

Exercise Treatment for Bipolar Disorder: Potential Mechanisms of Action Mediated through Increased Neurogenesis and Decreased Allostatic Load

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Key Words

Exercise · Brain-derived neurotrophic factor · Allostatic load · Bipolar disorder

Abstract

Outcomes are frequently suboptimal for patients with bipolar disorder who are treated with pharmacotherapy alone. Adjunct exercise has the potential to substantially improve acute and long-term outcomes, although how exercise would improve the course of bipolar disorder needs to be elucidated. We propose that exercise may improve mood and functioning by increasing neurogenesis and reducing allostatic load. We review data suggesting that exercise increases levels of brain-derived neurotrophic factor, which in turn increases neurogenesis and decreases allostatic load. Exercise as a psychosocial adjunct for bipolar disorder should be assessed with rigorous randomized clinical trials.

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Introduction

Evidence suggests that exercise is an effective adjunct psychosocial treatment for unipolar depression [1], with promising results for bipolar disorder. Ng et al. [2] found

that bipolar inpatients who participated in a walking group 5 days per week for 40 min per session reported lower depression and anxiety symptoms than those who did not. Additionally, an acute bout of exercise significantly improved bipolar participants' mood [3]. Individuals with bipolar disorder who participated in an exercise program (i.e. eight 30-minute walking sessions) had better perceptions of stress reactivity to an acute stressor as well as reduced physiological reactions to stress [4].

Exercise may also be effective as creating an exercise program is a very individualized and collaborative process between patients and doctors. This is likely due to adherence rates typically being low (i.e. <50%) for exercise programs, and thus the need for clinicians to increase patient motivation and 'buy in' for the exercise program. Evidence suggests that shared decision-making between clinicians and patients improved outcomes in psychiatric patients [5]. This collaborative process, in addition to completing an exercise program, may also enhance patients' sense of self-efficacy and mastery and contribute to its antidepressant effect [6]. Evidence-based intervention programs that target resiliency and an overall sense of well-being are needed, given the focus on 'after the diagnosis' symptom-focused treatment [7]. Exercise is primed as such an intervention to enhance resiliency in vulnerable populations, such as those with bipolar disorder.

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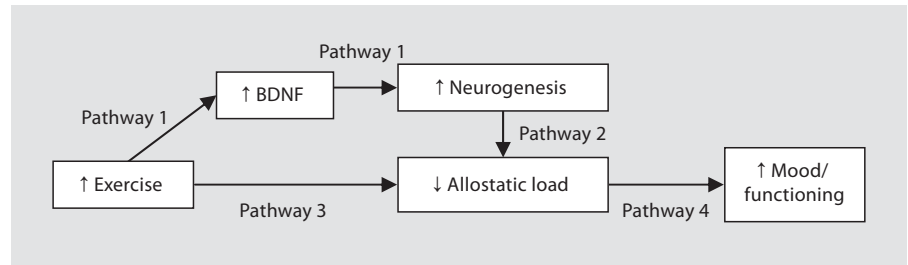


Fig. 1. Proposed antidepressant mechanism of exercise.

der, given its positive cumulative effect on one's mood and physical health.

This dual benefit of exercise is particularly important for bipolar disorder, given that bipolar individuals are at high risk of developing metabolic syndrome and type 2 diabetes [8, 9]. Bipolar disorder is associated with poor eating habits, high rates of cigarette smoking, and weight gain associated with prescribed medications [10–14]. In a study of patients with severe mental illness, including those with bipolar disorder, 65% were overweight and 50% had exercised, on average, less than once a week in the past year [15]. Those who reported exercising more frequently in the past year were less likely to be overweight, despite their medication regime and sedentary lifestyle.

While the mechanism of physical health benefits of exercise has been established, how exercise can ameliorate depression is less clear. Recent studies have found that exercise increases the gene expression of brain-derived neurotrophic factor (BDNF) [16–20], although the exact mechanism is unknown. BDNF promotes proliferation and differentiation of neural stem cells in the hippocampus and enhances the survival of these new neurons, a process known as neurogenesis. It is possible that this exercise-induced increase in neurogenesis enhances cognitive functioning, allowing patients greater cognitive capacity or flexibility to adapt to stressful events. Alternatively, exercise could directly decrease the physiological burden associated with repeated adaptations to stress known as allostatic load. Exercise-induced decreases in allostatic load could protect against developing further mood episodes [21].

In this paper, we propose that decreased allostatic load could mediate the association of exercise-induced neurogenesis and improved functioning in individuals with bipolar disorder (fig. 1) [22, 23]. We will review the evidence for this proposed antidepressant mechanism of exercise and the potential implications of exercise as an intervention for individuals with bipolar disorder.

Proposed Mechanism

Pathway 1: Exercise, BDNF, and Neurogenesis

Evidence has accumulated that exercise offsets cognitive decline and functioning by causing neurogenesis or the growth of new neurons from neural stem cells in the hippocampus [24–28]. Although it is likely that multiple neuromodulators (i.e. β -endorphins, vascular endothelial growth hormone, fibroblast growth factor 2) may explain the antidepressant properties of exercise, most of the recent work has focused on the role of BDNF for several reasons (pathway 1 in fig. 1).

First, BDNF is a primary modulator of several neurotransmitters and plays a key role in neuronal survival and synaptic strength [27]. BDNF (12 or 36 $\mu\text{g}/\text{day}$) infused directly into the dorsal hippocampus of rats significantly increased the granule cell layer, indicating neurogenesis [29]. BDNF enhances brain plasticity and could be involved in improving aspects of cognition, such as learning and memory functions of the hippocampus (i.e. memory consolidation, storage, or long-term memory) [28, 30, 31]. In this way, BDNF effects resemble 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 increases in grey matter density, in the anterior cingulate gyrus [32, 33] and the hippocampus [34]. Conversely, cognitive deficits are associated with low levels of BDNF [28] and decreased BDNF mRNA in the hippocampus occurs in Alzheimer's disease [31, 35]. Thus, we propose that exercise-induced BDNF, by increasing neurogenesis, has a possible role in improving mood (fig. 1).

Second, antidepressant medications upregulate BDNF [19, 36]. BDNF also enhances the effect of antidepressants in animal models, suggesting that antidepressants and BDNF may operate through similar neurochemical pathways [17]. A meta-analysis concluded that antidepressants

sants are associated with increases in serum BDNF (range 0.5–16.7 $\mu\text{g/ml}$, mean 7.41 $\mu\text{g/ml}$) [37]. Depressed individuals taking antidepressants had BDNF levels similar to the normal control subjects (i.e. 30.6 vs. 27.7 $\mu\text{g/ml}$) and both groups had significantly higher BDNF levels, but fewer depressive symptoms, compared to depressed individuals not taking any medications (17.6 $\mu\text{g/ml}$) [38]. BDNF also mimics the effect of antipsychotic drugs on the expression of dopamine receptors in the brain, suggesting that it may reduce manic or elevated mood [39]. A region of untranslated BDNF was also associated with antidepressant response in individuals with unipolar depression, after controlling for age, sex, medication, and depressive symptoms [40]. Results have been mixed on whether Val66Met, a polymorphism in the BDNF gene, is associated with bipolar disorder [41, 42], but it seems that BDNF levels are lower for patients with this polymorphism, regardless of their current mood state [43–45]. BDNF is likely a primary mediator in this model (fig. 1) due to its possible genetic association with mood episodes as well as its functionality as an antidepressant and mood stabilizer.

Third, exercise, similarly to antidepressants, upregulates BDNF mRNA levels in the hippocampus [20, 46]. Although growth and nerve growth factors may mediate the effects of exercise on neurogenesis, it is likely that they modulate the effects of BDNF as opposed to mediating the overall relationship of exercise and neurogenesis [47]. Exercise appears to utilize a feedback loop, through the activation of mRNA and cAMP-response-element binding, to augment the effects of BDNF on neurogenesis [18, 48]. Finally, the BDNF gene moderates the effect of exercise on mood, heart rate, and perceived exertion [49].

An important caveat to the association of BDNF and antidepressants is the potential for BDNF to trigger mania similar to the effect of standard antidepressants. A pilot study found that BDNF was decreased during a manic episode, but rebounded in 6 of the 10 subjects after the episode [50]. These data suggest that BDNF is associated with mania and that it may be a biological marker of the treatment response for individuals with bipolar disorder. Given that switching into mania with the use of antidepressants is minimized by prescribing a mood stabilizer in combination with an antidepressant [51], we suggest that exercise also be prescribed in combination with a mood stabilizer. This recommendation is intended to be cautious as it is not clear how exercise and mania may be associated, but it is possible that exercise may induce mania. A recent study from the Munich registry ($n = 2,548$) found that adolescents who exercised at all

(i.e., either non-regularly or regularly) were more likely to be diagnosed with bipolar disorder than adolescents who did not exercise [52]. Thus, future research is needed to further explore the role of exercise, BDNF, and mania.

Taken together, these data suggest that BDNF is a candidate for the primary mediator of exercise-induced neurogenesis (pathway 1 in fig. 1). BDNF is a neuromodulator that aids in cell growth and neuroprotection, mimics psychotropic medications, and is closely linked to exercise manipulations.

Pathway 2: BDNF, Neurogenesis, and Allostatic Load

Exercise-induced BDNF, through the process of neurogenesis, could reduce allostatic load (pathway 2 in fig. 1). Allostasis is the release of neuromodulators as a result of a potentially stressful event that triggers an adaptive response to the event. The burden of stress, due to repeated cycles of allostasis, is the allostatic load. Because BDNF increases synaptic connectivity and signal transduction, BDNF could modulate responsiveness to environmental stress [22, 28, 53–55]. Stress decreases the gene expression of BDNF, but it is possible that lower levels of BDNF increase susceptibility to the adverse effects of stress and higher levels of BDNF could mitigate the effects of stress and decrease the allostatic load. Exercise-induced increases in BDNF may decrease stress reactivity and markers of allostatic load (pathway 2 in fig. 1). The allostatic markers that reflect the physiologic burden of stress include fasting glucose levels, fasting insulin levels, waist-hip ratio, triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol levels [56, 57].

Markers of allostatic load and BDNF can change with diet and exercise. A reduced-calorie diet given to overweight and obese adults over 3 months decreased waist circumference, body fat percentage, and fasting glucose, and increased BDNF (3.97–6.75 ng/ml) [58]. In mice, exogenous BDNF prevented increases in blood glucose levels [59]. Three weeks of BDNF treatment in rats reduced liver triglycerides, total cholesterol and blood glucose levels compared to a control group [60]. The control group did not, however, differ in body weight or white adipose tissue, suggesting that these markers may be less responsive to BDNF (table 1).

BDNF could be a key mediator of obesity-related diseases [61, 62]. Circulating BDNF levels are reduced in patients with metabolic syndrome and in those with an acute coronary syndrome. Conversely, it is possible that increased BDNF levels may buffer against these diseases

Table 1. BDNF and markers of allostatic load

Study	Population	Treatment	Markers changed	Conclusion
Araya et al. [58]	overweight/obese subjects (n = 17; age 24–48 years)	25% reduced calorie diet	increase in BDNF (3.97 ± 0.87 to 6.75 ± 1.62 ng/ml); decrease in BMI, WC, glucose, fat percentage; BDNF correlated negatively with weight	BDNF responds to change in diet to increase insulin resistance
Yamanaka et al. [59]	diabetic mice	1 injection of 70 mg/kg of BDNF; next, BDNF injected $2 \times$ /week and $1 \times$ /week at 4, 10, 25, and 62.5 mg/kg	70-mg/kg injection reduced glucose and maintained it for 6 days; BDNF dose-dependently reduced glucose in $2 \times$ /week and $1 \times$ /week administration	BDNF directly influences glucose metabolism, even if injected only $1 \times$ /week
Tsuchida et al. [60]	diabetic mice	injected 50 mg/kg per week of BDNF for 3 weeks	reduced liver triglycerides, TC, blood glucose compared to non-BDNF-treated mice	BDNF improves glucose and lipid metabolism without enlarging liver or adipose tissues
Chaldakov et al. [61]	deceased human atherosclerotic coronary arteries (n = 12) and control specimens (n = 9)	naturalistic	lower levels of BDNF in metabolic syndrome patients than controls	increased levels of BDNF may buffer against coronary artery disease and metabolic syndrome

BMI = Body mass index; WC = waist circumference; TC = total cholesterol.

and reduce allostatic load, but the causal direction is uncertain [63, 64] (table 1). Reduced availability of a neurotrophin, such as BDNF, may result in a metabotropic deficit and explain the pathogenesis of obesity and related metabolic diseases, such as metabolic syndrome, type 2 diabetes, and atherosclerosis [62].

BDNF appears to be a primary neuroimmune mediator involved in the development of cardiovascular disease and related disorders [61–63]. These data suggest that BDNF may mediate the effect of exercise in decreasing the risk of these diseases as depicted by pathway 2 (fig. 1).

Pathway 3: Exercise and Allostatic Load

Exercise increases the ability to adapt to environmental stressors [65, 66] and could decrease markers of allostatic load by decreasing the activity of the hypothalamic pituitary-adrenal axis, the sympathetic nervous system, and glucocorticoids [66]. For example, endurance and interval exercise training reduced weight, glucose levels, waist circumferences, and BMI [67]. Total cholesterol was also reduced in the endurance group. A decrease in physical activity during a 6-year period was associated with higher fasting insulin and insulin resistance levels in a sample of adolescents [70]. In men with metabolic syndrome, light intensity exercise, but not moderate intensity, reduced blood pressure [68] (table 2).

Patients with coronary artery disease and who had high and low levels of psychological distress participated in a 12-week outpatient cardiac rehabilitation and exercise training program [69]. After the program, patients in the high-stress group had significant reductions in weight, percentage of fat, BMI, and increases in exercise capacity, high-density lipoprotein, and total quality of life (table 2). Similar to the results with BDNF, an 8-week exercise intervention for individuals with major depression did not significantly change concentrations of serum lipid levels [72]. This may again suggest that lipid, or adipose tissue, could be the allostatic marker most resistant to change.

Levels of glycosylated hemoglobin (HbA_{1c}) with type 1 diabetes was associated with an increase in depressive symptoms, and this relationship was mediated by diabetes self-care (i.e. diet, exercise) [73]. Including the Summary of Diabetes Self-Care Activities measure in the statistical model attenuated the effect of depressive symptoms, suggesting that diet and exercise mediated this association. These data and other studies examining the treatment of diabetes recommend exercise as a primary intervention to reduce markers of allostatic load (fasting glucose and insulin) in this high-risk population [74]. In a psychiatric population, a weight and exercise program improved markers of allostatic load compared to a control group [71] (table 2). Increased markers of allostatic load are also associated with bipolar disorder [75]. Given that exercise reduces markers of allostatic load (path-

Table 2. Exercise and markers of allostatic load

Study	Population	Exercise condition/group	Control condition/group ¹	Duration, frequency	Markers changed	Conclusion
Moreira et al. [67]	overweight/obese subjects (n = 22; mean age 40 years)	endurance intensity (10% above anaerobic threshold), 20–60 min cycling	interval intensity (20% above anaerobic threshold), 20–60 min cycling with 2:1 (exercise: pause) ratio	12 weeks, 3 × /week	reduced weight, BMI, WC, glucose; reduced TC with endurance intensity only	exercise reduces cardiac risk variables
Pescatello et al. [68]	men with MS (n = 18) and without MS (n = 28) (mean age 46 years)	two 40-min exercise sessions at 40 and 60% VO ₂ peak	one 40-min seated rest	3 days, 1 × /day	reduced blood pressure	exercise reduces MS risk variables
Artham et al. [69]	subjects with CAD with high (n = 109) and low (n = 115) psychological distress	40 min exercise (max = 10/15 HR beats/min), diet counseling, psychoeducation, group therapy	none	12 weeks, 1–3 × /week	reduced weight, body fat, BMI, high-density lipoprotein cholesterol	exercise reduces CAD risk factors, even with high distress
Jago et al. [70]	subjects from Denmark registry (n = 384; mean age 15 years)	monitoring lifestyle activity	none	3 days, continuous	activity negatively associated with fasting insulin	increasing physical activity may prevent insulin resistance
Poulin et al. [71]	subjects (n = 110) with schizophrenia, schizoaffective, or bipolar on atypical antipsychotics	education/counseling with structured, supervised, facility-based exercise program (n = 59)	same assessment, no exercise (n = 51)	18 months, 2 × /month	reduced weight, BMI, WC, TC, glucose, triglycerides	exercise reduces metabolic risk factors even on atypicals

This is not intended to be an exhaustive list of studies. MS = Metabolic syndrome; CAD = coronary artery disease; BMI = body mass index; WC = waist circumference; TC = total cholesterol; HR = heart rate.

¹ Poulin et al. [71] is the only study that used a different sample of subjects as a control group.

way 3, fig. 1), clinicians have started to prescribe exercise to manage bipolar patients' metabolic syndrome associated with second-generation antipsychotics, consistent with recommendations from the American Diabetes Association [74, 76–78].

Pathway 4: Implications for Bipolar Disorder

Exercise has mental and physical health benefits with few side effects. The positive impact of exercise in clinical populations makes it attractive as an adjunct treatment for bipolar disorder, yet it is still unclear how it reduces mood symptoms and whether or not exercise buffers against future bipolar episodes. As mentioned, the role of exercise in acute mania also needs to be further examined, given the overlap of BDNF and antidepressants. Exercise, by increasing BDNF levels and neurogenesis, may improve one's ability to tolerate environmental stress by reducing allostatic load (fig. 1).

Mood disorders are characterized by a reduction in neuronal plasticity [53, 79]. Hippocampal volume is reduced in major depression compared to age- and sex-matched controls [80, 81]. Although the results are mixed,

brain abnormalities have also been associated with mania. After the first episode of mania, compared to normal controls, subjects had a 6% reduction in the left anterior cingulate [82], increased third ventricular to cerebral volume ratio [83], and decreased cortical thickness in the cingulate, frontal, angular, fusiform, and occipital cortices [84]. Bipolar patients, compared to normal controls, also exhibit significant cognitive impairment [85, 86].

These structural brain abnormalities and cognitive impairment appear to predict treatment response, in addition to course of illness [87]. Reduced hippocampal volume is associated with poor treatment response in individuals with mood disorders [79]. Patients taking antidepressants for 3 years showed significant increases in volume [88, 89]. Similar findings have been observed in individuals with schizophrenia [90, 91] and bipolar disorder [92, 93] compared to normal controls. Cognitive impairment, in particular divided attention performance, predicted response to treatment, remission of symptoms, and risk of relapse [94]. Similar to improvements in structural abnormalities, cognitive impairment responds to bipolar medications [95].

BDNF-associated reversal of structural brain abnormalities and cognitive impairment found in bipolar disorder is a promising mechanism of potential therapeutic effects of exercise for bipolar disorder. Reduced levels of BDNF may be associated with the onset of a mood episode and response to treatment in bipolar disorder [43–45]. Responsiveness to lithium seems to be mediated by the Val66Met polymorphism of the BDNF gene, with increased gene expression of BDNF associated with greater response [96, 97]. BDNF could be a potential biomarker for diagnosis and early intervention of bipolar disorder [50, 98, 99].

Given that BDNF levels in bipolar disorder can be associated with cognitive deficits, poor judgment, and poor risk assessment, we suggest that the decrease in BDNF may increase the likelihood that those with bipolar disorder will perceive events as stressful and act in ways that increase the probability of being in a stressful situation [100–104]. Individuals with bipolar disorder exposed to more traumatic events, who were likely to have increased allostatic loads, had lower serum BDNF levels compared to a control group [105]. Bipolar patients treated with mifepristone, a glucocorticoid receptor antagonist, exhibited lower levels of BDNF, but higher levels of cortisol [106]. In animal models, the autonomic response to severe environmental stress is associated with decreased levels of BDNF [107]. Individuals exposed to severe trauma or stress experience an upregulation of glutamate in the hippocampus causing excitotoxicity, or cell destruction due to excessive neural excitation or activity [108].

These data suggest that BDNF could be involved in the pathophysiology of bipolar disorder and particularly responsible for the transduction of psychosocial stress [54]. As discussed in ‘Pathway 2’, BDNF seems to directly influence markers of allostatic load, an indicator of the ability to manage stress. It follows that enhancing neurogenesis, or increasing the size and connectivity of and within the hippocampus, could increase resiliency to stress and buffer against depressive episodes [23].

Other evidence for the proposed model (fig. 1) is the association of BDNF gene expression and unipolar disorder, bipolar disorder, and schizophrenia [41, 109, 110]. Individuals with major depression who had functional variations of the BDNF gene showed greater reductions in their hippocampal volumes [111]. Reduced serum BDNF levels have also been reported in unipolar and bipolar depression [44, 112]. Early life stress and circadian rhythm dysregulation have also been associated with lower BDNF levels, further suggesting that this may be a vulnerability factor for developing mood disorders [113,

114]. Thus, the role of BDNF in neuroplasticity, synaptic connectivity, and behavioral sensitization may be an important factor in increasing the vulnerability to developing psychiatric disorders [115].

Conclusion

In summary, exercise has the potential to improve mood, functioning, and the course of bipolar disorder, mediated by BDNF increases in neurogenesis and decreases in allostatic load. Exercise enhances BDNF and neurogenesis (pathway 1 in fig. 1), which counteracts the negative impact of stress hormones, with the result of decreased allostatic load (pathway 2). This mediational model is plausible given that exercise reduces markers of allostatic load (pathway 3), which may decrease susceptibility to mood episodes (pathway 4).

Pathways 1 (exercise increases BDNF) and 3 (exercise decreases markers of allostatic load) currently have the most supportive evidence, especially from studies of activity-dependent transcription of the BDNF gene in animal models [31]. Further investigation is needed to explore the relationship of BDNF gene expression and markers of allostatic load to bipolar disorder (pathway 4). In particular, the directionality is unclear in both pathways 2 and 4 (fig. 1). Do changes in markers of allostatic load and physiological stress alter gene expression of BDNF or would increases in BDNF decrease these markers? Similarly, do lower levels of BDNF predispose individuals to bipolar mood episodes or do mood episodes lower BDNF levels? Recently, Kapczynski et al. [116] have suggested that BDNF may be a trait as well as a state marker of bipolar disorder that responds to environmental and self-generated stress.

Exercise interventions for bipolar disorder should be assessed in rigorous randomized clinical trials to examine the postulated mediational model as well as the optimal dose and timing of exercise for bipolar disorder. Preliminary evidence suggests that either the recommended amount of exercise for adults or 30 min/5 days a week at moderate intensity [117] improves mood in bipolar disorder [2]. A series of well-designed studies in unipolar depression found that a less frequent, but more intense, 4-month exercise program (frequency: 3×/week; duration: 45-minute sessions; intensity: 70–85% max. heart rate) was as effective in reducing depressive symptoms as an antidepressant (i.e. sertraline) [118, 119]. Also, outcomes did not vary if the exercise program was conducted at home or in a supervised setting [120]. A 5 days/week

exercise program at moderate to high intensity (with energy expenditure of 17.5 kcal/kg/week) also significantly reduced depressive symptoms compared to the control group [121]. Although dose-response studies are needed for bipolar disorder, these data suggest that researchers should consider evaluating 30-minute sessions 5 days/week of moderate-intensity exercise as a target goal to obtain an antidepressant effect. Importantly, any amount

of exercise is beneficial for one's physical health. It has also been suggested that exercise be considered for 'partial responders' or those who have 'very specific residual symptoms' [122, p. 675]. Future research is needed to better understand these aspects of exercise interventions, as elucidating the potential mood-stabilizing properties of exercise would aid our understanding of the etiology of bipolar episodes.

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