Potential Therapeutic Effects of Physical Exercise for Bipolar Disorder

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Abstract

Cognitive deficits are observed in a variety of domains in patients with bipolar disorder (BD). These deficits are attributed to neurobiological, functional and structural brain factors, particularly in prefrontal cortex. Furthermore, cortical alterations in each phase (mania/hypomania, euthymia and depression) are also present. A growing basis of evidence supports aerobic exercise as an alternative treatment method for BD symptoms. Its benefits for physical health in healthy subjects and some psychiatric disorders are fairly established; however evidence directly addressed to BD is scant. Lack of methodological consistency, mainly related to exercise, makes it difficult accuracy and extrapolation of the results. Nevertheless, mechanisms related to BD physiopathology, such as hormonal and neurotransmitters alterations and mainly related to brain-derived neurotrophic factors (BDNF) can be explored. BDNF, specially, have a large influence on brain ability and its gene expression is highly responsive to aerobic exercise. Moreover, aerobic exercise trough BDNF may induce chronic stress suppression, commonly observed in patients with BD, and reduce deleterious effects caused by allostatic loads. Therefore, it is prudent to propose that aerobic exercise plays an important role in BD physiopathological mechanisms and it is a new way for the treatment for this and others psychiatric disorders.

Keywords

Bipolar disorder, brain-derived neurotrophic factor, depression, exercise, mania, neuroplasticity.

INTRODUCTION

Bipolar disorder (BD) affects 1 to 1.5% of the world population [1] and consists of recurrent manic and depressive episodes, interspersed with periods of euthymic mood [2]. BD patients exhibit cognitive dysfunction in a variety of domains, even during periods of clinical remission [3, 4]. In this sense, the prefrontal cortex (PFC) is an important part of the pathophysiology of BD, and has a leading role on several cognitive functions [5, 6]. Such functions have significant impairments that correlate negatively with social and occupational adjustment [3]. Its chronicity has been consistently attributed to functional and neuroanatomical changes in the cortex that occurs in different magnitudes [5, 7-10]. Given this scenario, the literature starts speculating that programs of physical exercise could act as an important adjuvant and no pharmacological strategy for the treatment of patients with BD [11-14]. Physical exercise, specially aerobic exercise, is recognized for modulate an affective behavior in healthy subjects in moderate intensities of effort [15, 16], modify cerebral activity [17], promote neurogenesis [18], and improve cognitive function [15]. Despite little consistent, significant reduction of symptoms are found with the practice of aerobic exercise in bipolar patients [12, 19- 21], and its effects related to exercise begin to be established in the literature [13]. Ng et al. [12], for example, observed in

24 patients diagnosed with BD, inserted in a walking group (effort not controlled), an improvement in the Depression Anxiety and Stress Scale (DASS – p=0.005) and all its subscales (Depression p=0,048, Anxiety p=0,002, and Stress p=0,01), compared to 74 bipolar patients who not participated in walking group. In this sense, mechanisms sustaining improvement and insertion of aerobic exercise in lifestyle of patients with BD would be related to alterations in hormonal responses [22], neurotransmitters, such as monoamines, and physiological biomarkers produced by the brain, such as the brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) [22, 23]. Although understanding these mechanisms, the evidence still lacks of consistent data that supports the link between remission and BD symptoms to programs of aerobic exercise. Thus, this review paper aims to show the experimental advances of aerobic exercise that can become available as clinical applications in the coming years for bipolar disorder. The literature search was conducted using the databases PubMed, ISI Web of Knowledge and PsycInfo using the following terms and their combinations: “aerobic exercise”, “bipolar disorder”, “mechanism”, “manic/hippomanic”, “depressive”, “electroencephalogram”, “functional magnetic resonance imaging”, “cognitive function”, "biomarkers". All articles were published between 1980 and 2015 and in English. Additional references were identified through hand search of the possessed articles. Due to the lack of randomized clinical trials on the issue, we decided to select any study, i.e., open and controlled studies, case reports, and cohort and observational studies.

EFFECTS OF AEROBIC EXERCISE ON BIPOLAR DISORDER

Benefits and/or General Adaptations of the Exercise for Health Promotion – Initial Contextualization

The American College of Sports Medicine (ACSM) recommends an accumulation of at least 150 minutes of moderate aerobic activity (50-55% VO2 of reserve – VO2R) weekly or 60 minutes of vigorous activity (70-75% VO2R) weekly, for health promotion. The result of this summation is observed, primarily, in physical, metabolic and systemic state, providing protection over risk factors associated to coronary artery disease (lipid profile, body mass control, changes in resting glucose and blood pressure) [24]. It is also known that an increase of only 1 MET (1 metabolic equivalent = 3,5 mL/kg/min) in cardiorespiratory fitness (VO2Max) represents an decrease in relative in mortality of about 13%, independent of any type of disease previously installed, such as coronary artery disease (CAD) [25, 26]. In addition to physical health, mental health aspects should also be emphasized 22, 25, 74]. The promotion of morphological and functinal changes in several brain areas (PFC, hippocampus) [27], and the formation of new neuronal synapses [28] may reduce the deleterious effects to the brain associated to age and different psychiatric disorders. In this sense, evidence tends to demonstrate positive effects on reducing the severity of symptoms related to illnesses such as BD [12, 20, 21, 29]. Moreover, significant positive modifications in mood with the practice of aerobic exercises [15, 20] and the cognitive function [27] are considered, and these benefits are observed in both healthy subjects and in patients with different psychiatric disorders. Bipolar patients, regardless of their clinical status, have low cardiorespiratory fitness and resistance exercise [13], as well, diverse deleterious effects to functional and structural ability of the brain [3, 4, 6, 8, 10, 23, 30-34]. Therefore, it is prudent to propose that cardiorespiratory conditioning, that is, improvement of VO2Max is an important pathway for the treatment of different psychiatric disorders, given that their physiopathological mechanisms can be minimized and/or reorganized.

Relationship Between Exercise and Bipolar Disorder

The current state of art exposes results that confront the real benefit of controlling bipolar illness with programs of aerobic exercises [12-14, 16, 19-21, 27, 35-40]. Few studies were published about this particular topic and these fail to methodological controlling the relation of “dose x response” and/or in several times, there isn’t any control. This is a factor that makes the results inconsistent and impossible for future comparisons. For example, Ng, Dodd and Berk [12] evaluated the effects of walking exercise on acute treatment of BD. Twenty four participants diagnosed with BD joined to the program and 74 not participants with the same psychiatric profile were compared. The main results showed a significant reduction on BD symptoms evaluated with Depression Anxiety Stress Scales (DASS; mean ± standard deviation of participants; 58.2 ± 25.4 > 23.0 ± 14.9). These results should be analyzed careful as well as those reported by Van Citters et al. [39]. The authors produced a pilot study using a specific program of diet reeducation, social behavior and fitness, called SHAPE, with different psychiatric disorders. Within this program, participants performed aerobic activities such as swimming and walking, or strength training or yoga. The criteria of training duration and intensity were adjusted according to an initial observation of the participant’s physical state and evaluation scales of psychiatric progress were carried out. Reduction of the severity of symptoms, such as depression, was an important result to be noted ($p = 0.003$) after 9 months follow up, in addition to benefits related to comorbidity in these patients. Other satisfactory results with effect sizes varying from moderate to high were found in different mania and depression scales and an improvement (mean %) of BD symptoms (MADRS – Montgomery Asberg Depression Scale (-23%); YMRS – Young Mania Rating Scale (27%) ; CGI Mania – Clinical Global Impression Mania Subscale (43%); CGI Depression – Clinical Global Impression Depression Subscale (22%); CGI Overall – Clinical Global Impression Overall Bipolar Illness (-16%); LIFE-RIFT – Longitudinal Interval Range Impaired Functioning Tool (- 22%)) [38].

In contrast, a meta-analysis of Pearsall et al. [21] summarizes the possible effects obtained with exercise in a modest and not significant response over the physical activity level in patients with psychiatric disorders, such as bipolar, without effects on negative symptoms of depression ($p = 0.43$) and anxiety ($p = 0.14$). These results should be interpreted carefully given that the control of the relation “dose x response” is questioned in almost all studies. Moreover, and inadequate stimulus may tend to extremes, or to a result without effects in BD symptoms, or the stimulus may be interpreted as an stressor agent, contributing to the relapse of the symptoms [41]. An high intensity of exercise, though still uncertain, seems to be associated to a positive association with BD symptoms [42] and more precisely, to a negative effect on mood [43]. Contextualizing this data, after performing aerobic exercise to exhaustion, cortisol concentrations remain high for hours while BDNF concentrations are reduced to baseline values in a small amount of time [22] (Table 1).

Table 1. Papers that investigated the chronic effect of the exercise in patients with bipolar disorder.

Article	General Features				Sample Features						Exercise Features					Results			
	Control	Random	Evaluation	Patient	n	Group	Age	Gender	Med	Instrument	Exercise			Times a week	Follow-up	Instrument	Absolut	Δ	ES
											Modality	Time	Intensity						
Ng, Dood & Berk, [12]	Yes	Not	(ICD-10)	Bipolar (100%)	14	Exercise	43.6 (15.0)	M + F	?	CGI-S, CGI-I, DASS Scale & Sub-scales	Walk	40 min	Free	?	24 month	CGI-S	4.2 ± 1.0 > 2.5 ± 1.2	40.5%	1.7
																CGI-I	Non-reported	-	-
																DASS Depres	24.0 ± 12.4 > 7.2 ± 7.3	70.0%*	1.4
																DASS Stress	19.4 ± 12.3 > 9.2 ± 7.2	52.6%*	0.8
																DASS Anxiety	14.8 ± 11.2 > 6.6 ± 4.5	55.4%*	0.7
					35	Non-exercise	43.9 (18.5)	M + F	?		-	-	-	-		CGI-S	4.3 ± 0.8 > 2,4 ± 0,8	44.2%	2.4
																CGI-I	Non-reported	-	-
																DASS Depres	27.3 ± 12.3 > 13.7 ± 12.8	49.8%	1.1
																DASS Stress	25.3 ± 9.3 > 17.1 ± 11.6	32.4%	0.9
																DASS Anxiety	18.2 ± 8.9 > 13.8 ± 8.9	24.2%	0.5
Van Citters, et al. [39]	Not	Not	DSM-IV	Bipolar (19%)	76	Exercise Diet Relax Yoga	43.5 (11.4)	M+ F	?	(SF-12 MCS) (SF-12 PCS) CESD, RSES SANS	Walk, Swimming	20-60 min	Free	3-5 times	9 month	SF-12 MCS	32.2 ± 12.0 > 36.4 ± 13.4	13.0%*	0,30
																SF-12 PCS	44.7 ± 12.5 > 44.3 ± 11.1	0.9%	0
																CESD	28.6 ± 13.0 > 26.0 ± 15.4	9.1%	0.2
																RSES	53.3 ± 18.5 > 57.4 ± 18.4	7.7%	0.2
																SANS	2.4 ± 0.7 > 2.3 ± 0.6	4.2%*	0.1
Sylvia, et al. [38]	Not	Not	MINI-Plus CGI-BP	Bipolar (100%)	5	Diet Exercise Lifestyle Changes Cognitive Work	44.0 (16.0)	M + F	?	MADRS YMRS (CGI-BP M, D, O) (LIFE-RIFT)	?	30 min	Moderate Effort (% non-reported)	5 times	5 month	MADRS	17.2 ± 5.2 > 13.2 ± 10.1	23.3%*	0.8
																YMRS	4.4 ± 2.0 > 5.6 ± 3.9	27.3%*	0.6
																CGI-BP M	1.4 ± 0.9 > 2.0 ± 0.7	42.9%*	0.6
																CGI-BP D	3.6 ± 0.6 > 2.8 ± 1.3	22.2%*	1.3
																CGI-BP O	3.8 ± 0.5 > 3.2 ± 0.8	15.8%*	1.2
																LIFE-RIFT	12.0 ± 3.1 > 9.4 ± 2.1	21.7%*	0.8
Verhaeghe, et al.	Yes	Yes	DSM-IV	Bipolar (24%)	123	Exercise Social Cognitive	44.2 (12.5)	M + F	Yes	(SF36 PCS) (SF36 MCS) (BSI PST)	Walk	30 min	Moderate Effort	3 times	2.5 month + 6 month	SF36 PCS	40.4 ± 7.7 > 39.4 ± 7.5	2.5%	0.1
																SF36 MCS	35.6 ± 8.7 > 34.8 ± 7.9	2.2%	0.1
																BSI PST	27.6 ± 12.6 > 25.3 ± 12.8	8.3%	0.2
					50	Control	46.6 (11.9)	M + F	Yes		-	-	-	-		SF36 PCS	41.2 ± 5.9 > 40.2 ± 7.8	2.4%	0.2
																SF36 MCS	35.8 ± 7.9 > 35.3 ± 7.4	1.4%	0.1
																BSI PST	26.5 ± 13.8 > 24.0 ± 14.5	9.4%	0.2

Subtitles: * - Significant Difference; ES - Effect Size; Med - Medications; ICD-10 - International Statistical Classification of Deseases and Related Health Problems; CGI S - Clinical Global Impression Severity; CGI I - Clinical Global Impression Improvement; DASS - Depression Anxiety Stress Scale; Mental Health Functioning - (SF-12 MCS); Psysical Health Functioning - (SF-12 PCS); Depression - (CESD); Self-Efficacy - (RSES); Negative Symptoms (SANS); MINI-Plus - Mini International Neuropsychiatric Interview; CGI-BP - Clinical Impression-Bipolar; MADRS - Montgomery Asberg Depression Rating; YMRS - Young Mania Rating Scale; CGI-BP M - Clinical Impression-Bipolar Mania; CGI-BP D - Clinical Impression-Bipolar Depression; CGI-BP O - Clinical Impression-Bipolar Overall; LIFE-RIFT - Longitudinal Interval Follow-up Evaluation Range Impaired Functioning Tool; SF36 PCS - Physical component score; SF36 MCS - Mental component score; BSI PST – Brief Symptom Inventory Positive Symptom Total.

Possible Exercise Mechanisms that Influence Bipolar Disorder Despite of inconsistencies and limitations, there is a tendency to obtain positive results with exercise practice [11, 12, 16, 36, 38, 39]. The improvement mechanism of the severity of BD symptoms may be connected to stress reduction from physiopathology agent's characteristics of the illness. Chronic stress caused by the imbalance between proinflammatory cytokines, changes in corticosteroid and reduction of BDNF levels, create a propitious ambient to increased allostatic charges and consequent reduction of cerebral neuroplasticity [19]. Therefore, subjects that practice appropriated periods of exercise (threshold around 20 – 30 min) may produce appropriated results on anxiety and reduction of stress reactivity in long term [43]. Chronic stress is also suggested as the most precipitator of mood disorders, given that a great sensitivity to stress is related to recurrent episodes [44]. This fact can be explained also by a defective modulation of monoaminergic systems [45, 46], such as observed in different psychiatric disorders. Several theories support a possible influence of mechanisms of dopaminergic transport [46] or GABAergic influence on physiopathological characteristics of BD [19]. This last, in special, has an important influence on gene expression of BDNF by hippocampus during exercise, influencing directly the basal levels of this substance [19]. During acute exercise of mild to moderate effort, cortisol and BDNF concentrations was not significantly altered, but not for high intensities [22]. High cortisol concentration is normally co-regulated by BDNF concentration and both follow a linear increase pattern [47]. However, in bipolar patients, initial BDNF concentration is normally depressed [23] which may mitigate the co-regulator and protection effect of BNDF. Despite of acutely after exercise the BDNF concentrations come back closely to baseline values [22], chronically the main benefits on symptoms severity are primarily associated to basal BNDF concentrations. As explained, high basal concentrations of this substance are deeply connected to neuroplasticity and cerebral neurogenic capacity [11, 19, 40] and these responses extend

to different BD domains, including cognition [35]. Exercise effects on cerebral neurotrophins were demonstrated by Seifert et al. [37] in a cycling training program aiming 600 kcal/day (±70%

FC maximum/ ±60 min of exercise), during 3 months. The authors observed significant increases in arterial BDNF concentration in rest (baseline – 58 ± 106; follow-up – 206 ± 108 ng.100g-1.min-1), for the training group ($p<0.05$). The Control group was included just on a diet program (similar energy cost of exercise), but not reaching significant improvement. Exercise acts increasing gene expression of BDNF and messenger RNA in diverse body cells, including in muscular cells, but mainly in the hippocampal region [19].

Regarding cognition, BDNF can be an important key to cognitive recovery [18, 48]. The mechanism is associated mainly to synaptic plasticity changes, namely, better transmission and/or new synaptic connections [28]. It is demonstrated possible long term synaptic potentiating localized in hippocampal area, which is traduced in a better memory [18, 48]. Evidences suggest that effects produced by the relation between BDNF and new neurons formation may favor cognitive domains of adult learning [49]. Pharmacological administration helps maintaining and/or reducing cognitive deficit on bipolar subjects [50]. In these patients, treatment with lithium is the first treatment option and has significant effects on increasing volume of amygdala and hippocampus [51], neuroanatomical structures fundamental for cognitive performance and affective state [50]. Aerobic exercise seems to have similar effect on neuroanatomical organization and cognitive function in healthy subjects [27] and in different psychiatric disorders [52, 53]. Despite this understanding, little is known about aerobic exercise influence on different cognitive domains of BD. Exercise is recognized for inducing an increase in cerebral volume and consequently is associated to cognitive function changes. Colcombe et al. [27] implemented tree weekly sessions of 60 minutes training, initiating at 40 – 50% of heart rate reserve (HRR) and progressing along six months to prescribed intensities of 60 – 70% of HRR. The authors reported significant increases, mainly in white and grey matters, localized at PFC (right inferior frontal gyrus - $p \leq 0.05$) and temporal cortex (left superior temporal gyrus - $p \leq 0.05$). PFC region plays an important role in BD physiopathology and in motor control, attention and executive function [8]. Thus, larger changes in cerebral volume can bring important cognitive gains in long term.

CONCLUSION

Strong evidence in literature suggests using aerobic exercise as an important prophylactic strategy of actuation similar to pharmacology, aiming a reduction on symptoms severity and BD treatment in long term. Neurotrophins, mainly BDNF, obtained increasing relevance in what concerns aerobic exercise benefits. Complementary studies should be applied using different exercise protocols and controlled “dose x response” to evaluate better strategies for the symptoms treatment. Despite possible positive responses to exercise on BD symptoms, results still remain inconclusive and should be interpreted and implemented carefully.

LIST OF ABBREVIATIONS

ACSM = American College of Sports Medicine

BD = Bipolar Disorder

BDNF = Brain-Derived Neurotrophic Factor

CHD = Coronary Heart Disease

DASS = Depression Anxiety and Stress

ES = Effect Size

fMRI = Functional Magnetic Resonance Imaging

GDNF = Glial Cell-Derived Neurotrophic Factor

PFC = Prefrontal Cortex

VO_{2Max} = Maximal Oxygen Consumption

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