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Physical Exercise for Treatment of Mood Disorders: A Critical Review

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Abstract

Purpose of the review—The purpose of this review is to critically assess the evidence for exercise as an adjunct intervention for major depressive disorder and bipolar disorder, chronic conditions characterized by frequent comorbid conditions as well as interepisodic symptoms with poor quality of life and impaired functioning. Individuals with these mood disorders are at higher risk of cardiovascular disease and premature death in part because of increased rates of obesity, inactivity, and diabetes mellitus compared to the general population. Exercise may not only mitigate the increased risk of cardiovascular disease, but could also potentially improve the long term outcomes of mood disorders.

Recent findings—We conducted a literature review on the impact of exercise on mood disorders and associated comorbid conditions as well as possible biological mechanisms. We found that exercise impacts both the physical health parameters of mood disorders as well as mental health outcomes. Exercise also positively impacts conditions frequently comorbid with mood disorders (i.e. anxiety, pain, and insomnia). There are multiple candidate biomarkers for exercise, with brain-derived neurotrophic factor and oxidative stress as two main promising components of exercise's anti-depressant effect.

Summary—Exercise appears to be a promising adjunct treatment for mood disorders. We conclude with recommendations for future research of exercise as an adjunct intervention for mood disorders.

Keywords

Bipolar disorder; depression; mood disorders; exercise; cardiovascular disease; adjunctive intervention

Introduction

Major depressive disorder (MDD) affects approximately 16.6% of U.S. adults in their lifetimes and bipolar disorder has a lifetime prevalence of 2.1% in U.S. adults [1, 2]. Both MDD and bipolar disorder are marked by high rates of medical and psychological comorbid conditions as well as functional impairment [2–5]. At least 64.1% of patients with MDD have another comorbid psychiatric diagnosis, and primary care patients who have MDD have also reported an average of two to three concurrent chronic medical illnesses, which is approximately double those without depression [4, 5]. Similarly, in a national epidemiological study, Merikangas and colleagues found that 92.3% of bipolar individuals have a comorbid psychiatric diagnosis and 58.8% have a comorbid medical diagnosis [2]. More specifically, Forty and colleagues found that the most prevalent comorbid medical conditions of MDD and bipolar disorder are: migraines, asthma, elevated lipids, hypertension, thyroid disease and osteoarthritis [6]. Individuals with MDD and bipolar disorder also have a higher incidence of cardiovascular disease, diabetes, and metabolic syndromes, due in part to less engagement in physical activity and more sedentary behavior as well as medication side effects (e.g., weight gain) [7–15]. These risk factors lead to earlier and higher rates of mortality for individuals with MDD and bipolar disorder compared to the general population [16]. Moreover, despite major pharmacological advances in the treatment

of MDD and bipolar disorder, as many as 19–34% of depressed patients and 30–35% of patients with bipolar disorder do not achieve remission [17, 18]. Medications used to treat severe mood disorders, such as quetiapine and lithium, are often associated with weight gain [12]. Thus, alternative augmentation strategies that target mental and physical health would be desirable. Exercise represents a cost-effective and easily disseminated intervention that includes the benefits of minimal side effects and improved physical and mental health.

The data on the efficacy of exercise as an intervention for MDD and bipolar disorder have yielded effect sizes comparable to medications [19–23]. Given the high rates of partial and non-response to pharmacological treatment and the need to improve mental and physical health outcomes, exercise may be particularly helpful for serving as an adjunctive treatment option for individuals with MDD, treatment-resistant depression, and bipolar disorder. Preliminary research also reports the benefits of exercise augmentation strategies added to cognitive-behavioral therapy for anxiety disorders or treatment as usual for depression [24, 25].

While there are some promising initial findings for bipolar disorder, there is a paucity of well-controlled studies investigating the efficacy of exercise as an intervention strategy, as well as studies investigating the pathways by which exercise may exert its effects on mood [22, 26–28]. Preliminary studies indicate its acceptability, feasibility, and efficacy for depression, bipolar disorder, and anxiety [19–22, 26–28]. In summary, exercise is an established adjunct treatment of depression with promise as an effective treatment for bipolar disorder adjunctive to mood stabilizing medication because of its broad-reaching effects on mental and physical health outcomes.

In this review, we summarize findings from studies demonstrating the role of exercise in the treatment of MDD and bipolar disorder as well as comorbid conditions. We define exercise broadly in our review given the paucity of data and the lack of consistency in the field. Specifically, exercise in this review includes anaerobic (e.g., strength training) as well as aerobic exercise (e.g., walking, cycling, running, swimming) [24, 25, 29–33]. Moreover, all forms of exercise, whether anaerobic or aerobic, light or vigorous intensity, have been shown to have positive benefits, so we included both anaerobic and aerobic types of physical activity in defining exercise [24, 25, 29, 30, 32, 34]. We also discuss potential mechanisms of exercise. Finally, we propose future directions and examine clinical implications for exercise in the treatment of mood disorders.

Exercise for Major Depressive Disorder (MDD)

MDD is the leading cause of disability for individuals ages 18 to 44 in the United States and the third greatest cause of disease burden worldwide [35]. Even with adequate pharmacological and psychosocial interventions, the rate of relapse, quality of life, and functioning often remain impaired for individuals with MDD [3, 18, 36]. Thus, new, adjunctive treatments, such as exercise, to improve depression and its comorbid conditions are needed [20, 37].

Exercise has demonstrated moderate to large effect sizes for improving depressive symptoms, suggesting exercise may be an effective adjunct treatment [19–21, 38, 39]. Randomized clinical trials have also reported that exercise improves outcomes in treatment-resistant depression, depressed patients with a chronic medical illness, and women with antenatal depression [29, 40, 41]. Another trial randomized participants with MDD to group cognitive behavioral therapy plus home-based walking program or group cognitive behavioral therapy plus educational sessions. They found that the group cognitive behavioral therapy plus a walking program improved depression, anxiety, and stress more than the control group [24].

Studies have also found that physical activity reduces the symptoms of depression as effectively as cognitive-behavioral therapy (CBT), pharmacotherapy, and even bright light therapy in individuals with MDD [23, 42, 43]. For example, a recent study randomized participants to either supervised exercise in a group setting, home-based exercise, antidepressant medication (sertraline, 50–200 mg daily), or placebo for 16 weeks [23]. After 16 weeks of treatment, participants receiving active treatments tended to have higher remission rates than the placebo controls and those receiving supervised exercise had similar remission rates to that of antidepressants (i.e., supervised exercise = 45%; home-based exercise = 40%; medication = 47%; placebo = 31%). Similarly, a second study found that when compared to a sedentary control group, the patients randomized to an aerobic exercise group required a lower dosage of sertraline than did the individuals in the sertraline monotherapy treatment condition [30].

There have only been a few studies that have reported the effects of adding exercise to psychological treatments of depression. Previous reviews and meta-analyses have also raised concerns over the methodological quality of existing studies examining the effects of exercise on depression. Specifically, these reviews and meta-analyses noted overestimation of treatment effects, and lack of long term follow-up data as limitations to the existing literature [20, 38, 39]. Adherence rates for exercise-based interventions are comparable to those found in pharmacotherapy and other psychotherapeutic treatments, but still remain low. Another limitation of adjunctive exercise is that there appears to be many possible biomarkers of exercise that likely interact with one another, which makes interventions that target exercise challenging. It is also challenging to engage depressed individuals in exercise interventions, particularly those with anhedonia, given the lack of interest and motivation inherent in this condition [44, 45]. Thus, future research of adjunct exercise interventions should include randomized clinical trials with strong methodological designs and control groups, biological outcome measures, and examination of moderating variables (to identify those who may benefit most from these interventions).

Exercise for Bipolar Disorder

Bipolar individuals are more likely to lead a sedentary lifestyle [13–15]. They experience higher levels of pain when exercising, have lower exercise capacity, and engage in less overall physical activity because they perceive exercise to be aversive [46]. Low levels of exercise have been linked to poorer quality of life, worse functioning, and more depressive symptoms [28, 47]. Regular physical activity and higher levels of cardiorespiratory fitness in

individuals with bipolar disorder are associated with lower risk for premature mortality. Additionally, exercise training has also been demonstrated to improve a number of important risk factors, such as cardiorespiratory fitness, weight, and high-density lipoprotein cholesterol level, which has been implicated as a risk factor for diabetes due to its potential association with insulin insensitivity [48]. Given that individuals with bipolar disorder tend to be physically inactive, they are at greater risk for physical as well as mental health complications. This suggests that exercise may have a dual benefit for individuals with bipolar disorder [15].

Results from open trials of exercise as an adjunctive intervention for bipolar disorder show that it may benefit the physical and mental health of individuals with bipolar disorder. However, to date, no controlled randomized trials have been conducted. For example, these open trials have found that more engagement in exercise was associated with less depressive symptoms, better quality of life, increased functioning as well as less psychiatric comorbidity [22, 49, 50]. Furthermore, dehydroepiandrosterone sulfate (DHEAS), a physiological biomarker, which along with cortisol is implicated in the positive effects of exercise on mood and perceptions of well-being, increased following a bout of 20 minutes of acute exercise in 26 bipolar patients [51].

Only a few studies have investigated the effects of exercise interventions on the symptoms of bipolar disorder. One such study was a retrospective cohort pilot study conducted in an inpatient setting that aimed to identify the utility of an adjunctive walking group for bipolar individuals over the course of 24 months. After exercising, patients who participated in the group had lower levels of depression, anxiety, and stress [26]. An acute bout of exercise (i.e., walking on a treadmill for 20 min at 70% of the individual's maximum heart rate) also significantly improved the mood of bipolar participants [26]. Individuals with bipolar disorder who participated in an exercise program (i.e., eight 30 min walking sessions) had better perceptions of stress reactivity to an acute stressor as well as reduced physiological reactions to stress [52].

In response to the lack of randomized controlled trials examining an exercise-based intervention for bipolar patients, Sylvia and colleagues developed a 20-week cognitive-behavioral intervention for bipolar disorder consisting of three modules: nutrition, exercise, and wellness [28]. Over the course of treatment, participants showed improvements in exercise, nutritional habits, depressive symptoms, and overall functioning [28, 53]. This study provides preliminary data that exercise is acceptable, feasible, and associated with functional improvement of bipolar patients.

Exercise and Comorbid Conditions with Mood Disorders

Studies have also explored the positive effects of exercise on highly comorbid conditions with mood disorders, such as sleep, anxiety, and pain. The high rates of disturbed sleep, anxiety, and pain in mood disorders may indicate that interventions useful in improving these symptoms may also improve the course and functioning of individuals with mood disorders.

Sleep

Sleep disturbance, consisting of insomnia (a subjective perception of inadequate sleep) and sleep deprivation (an objectively measured decrement in sleep), is associated with both manic and depressive episodes [54]. For example, Harvey and colleagues found that 69–99% of patients experienced decreased need for sleep during manic episodes and 23–78% reported hypersomnia when depressed [54]. Rates of insomnia during mood episodes vary greatly with up to 97% of patients experiencing difficulties falling asleep or staying asleep during manic episodes [54]. These data reflect the prevalence of comorbid sleep disturbance amongst individuals with MDD or bipolar disorder. One potential explanation for the high degree of sleep disruption amongst individuals with MDD or bipolar disorder and its social impact is the social zeitgeber theory. This theory states that stress causes disruptions in social, daily routines (e.g., meals, exercise, sleep schedule) which disrupt circadian biological rhythms (e.g., body temperature, hormones). These disruptions may trigger episodes of mania or depression [55]. Studies have found that exercise is a key zeitgeber, or time cue, that helps to entrain other social rhythms [56, 57]. Thus, exercise could help to stabilize one's routines by both entraining rhythms, such as sleep, as well as improving sleep quality [58]. Additionally, previous research has shown that exercise is associated with fewer night time awakenings and less time spent in stage 1 sleep, thus improving sleep quality [59]. Data has also found that sleep disruptions are associated with changes, or reductions, in one's exercise routine [60].

A recent meta-analysis of 66 studies reported small to moderate effects on the positive benefit of both acute and regular exercise on sleep disturbance in non-clinical populations, suggesting that it may be useful to further investigate whether this positive benefit of regular exercise on sleep would also exist in clinical populations (e.g., mood disorders) [61] Most importantly, effect sizes for improvement in insomnia in this study were comparable between those who engaged in regular exercise and those taking pharmacological and receiving psychological interventions for insomnia. A study on resistance and aerobic exercise training in women with generalized anxiety disorder (often comorbid with primary mood disorders) found that participants reported improved sleep initiation and continuation after six weeks. Furthermore, there was a significant relationship between generalized anxiety disorder clinical severity rating scores and sleep efficiency [62]. Given these preliminary findings on the benefits of exercise for sleep in anxiety disorders and insomnia, exercise may also be beneficial for sleep disturbance in mood disorders given the high rates of comorbid anxiety [4, 63–66]. However, few rigorous studies have investigated the impact of exercise on sleep in psychiatric populations, and, thus, this requires further investigation.

Anxiety

Anxiety is prevalent in both individuals with MDD as well as those with bipolar disorder, with over half of individuals with MDD and 88% of individuals with bipolar disorder having a lifetime comorbid anxiety disorder [2, 4, 63, 65, 66]. In individuals with primary MDD, comorbid anxiety disorders negatively impact treatment outcome and are related to increased impairment, symptom severity, and incidence of suicide [66]. In individuals with primary bipolar disorder, comorbid anxiety disorders are associated with lower quality of life, poorer functioning, and greater likelihood of suicide attempts [63]. Furthermore, panic disorder has

been linked to a higher risk of cardiovascular events, thereby increasing mortality in this clinical population [67]. This increased risk is particularly concerning as only 14% of individuals in the general population report exercising regularly to reduce stress, highlighting the tendency for people to not exercise when anxious and further increasing cardiovascular risk in individuals with anxiety disorders [68].

Given these data, exercise has the potential to dually (i.e., mental and physical health outcomes) benefit individuals who have a mood disorder and comorbid anxiety. There have been several studies that have concluded that exercise is an effective adjunctive treatment for anxiety [21, 24, 69–73]. Specifically, exercise was as effective as psychotherapy in the treatment of anxiety and nearly as effective as pharmacotherapy. Broocks and colleagues found similar results in a randomized controlled study of exercise compared to clomipramine or placebo in 46 outpatients with panic disorder [71]. In particular, exercise was more effective than placebo in alleviating anxiety and depressive symptoms, but was not as effective as clomipramine [71]. Another study found that exercise was an effective adjunctive treatment to group CBT for anxiety with the most pronounced effects in patients diagnosed with social phobia [24]. In summary, there is strong evidence supporting the use of adjunctive exercise interventions for the treatment of comorbid anxiety in individuals with mood disorders.

Pain

Pain (e.g., migraines, chronic pain) is not only associated with functional limitations, poor physical health, higher unemployment, and more frequent doctor visits, but it is also associated with more severe depression [74]. Individuals with primary diagnoses of mood disorders will often also report experiencing some type of secondary pain concerns [74]. Specifically, approximately 65% of depressed patients and 29% of bipolar patients report experiencing pain (e.g., migraine, chronic pain) [74, 75]. In bipolar disorder, perceptions of physical health, including bodily pain, physical functioning, and general health, are associated with worse course of illness [76]. This finding highlights that pain is considered a primary and important component of one’s physical health in mood disorders and demonstrates the importance of a treatment that targets mental and physical health outcomes in this clinical population.

Evidence suggests that exercise may accomplish this dual effect by mitigating feelings of pain and reducing depressive symptoms, as well as improving both physical and mental health outcomes. Studies conducted on exercise for fibromyalgia may provide important information about the effects of exercise on pain that can be extended to mood disorders given that fibromyalgia is frequently associated with depression, anxiety, and posttraumatic stress disorder [77, 78]. For example, Ellingson et al. found that a short session of moderate intensity cycling mediated pain modulation in patients with fibromyalgia [31]. Similarly, a 12-week randomized controlled trial in women diagnosed with fibromyalgia found that swimming and walking significantly reduced pain and improved functioning and quality of life [33]. Given the promising data on exercise as a treatment for pain in individuals diagnosed with fibromyalgia, exercise warrants further investigation as an adjunctive treatment for mood disorders that could specifically improve comorbid pain.

Possible Mechanisms of Exercise on Mood Disorders

Several mechanisms have been proposed for the antidepressant effects of exercise, which can be divided in two categories: psychological and biological. Psychological variables include increased autonomy, physical wellbeing, enhanced quality of life, or increased self-esteem and mood [79, 80]. In this review, we opted to review the most promising biological causes of exercise given the burgeoning literature in this area. Specifically, key biological variables include several growth factors (e.g., brain derived neurotrophic factor; BDNF), oxidative stress, and genetics as they have been implicated in the role of exercise-induced neurogenesis and its antidepressant effects [27, 81–90].

Brain Derived Neurotrophic Factor (BDNF)

Data suggests that multiple neuromodulators may explain the antidepressant properties of exercise, yet most of the recent work has focused on the role that BDNF has on exercise for several reasons. First, BDNF supports neurogenesis and the survival and growth of many types of neurons. It is a primary modulator of several neurotransmitters and plays a key role in neuronal survival and synaptic strength [88]. BDNF enhances brain plasticity and could be involved in improving cognition by enhancing learning and memory functions of the hippocampus (i.e., memory consolidation, storage, and long-term memory) [91, 92]. Thus, BDNF resembles the neuroprotection observed from lithium treatment. Lithium decreases gene expression of the protein, GSK3, which increases levels of neuroprotective proteins, such as BDNF. Thus, BDNF may be a crucial mediator in the neurochemical pathway linking lithium with neuroprotection, or increase in grey matter density, in the anterior cingulate gyrus and the hippocampus [93, 94].

Second, BDNF may be an important biomarker as antidepressant medications up-regulate BDNF [95]. BDNF also enhances the effect of antidepressants in animal models, suggesting that antidepressants and BDNF may operate through similar neurochemical pathways [96]. BDNF mimics the effect of antipsychotic drugs on the expression of dopamine receptors in the brain, suggesting that it may reduce manic or elevated mood [97]. MDD patients exhibit lower levels of BDNF than their healthy counterparts, and higher levels of BDNF have been associated with fewer depressive symptoms as well as better cognitive functioning [98–100]. BDNF has also increased following acute and longer programs of exercise; however, some studies report no difference [101–103]. A meta-analysis noted a moderate effect size for increases in BDNF following a single session of exercise and a more pronounced pre- to post-exercise effect following a longer program of regular exercise [104]. Finally, exercise, similar to antidepressants, upregulates BDNF mRNA levels in the hippocampus [105]. BDNF has shown the most robust changes as a result of exercise manipulations [88, 106].

These findings suggest that BDNF may be a viable mechanism by which exercise exerts effects on mood [27]. Subsequent studies should identify the effect of both acute and regular exercise on pre- to post-exercise enhancement of BDNF as well as the effect on resting BDNF levels. Taken together, these data suggest that BDNF may be a primary mechanism of the antidepressant effects of exercise. However, future research is needed as it is likely that BDNF works in conjunction with (and is impacted by) several other signaling pathways.

Oxidative Stress

Evidence suggests that there is mitochondrial dysfunction and abnormal oxidative stress in individuals with MDD or bipolar disorder [83, 85, 86, 107–118]. Mitochondria regulate energy production and generation of ATP through the mitochondrial electron transport chain (ETC). During this process, reactive oxygen species (ROS) are produced, which can lead to oxidative stress and cellular damage, particularly in the absence of antioxidant defenses [117, 119]. Dysfunctional mitochondria can result in neuronal damage via multiple mechanisms: decreased ATP production, oxidative damage of membranes and DNA, abnormal calcium sequestration, and apoptosis [114, 117, 119].

Exercise may impact oxidative stress. This would have clear implications for mood disorders in which there are increases in inflammation and oxidative stress [116, 117, 120]. Specifically, Agarwal et al. found that 16 weeks of moderate-intensity exercise decreased oxidative stress and reduced proinflammatory cytokines in control and hypertensive rat models [121]. However, other studies have found increases in oxidative stress after exercise, particularly in higher intensity exercise [122, 123]. Thus, further research should be conducted to explore the relationship between exercise and oxidative stress in individuals with MDD or bipolar disorder [27, 32, 88, 89, 120, 124].

Epigenetics

Epigenetic changes are modifications to gene expression that do not involve changes in the nucleotide sequence [125]. Even though epigenetic changes do not affect the nucleotide sequence, these changes can persist through multiple cell divisions and across generations [126]. Recent research has indicated that BDNF is upregulated through epigenetic changes. For example, Gomez-Pinilla and colleagues observed increases in rat hippocampal BDNF mRNA and protein through mechanisms of epigenetic regulation after one week of voluntary exercise [87]. Researchers have posited that exercise promotes epigenetic changes, thus promoting homeostasis, including neural plasticity, circadian rhythms, and endocrine and immune regulations [127]. Other investigators have proposed that the epigenetic changes produced through exercise, which they call “eustress” or good stress, can reduce the aging process and have beneficial effects on the musculoskeletal system across the lifespan [128]. Based on recent research, it is possible that exercise is associated with epigenetic changes that are beneficial for individuals with mood disorders [27].

Conclusions

This review suggests that exercise may be an acceptable and feasible alternative or adjunctive intervention to enhance mood, functioning, and comorbid conditions for individuals with MDD or bipolar disorder. The literature suggests that exercise is beneficial as an adjunctive intervention for depression; however, few rigorous studies have been conducted with exercise as an adjunct to treatment as usual, especially for bipolar disorder. For this reason, we included all forms and intensity of exercise in this review, but it is also important to note that not all exercise has the same positive effect. For example, aerobic exercise is typically considered more effective for improving cardiovascular health, increasing well-being, and managing chronic conditions such as diabetes mellitus [34, 129],

while anaerobic exercise has particular benefit for improving respiratory fitness and reducing oxidative stress, and fatigue [32]. Further research is needed to determine the most effective type, duration, and intensity of exercise for individuals with mood disorders, but it is likely that a balance between aerobic and anaerobic exercises would provide the most health benefits. For example, given that mood disorders are characterized by lack of interest and motivation, it may prove beneficial in psychiatric populations to begin an exercise regime that is less extensive than what is currently recommended by the American College of Sports Medicine (5 days a week of at least 30 minutes of moderate to vigorous physical activity) [130].

Future studies should also examine personalized exercise augmentation strategies to both pharmacological and psychological treatments for MDD and bipolar disorder, or strategies based on specific moderators and mediators of outcomes. It is likely that different individuals will benefit greater from (or will be more likely to adhere to) specific types and duration of exercise and thus, developing treatment algorithms based one's demographic and clinical features would maximize treatment efficacy. Further research is also warranted to elucidate the specific mechanisms of action by which exercise improves mood. We highlight a few key pathways (BDNF, oxidative stress, and epigenetics) that have been peripherally demonstrated in clinical trials, but it is likely that multiple interacting pathways are responsible for the antidepressant effects of exercise. With a deeper understanding of these pathways, we can create more effective, and targeted, interventions as well as begin to identify individuals for whom exercise may be the most appropriate or helpful by investigating moderators of exercise.

A key area that necessitates further examination is the role of exercise on mania. Some evidence suggests that mania is associated with increased exercise [27, 53, 131]. This finding remains limited to cross-sectional data, and, to our knowledge, no studies have examined prospectively the impact of increased exercise on mania and vice versa. Future studies should aim to identify order effects as well as optimal exercise levels that improve depressive symptoms but prevent mania.

Overall, there is promising evidence to support the use of exercise in the treatment of mood disorders. With further research determining the ideal frequency, duration, and intensity of exercise and potential mechanisms of action, exercise may become a well-established and efficacious intervention for mood disorders.

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• Of importance

•• Of major importance

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