46] Finally, a majority of depressive episodes go untreated.[47-50] Some potential barriers to treatment for depression include under-detection of the disorder, lack of financial resources, social stigma, and, in the case of somatic therapies, concern about adverse effects or drug-drug interactions.[32] If effective, exercise training has the potential to be an attractive treatment alternative with few social and financial impediments.

## 2. Exercise Training and Depression

There has been a growing literature on the psychological benefits of regular physical exercise. There are three basic types of exercise: (i) cardiorespiratory or aerobic exercise (e.g. walking, jogging) in which oxygen is metabolised to produce energy; (ii) muscular strength and isometric anaerobic exercise (e.g. weightlifting) in which energy is provided without the use of inspired oxygen; and (iii) flexibility exercise (e.g. yoga, stretching) that is designed to improve range of motion.[51] Most exercise intervention studies have investigated the effects of aerobic exercise, usually enrolling participants in a brisk walking or jogging programme. Commonly, participants met in a supervised setting three times a week to exercise with a group for 30 to 60 minutes.

### 2.1 Cross-Sectional and Prospective Studies

Cross-sectional studies of clinical and nonclinical samples have consistently found that more active individuals report lower depression scores than more sedentary individuals.[52-59] Large-scale prospective studies also suggest that regular physical activity is associated with lower scores on depression questionnaires.[60-64] For example, in the Alameda County Study, Camacho and colleagues[60] measured participants' activity levels and depressive symptoms in 1965, 1974 and 1983. Compared with men and women who reported higher activity levels, those who were inactive at baseline were at greater risk for higher depression scores at the first follow-up. Participants who increased their physical activity level between 1965 and 1974 were at no greater risk for depression in 1983 than those who were active throughout the period. Conversely, those who became more inactive by 1974 were more likely to have higher depression scores in 1983 than those maintaining a high level of physical activity.

Cross-sectional methodologies are limited, however, in that they do not allow for causal inferences. Individuals may be more depressed because they are inactive, they may be inactive because they are depressed, or there may be another factor (e.g. illness) that contributes to both higher depression and greater inactivity. Although the longitudinal design of the Alameda County Study is suggestive of a causal relationship, it is still a correlational study and the time interval between measurements is too long to conclude that change in exercise is a proximal cause of change in depressive symptoms. Only interventional studies can establish the effectiveness of exercise training as a treatment for depression.

### 2.2 Exercise Training in Healthy Individuals

Exercise training has often been shown to improve depressive symptoms in healthy, nondepressed samples.[65-69] For example, DiLorenzo et al.[65] randomly assigned 111 healthy adults to a variable-intensity exercise training programme, a

fixed-intensity exercise training programme, or a wait-list control group. Compared with controls, exercise participants reported larger decreases in depressive symptomatology over time. However, other randomised studies have not found significant improvements in mood for exercisers compared with sedentary controls.[70-78] These results may be explained by a floor effect: that is, there was not much room for improvement in these healthy, nondepressed participants. Clinical samples (i.e. patients who initially report more severe symptomatology) allow for greater change between baseline and post-treatment depression scores. Additionally, studies of depressed samples are of greater clinical significance since these individuals are in need of symptomatic relief.

### 2.3 Exercise Training in Patients with Chronic Medical Conditions

Exercise training is an integral part of cardiac rehabilitation programmes.[79] A number of studies have examined the potential benefits of exercise in ameliorating depression in cardiac patients.[80-92] The majority reported significant improvements in depressive symptoms after completing an exercise programme. For example, Milani et al.[83] studied 338 patients seeking cardiac rehabilitation after experiencing a major cardiac event. At baseline, 20% of the sample self-reported elevated depressive symptomatology. After 3 months of aerobic exercise training, two-thirds of the initially depressed patients reported resolution of their depressive symptoms. Additionally, the depressed group demonstrated significant improvements in other quality-of-life parameters.

The addition of high-intensity strength training to aerobic exercise training programmes may further ameliorate depression in cardiac patients. Beniamini and colleagues[85] randomised 38 cardiac patients in an aerobic exercise programme to either an adjunctive strength training programme or an adjunctive flexibility training programme. After 12 weeks of treatment, patients in the strength training programme demonstrated significantly greater improvement on the depression subscale of the Profile of Mood States than did patients in the flexibility training programme. It is important to note that these studies of cardiac patients were limited by their failure to include no-treatment control groups. Furthermore, given the likelihood of self-selection bias, the results may not generalise to all cardiac patients, but only to those referred to, and willing to participate in, a cardiac rehabilitation programme. Despite these limitations, research on exercise training of cardiac patients provides preliminary evidence of psychological benefits of regular physical activity in clinical populations.

Investigations of pulmonary rehabilitation programmes for patients with chronic obstructive pulmonary disease (COPD) also are suggestive of the mental health benefits of exercise. Several studies noted that regular participation in an exercise programme significantly reduced depressive symptomatology in the study participant,[93-97] with improvements being maintained at 6-month[93,94] and 1-year follow-up.[97] In a randomised, controlled trial, Emery et al.[95] assigned 79 older adults with COPD to one of three treatment groups: (i) exercise, education, and stress management; (ii) education and stress management; or (iii) wait-list control. After 10 weeks of treatment, patients in the exercise, education, and stress management group and those in the wait-list group reported significant reductions in depression, with exercisers reporting the greatest improvement. On the other hand, a randomised trial comparing an 8-week comprehensive pulmonary rehabilitation programme with an 8-week education programme did not find significant group differences in reduced depression.[98] The majority of studies of pulmonary rehabilitation programmes were limited by their single group design and the possibility of a self-selection bias.[93,94,96,97,99] Additionally, inadequate assessments of depression[99] and brief trial periods[96,97,99] limit their clinical significance.

Research focusing on patients with neuromuscular disorders provides additional support for the efficacy of exercise in the treatment of depression. For example, Hakkinen et al.[100] randomly as-

signed 21 women with fibromyalgia to 21 weeks of progressive strength training or to a control group. Strength-training participants reported significant improvement in depressive symptoms compared with controls. Significant reductions in depression also have been reported for fibromyalgia patients randomised to a pool-based exercise programme, but not for those assigned to land-based exercise.[101] Other studies of fibromyalgia patients have not found a significant antidepressant effect for exercise, but these investigations are limited by small sample sizes[102] and poor treatment compliance.[102,103]

Studies examining exercise training for patients with rheumatoid arthritis and osteoarthritis provide modest evidence of an antidepressant effect in this population. In a randomised trial of 439 adults 60 years of age or older, with knee osteoarthritis, Penninx et al.[104] found that patients assigned to 18 months of aerobic exercise reported significantly reduced depressive symptoms compared with individuals in a health-education control group; no such effect was noted for patients randomised to resistance exercise. Investigations examining dance-based exercise programmes reported significant reductions in participants' depressive symptoms following treatment,[105-107] but these studies were limited by their single-group design,[105,107] lack of randomisation,[105-107] and small sample sizes.[105,106] Other randomised, controlled trials with rheumatoid arthritis and osteoarthritis patients indicated temporary[108] or nonsignificant trends of improvement[109,110] following participation in an aerobic exercise programme.

Preliminary studies in cancer patients suggest that exercise improves mood.[111-115] However, the samples were small, and the studies lacked adequate controls[113,115] and used a nonstandardised measure of depression.[112]

There are only a handful of studies investigating the effect of exercise on depression in other medical populations. In a two-by-two randomised, controlled study[116] of chronic fatigue syndrome, 136 patients were allocated to one of four treatment conditions: (i) exercise and the antidepressant medication, fluoxetine; (ii) exercise and placebo pill; (iii) fluoxetine only; or (iv) placebo pill only. Medication, relative to placebo pill, was associated with reduced depression at week 12, but not at week 26, while exercise had no significant effect on depression scores. It is important to note that this study was limited by a high dropout rate (29%) and fixed dose (20mg) of the antidepressant. A randomised, controlled study[117] of exercise for 54 patients with multiple sclerosis found that, along with significantly increasing maximal aerobic capacity, aerobic training significantly reduced depression scores at weeks 5 and 10, but not at the end of the 15 week trial.

A limitation common to many investigations of exercise in medically compromised populations should be noted. These studies examined change in self-reported depressive symptomatology in patients selected for their medical diagnosis, regardless of their depression status. Thus, the effect of exercise training on clinically depressed medical patients remains untested.

### 2.4 Exercise Training in Depressed Patients

To fully examine exercise training as an alternative treatment for depression, it is critical to examine patients with clinical depression. This section reviews studies that: (i) selected participants who met diagnostic criteria for depression or reported elevated depressive symptomatology; (ii) did not require a specific comorbid medical condition (e.g. arthritis); (iii) used a randomised design; and (iv) were published in English. Table II summarises the methodology and primary findings of these studies.

Several early investigations of depressed individuals compared exercise training to psychotherapy. Greist et al.[1] randomly assigned 28 patients with RDC-defined minor depression to one of three treatment conditions: (i) a running group; (ii) ten sessions of time-limited psychotherapy; or (iii) ten sessions of time-unlimited psychotherapy. After 12 weeks, significant reductions in depression scores were reported in all groups, with no significant differences between the treatment groups.

**Table II.** Summary of published randomised trials investigating exercise training in depressed adults

| Authors | Sample | Intervention groups | Treatment duration/ follow-up | Depression inclusion criteria | Key findings |
|---|---|---|---|---|---|
| Blumenthal et al.[118] | 156 patients, 50-77y | (1) Aerobic exercise; (2) medication; (3) aerobic exercise and medication | 16wk; 6mo follow-up | DSM-IV MDD; HRSD > 12 | Aerobic = medication = aerobic and medication |
| Doyne et al.[119] | 40 females, 18-35y | (1) Running; (2) weightlifting; (3) wait-list | 8wk; 1, 7 and 12mo follow-up | RDC major or minor depression | Aerobic = nonaerobic > wait-list |
| Fremont & Craighead[120] | 49 participants, 19-62y | (1) Running; (2) CBT; (3) running and CBT | 10wk; 2 and 4mo follow-up | 9 < BDI < 30 | Running = CBT = running and CBT |
| Greist et al.[1] | 28 outpatients, 18-30y | (1) Running; (2) time-limited psychotherapy; (3) time-unlimited psychotherapy | 12wk; no follow-up | SCL-90 > 50%; RDC minor depression | Running = time-limited psychotherapy = time-unlimited psychotherapy |
| Klein et al.[121] | 74 participants, mean age = 30y | (1) Running; (2) group therapy; (3) meditation-relaxation | 12wk; 3 and 9mo follow-up | SCL-revised > 60%; RDC major or minor depression | Running = group therapy = meditation-relaxation |
| Martinsen et al.[122] | 99 inpatients, mean age = 41y | (1) Aerobic exercise; (2) nonaerobic exercise | 8wk; follow-up not reported | DSM-III-R MDD, dysthymic disorder, or depressive disorder NOS; BDI > 8 | Aerobic = nonaerobic |
| Martinsen et al.[123] | 49 inpatients, 17-60y | (1) Aerobic exercise and occupational therapy; (2) occupational therapy | 9wk; no follow-up | DSM MDD | Aerobic and occupational therapy > occupational therapy |
| McCann & Holmes[124] | 43 college females | (1) Aerobic exercise; (2) muscle relaxation; (3) no treatment | 10wk; no follow-up | BDI > 11 | Aerobic > relaxation = no treatment |
| McNeil et al.[125] | 30 older adults, mean age = 72.5y | (1) Aerobic walking; (2) social contact; (3) wait-list | 6wk; no follow-up | 12 < BDI < 24 | Aerobic walking = social contact > wait-list |
| Singh et al.[126] | 32 participants, 60-84y | (1) PRT; (2) attention-control | 20wk; 21mo follow-up | BDI > 12; DSM-IV MDD, minor depression, or dysthymia | PRT > control |
| Veale et al.[127] study 1 | 83 participants, 19-58y | (1) Aerobic running and routine psychiatric care; (2) routine care control | 12wk; no follow-up | CIS total > 16 and depression severity > 1 | Aerobic and routine care = routine care control |
| study 2 | 89 participants, 19-58y | (1) Aerobic exercise; (2) relaxation/yoga | 12wk; no follow-up | CIS total > 16 and depression severity > 1 | Aerobic = relaxation/yoga |

**BDI** = Beck Depression Inventory; **CBT** = cognitive behaviour therapy; **CIS** = Clinical Interview Scale; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **HRSD** = Hamilton Rating Scale for Depression; **MDD** = major depressive disorder; **NOS** = not otherwise specified; **PRT** = progressive resistance training; **RDC** = Research Diagnostic Criteria; **SCL** = Symptom Checklist.

Klein et al.[121] similarly found aerobic exercise to be as effective in reducing depressive symptoms as psychotherapy. Seventy-four participants meeting RDC criteria for major or minor depression were randomly assigned to one of three treatment conditions: (i) running therapy; (ii) group psychotherapy that included components of cognitive and interpersonal therapies; or (iii) meditation-relaxation therapy. All treatment groups reported significantly reduced symptoms after 12 weeks of treatment; statistical comparisons between groups were nonsignificant. Patients in all groups continued to report symptom reductions at 3- and 9-month follow-up.

Fremont and Craighead[120] also found exercise to be as effective as psychotherapy in treating depressed individuals, but failed to find an additive effect. Forty-nine individuals reporting mild to moderate depressive symptomatology were randomly assigned to one of three treatment groups: (i) a cognitive therapy group; (ii) an aerobic exercise group; or (iii) a combination of cognitive therapy and exercise. All treatment groups significantly improved after 10 weeks of treatment and maintained their improvement at 4-month follow-up; there were no significant differences between treatment conditions. On the other hand, Martinsen et al.[123] found that the combination of psychotherapy and exercise training was more effective in decreasing depressive symptoms than the combination of psychotherapy and occupational therapy. Forty-nine inpatients meeting DSM-III criteria for MDD were randomly allocated to 9 weeks of combination treatment. Mean reductions in depression scores were significantly larger for the exercise training group. The authors noted that patients with a moderate (15 to 30%) or large (>30%) pre-post increase in oxygen uptake experienced a larger antidepressant effect than did participants with a small increase (<15%). Because 9 patients in the exercise group and 14 patients in the control group were taking tricyclic antidepressant medication, this study is limited by the disparity between treatment conditions. Nevertheless, the study suggests that an adjunctive aerobic training programme offers additional benefits to psychiatric patients receiving psychotherapy.

Veale and colleagues[127] examined whether the addition of aerobic training to standard psychiatric care provides added benefit for depressed patients. Eighty-three individuals receiving a total weighted score of 17 or greater, and a depression severity score of 2 or more, on the Clinical Interview Schedule (CIS) were randomly assigned to an aerobic running programme or a usual care control group. At the end of the 12-week trial, exercisers scored significantly lower than controls on the CIS, but not on the BDI. The study had several methodological limitations. First, despite randomisation the control group scored significantly higher on the BDI at baseline. Second, the exercise programme did not adequately improve aerobic fitness, as there were no post-treatment between-group differences in aerobic fitness. Finally, although the study was designed to evaluate exercise as an adjunct to 'standard care', the failure to control other treatments during the study period may have confounded the results; for example, 45% of the exercise group and 34% of the controls were taking antidepressant medication at baseline.

*In summary*, these studies provide inconclusive evidence of the additive value of exercise therapy for depressed patients being treated with standard psychotherapy or psychiatric care.

In order to determine whether the effectiveness of exercise therapy is specific to the effects of physical exertion or is a result of the regular social interaction derived from group exercise, several studies have compared aerobic exercise to social-contact control conditions. McCann and Holmes[124] randomly assigned 43 women who scored more than 11 on the BDI to one of three conditions for 10 weeks of treatment: (i) an aerobic exercise group in which they engaged in strenuous exercise; (ii) a 'placebo' treatment condition in which they performed relaxation exercises in a group; or (iii) a no-treatment control condition. Participants in the exercise group evidenced significant improvements in aerobic capacity and greater reductions in depressive symptoms compared with participants

in the relaxation or no-treatment conditions. McNeil et al.[125] randomly assigned 30 elderly participants to one of three treatment conditions: (i) an experimenter-accompanied walking exercise condition; (ii) a social-contact condition; or (iii) a wait-list control condition. Following treatment, only patients in the exercise condition demonstrated aerobic improvement. Patients in the exercise and social-contact conditions exhibited significant reductions in depressive symptoms relative to wait-list controls. Although the two groups reported a similar magnitude of change, only exercisers reported decreases in the somatic symptoms of depression.

In another investigation of depression in the elderly,[126] 32 individuals (aged 60 to 84 years) with DSM-IV-defined MDD were assigned randomly to either 10 weeks of supervised weightlifting or to an education control condition involving attendance at a series of health lectures. Results indicated a 60% reduction in BDI scores for exercisers compared with a 30% improvement for controls. Individuals in the exercise group then participated in an additional 10 weeks of unsupervised resistance training while controls received no recommendations for exercise. At 20 weeks, reductions in depression were 1.5 to 2.5 times greater for exercisers than for controls.[128] Furthermore, more than 2 years after randomisation, one-third of the individuals in the exercise group were still lifting weights regularly, while no controls participated in resistance training. Moreover, individuals in the exercise group continued to report significantly diminished depression scores on the BDI compared with education controls.[128] *In summary*, two out of three studies found significant benefit for exercise over social contact alone. However, these studies were limited by small sample sizes and, in two of the studies, failure to conduct a follow-up.

A small number of studies have compared the effects of aerobic versus anaerobic forms of exercise for depressed patients. Overall, these studies suggest that increases in aerobic conditioning are not required for the antidepressant effect of exercise. Doyne et al.[119] randomly assigned 40 women with RDC-defined major or minor depressive disorder to 8 weeks of running (aerobic exercise), weightlifting (anaerobic exercise), or wait-list control. Compared with the wait-list controls, both exercise groups significantly reduced depression scores, with no significant differences between exercise conditions. These improvements were maintained through 1-year follow-up with a nonsignificant trend suggesting anaerobic exercise had greater long-term benefit for depression. It is important to note that participants in both exercise conditions did not demonstrate significant improvement in cardiovascular fitness by the end of treatment. Thus, this study does not prove anaerobic exercise to be as beneficial as aerobic exercise in treating depression. Rather, these findings suggest that anaerobic exercise is more effective than wait-list control.

Veale and colleagues[127] extended a study reviewed above by recruiting 15 additional patients for the aerobic exercise group and 26 patients for a low-intensity exercise comparison group (consisting of relaxation, stretching, and yoga exercises), for a total of 89 patients in the two exercise conditions. It is unclear if patients selected during the second wave of recruitment were randomly assigned to treatment. Following 12 weeks of treatment, there were no significant between-group differences in CIS or BDI scores. However, there also was no significant difference between the exercise conditions in post-treatment maximum oxygen uptake, raising concerns about the adequacy of the training stimulus. Moreover, the findings are limited by an unequal proportion of exercise participants being prescribed anti-depressant medication at baseline (41.2% of aerobic exercisers and 11.5% of low-intensity exercisers).

Martinsen et al.[122] randomly assigned 99 inpatients with MDD, dysthymic disorder or depressive disorder not otherwise specified and a BDI score of 9 or more to 8 weeks of thrice-weekly aerobic exercise or resistance training. In contrast to the studies of Doyne et al.[119] and Veale et al.,[127] only the aerobic group displayed a significant increase in maximum oxygen uptake on post-treatment ex-

ercise testing. Nevertheless, the two groups reported equivalent reductions in depressive symptoms. Although the lack of between-group differences in these studies suggests that the antidepressant effect of exercise occurs independent of change in aerobic capacity, the lack of a no-exercise control group limits interpretation of the results.

Few studies have examined the effectiveness of exercise training compared with standard antidepressant medications. In a study reviewed above,[123] 9 of 24 patients in an aerobic training group and 14 of 19 controls were receiving tricyclic antidepressants during the trial. Responders were defined as having at least a 50% reduction in the baseline BDI score.[129] All 6 responders in the control group were receiving antidepressant medication, while 5 of the 15 responders in the exercise training group were taking antidepressants. These results may be interpreted to suggest that exercise and medication were no more efficacious than exercise alone. In another study,[122] 14 patients in each exercise group received tricyclic antidepressant medication. There was a nonsignificant trend favouring the combination of exercise and medication over exercise alone.[130] Because participants were not randomised to medication, these studies do not adequately evaluate the effect of combining antidepressant medication and exercise training.

To date, there has been published only one randomised controlled trial designed to compare exercise training with antidepressant medication. Blumenthal et al.[118] randomly assigned 156 middle-aged and older adults with DSM-IV MDD to one of three treatment conditions: (i) aerobic exercise training; (ii) standard pharmacotherapy (sertraline); and (iii) a combination of these treatments. After 16 weeks of treatment, groups did not differ significantly on percentage remitted, self-reported depression severity (BDI), or clinician-rated depression severity (HRSD). All treatment conditions demonstrated statistically and clinically significant reductions in depression. At 6-month follow-up, individuals who remitted with exercise alone exhibited significantly lower relapse rates than remitted individuals in the medication or combination groups.[131] Furthermore, there was an association between exercising during the follow-up period (regardless of initial treatment group) and reduced risk of depression diagnosis at 6 months post-treatment, such that 50 minutes of exercise per week was associated with a 50% reduction in risk. This study was limited by the absence of a no-treatment control group and by the fact that the exercise was conducted in a supervised setting, so that the effects of exercise may have been confounded by social support.

Although many individuals prefer to exercise on their own rather than in supervised settings,[132] few studies have examined unsupervised exercise training. By comparing supervised exercise to home-based exercise, researchers can separate the effects of exercise from those of social support. We are currently conducting a randomised, placebo-controlled study comparing the antidepressant efficacy of supervised exercise, home-based exercise, and medication in middle-aged and older adults with MDD.[133]

*In summary*, the reviewed research suggests that exercise treatment is more effective in treating depression than no treatment, and is as effective as psychotherapy and antidepressant medication. However, the majority of studies suffer from significant methodological shortcomings. These conclusions are consistent with three recent meta-analyses.[134-136] In the most recent meta-analysis, Lawlor and Hopker[135] found that exercise was associated with a greater reduction in depressive symptoms when compared with no treatment, and was as effective as cognitive therapy. However, because of the poor quality of much of the evidence reviewed, they concluded that the effectiveness of exercise in reducing symptoms of depression could not be determined.

## 3. Hypothesised Mechanisms of Action

A variety of biological and psychosocial pathways have been hypothesised to mediate the antidepressant effects of exercise. Several hypothesised mechanisms of action are considered: central monoamines, regulation of the hypothalamic-pituitary-

adrenal (HPA) axis, increased β-endorphin levels, and improved self-evaluations. It should be noted that the evidence to date is derived from studies that investigated the relationship between these variables and either depression or exercise. We could locate no published reports of direct investigations of the causal pathway in depressed patients successfully treated with exercise training. Furthermore, several studies cited in this section have made inferences about MDD using samples defined by self-reported elevated depressive symptomatology; as previously discussed, this is not a precise method to diagnose MDD.

### 3.1 Physiological Mechanisms

Central monoamines – especially serotonin, noradrenaline and dopamine – have long been implicated in the aetiology of major depression.[137-139] Whereas early theories posited that a simple deficit in the levels of these neurotransmitters underlies depressive disorders, more current theories emphasise the complexity of the underlying mechanism, including the role of monoamines in the functioning of specific brain regions[140] and in treating subsets of depressed patients.[141,142]

If dysregulations in central monoamine systems trigger or maintain MDD, a successful treatment might work by correcting these imbalances. Indeed, there is a growing body of evidence to support the hypothesis that exercise affects central monoamine functioning in a manner relevant to MDD. For example, animal studies have suggested that exercise affects central nervous system (CNS) noradrenaline levels and metabolism generally,[143] and in specific brain regions related to stress reactivity[144] and learned helplessness.[145] However, as discussed in a recent review,[144] these studies have often involved forcing animals to exercise. The stress caused by forced exercise may create a confound, limiting the ability to measure the effects of exercise alone. At the same time, human data have been limited because of the impracticality of obtaining CNS samples from humans. Indeed, much of the research in humans relies on indirect evidence from plasma data, the effects of antidepressant medications, and monoamine-depletion studies. Although plasma data available from humans provide poor estimates of CNS amine levels, these studies did find that exercise is associated with increases in plasma monoamine levels.[146-150] In addition, research in humans has shown that exercise increases basal free fatty acids and free tryptophan levels, which could increase the rate of synthesis of serotonin by increasing the CNS availability of its amino acid precursor.[151] Thus, there is ample evidence that MDD is associated with altered central monoamine functioning, and preliminary evidence that exercise may affect this pathway.

In a similar vein, imbalances in HPA axis functioning (a neuroendocrine reaction to stress) have been linked to depression. Indeed, it is well established that depressed patients tend to exhibit higher baseline basal cortisol levels[152,153] and nonsuppression of endogenous cortisol secretion following dexamethasone (a ligand of glucocorticoid receptors) administration, providing an overall picture of HPA axis hyperactivity in depression.[154,155]

Because HPA axis imbalances are implicated in the pathophysiology of depression, interventions that reduce depression may do so by targeting this mechanism. Indeed, whereas depression is generally marked by hyperactivity of the HPA axis, exercise training can lead to an attenuation of the HPA axis response to stress. In a review, Dienstbier[156] summarised the pertinent animal studies by stating that exercise training resulted in physiological 'toughness' marked by a delay in the HPA axis response to stress. Research in humans has been largely consistent with the 'toughness' model. Exercise-trained individuals exhibit a hyposensitive HPA axis response to exercise challenge[157,158] and mental stress.[159] This suggests that exercise may reduce depression, in part, by regulating the HPA axis response to stress. However, it is important to note that not all depressed patients show HPA axis hyperactivity. In fact, according to a recent review, although approximately half of patients with MDD show hyperactivity of the HPA axis, others (especially older adults and women)[152] actually show

hypoactivity.[160] Additionally, there is emerging evidence of a complex interplay of HPA axis functioning and biogenic amines.[161-163] Future research might evaluate the effectiveness of exercise training in subgroups of depressed patients defined by the presence or absence of HPA dysregulation at study entry.

The role of β-endorphin, an endogenous opioid, in exercise treatment for depression has also been considered. It is well known that exercise leads to a surge of β-endorphin released into the blood stream to calm the sympathetic nervous system and provide analgesic relief from pain associated with strenuous exercise. Preliminary support for the hypothesis that β-endorphin surges mediate the antidepressant effects of exercise is provided by studies showing that post-exercise mood elevations are associated with increases in basal β-endorphin levels[164] and are attenuated with the administration of naloxone (an opioid antagonist).[165] Furthermore, evidence from animal studies suggests that exercise may affect CNS β-endorphin levels for 2 to 3 days.[166]

Although there is evidence that post-exercise β-endorphin surges are associated with short-term mood improvements, the link between β-endorphin levels and MDD is less clear. In fact, in an exercise trial of nonclinically depressed human participants, decreases in depressive symptomatology were accompanied by decreases in plasma β-endorphin levels.[167] Indeed, it appears that there is either no relationship[168,169] or a positive correlation between severity of depression and β-endorphin levels,[170] suggesting that β-endorphin may be best interpreted as a marker of stress in MDD patients. Thus, post-exercise β-endorphin surges may cause short-lived mood improvements, but it seems less certain that they mediate the relationship between exercise and sustained relief from MDD.

### 3.2 Psychosocial Mechanisms

There is a well established link between depression and negative self-evaluations, including lowered self-esteem[171,172] and self-efficacy.[173-176] In fact, prospective data suggest that negative self-evaluations may play a causal role in MDD.[173,174] It has therefore been hypothesised that effective depression interventions work by improving self-evaluations. Indeed, research suggests that exercise affects both global self-evaluations (such as overall self-esteem)[118,177,178] and domain specific self-evaluations (such as exercise self-efficacy,[179] body image,[177,179,180] and physical self-worth).[181] This suggests that the antidepressant effects of exercise may be mediated by improved self-evaluations.

There are several other psychosocial mechanisms that have been linked to depression that are promising targets for future research in this area. For example, a response style that favours distraction from negative emotion (as opposed to rumination or repetitive analytical focus on one's negative feelings) is associated with a more favourable prognosis for depression; exercise may be a means of distraction.[182,183] In addition, exercise may be a form of behavioural activation, which is a key component of some effective psychotherapies for depression.[184] Others have theorised that the social reinforcement that new exercisers may receive may have a beneficial effect.[185]

## 4. Exercise Adherence

Across a number of patient and nonpatient study samples, only 50% of individuals who initiate an exercise-training programme complete it.[186] Recent reviews [186,187] have found the following individual-level factors to be associated with improved exercise adherence: attitudes towards the value and importance of exercise; perceived behavioural control (i.e. an individual's belief of how easy or difficult it will be to perform the behaviour); self-efficacy (i.e. the belief that one can successfully perform a desired behaviour); exercise intention; early exercise experiences and recent involvement in physical activity; physical condition (e.g. greater cardiorespiratory endurance; faster psychomotor speed; less illness); knowledge about fitness and exercise; and perceived social support/encouragement to exercise. These psychosocial factors can be conceptually integrated using the Transtheoretical Model of Behavior Change

(TM). The TM was initially developed to describe smoking behaviour,[188] but has been adapted to the study of exercise adherence.[189] Briefly, the TM postulates that individuals move back and forth through five stages of change – pre-contemplation, contemplation, preparation, action and maintenance – before establishing a stable behaviour pattern (e.g. regular exercise). 'Processes of change' (e.g. reinforcement, helping relationships, self re-evaluation) are the mechanisms that facilitate movement between stages. A series of intermediate measures, such as self-efficacy and attitudes, are sensitive to progress through the stages of change.

As with pharmacotherapy and psychotherapy, depressed patients must complete an adequate trial of exercise in order to derive therapeutic benefit (although the necessary 'dose' and duration have not yet been determined). Furthermore, continued exercise after remission of MDD may be an important prophylaxis against relapse.[131] Thus, clinicians who prescribe exercise training for depressed patients would do well to understand, evaluate, and work to enhance patient characteristics that are associated with exercise adherence.

## 5. Conclusions and Future Directions

This paper reviewed the evidence that exercise training reduces depression in healthy and clinical populations. In a review published in *Sports Medicine* over a decade ago, Martinsen[190] concluded that exercise represents 'a promising new approach in the treatment of nonbipolar depressive disorders of mild to moderate severity' (page 388). However, in their recent meta-regression analysis of randomised trials, Lawlor and Hopker[135] concluded that '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' (page 1). It would appear that this assessment is a bit harsh, insofar as there are many studies that, taken together, offer considerable evidence for the benefits of exercise in reducing depression in clinical populations. However, it also is true that there are limited data from well designed clinical trials, which are often considered the gold standard for evaluating the effectiveness of a new therapy. Indeed, over the past decade only three randomised clinical trials[118,125-127] of exercise as a treatment for depression have been published, and only one[118,131] included both an adequate sample size and sufficient follow-up. Because of the limited data currently available, it could be stated that if the prescription of exercise for MDD required approval from the Food and Drug Administration, it probably would not pass current standards. Therefore, clearly one major priority for future research is to determine if exercise *is* effective in treating patients with MDD. More specifically, it will be important to determine what *kinds* of exercise, over what *duration* and at what level of *intensity* are effective for *which* individuals.

Furthermore, there are a number of additional directions for future research in this area:

(i) *Focus on underserved and understudied populations*. Most previous research has focused on younger and middle-aged Caucasian adults. Future research should target the elderly, minorities, children, and individuals from rural areas.

(ii) *Environmental and social issues*. Previous research has generally focused on the effects of supervised exercise in medical school or university settings. In order to generalise to more 'real world' environments, it will be important to examine the use of exercise to prevent or treat MDD in schools, work settings, and in the general community. The value of home-based versus supervised exercise is only currently being addressed empirically.[133]

(iii) *Technological advances*. Exercise interventions have generally failed to incorporate recent advances in technology. Ambulatory activity monitors, internet-based programmes, and personal data assist devices (e.g. Palm Organizers) offer considerable promise to monitor and enhance exercise adherence and monitor therapeutic response. Inclusion of these strategies in clinical trials would be potentially very worthwhile.

(iv) *Tailoring treatment*. The identification of which individuals will benefit from exercise has not been critically evaluated. This is especially important insofar as 40% of patients may not respond to exercise training. Although there have been some recent attempts to identify predictors of response to exercise,[191] being able to identify which individuals are most likely to benefit from exercise therapy is a high priority for future research in this area.

(v) *Mechanisms*. A number of plausible behavioural, social, psychological and physiological mechanisms by which exercise may reduce symptoms of depression have been suggested, but few mechanisms have been systematically examined. Identification of the mechanisms by which exercise is effective may help to refine exercise prescriptions to maximise its effectiveness, and to identify subgroups of depressed patients who are most likely to respond to exercise treatment.

(vi) *Well controlled experimental designs*. Additional studies employing randomised designs with appropriate controls and an adequate sample size will be critically important in further evaluating the short-term benefits of exercise for individuals with MDD. Furthermore, studies with longer follow-up intervals are needed to establish the long-term antidepressant effects of exercise training. As previously reviewed, individuals with MDD are at high risk for relapse, especially when treatment is discontinued. Thus, it will be important to determine if patients are able to maintain exercise over extended periods of time, and if continued exercise lowers the risk of relapse of MDD. There is preliminary evidence[131] that patients treated with exercise have a lower risk of relapse (9%) than do patients treated with antidepressant medication (over 30%), and that continued exercise over a 6-month follow-up period may be associated with a 50% reduction in the risk of relapse.

(vii) *Prevention*. Epidemiologic studies[60] have suggested that exercise may reduce the risk of elevated depressive symptomatology in general population samples. However, no studies have examined the prophylactic effects of exercise training in individuals who may be vulnerable to MDD (e.g. individuals with a family history of MDD; patients who are not currently depressed, but who have a history of MDD). Future investigations might evaluate the effectiveness of exercise in preventing the onset of MDD.

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