Considerations regarding physical activity in bipolar disorder, mechanisms, recommendations, and limitations

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There is a long history of recommendation of physical activity for the maintenance of well-being and health in the history of medicine, progressively generating more and more specific recommendations for the specific management of some pathologies in accordance to new knowledge. In recent decades, a significant amount of literature addressing the impact of physical activity in Bipolar Disorder (BD) has been published, where it is proposed that some pathophysiological changes could be positively modified with physical activity--suggesting some mechanisms for this, as well as helping to manage somatic comorbidities and some psychosocial difficulties generated in this group of patients. Some aspects of the multidimensional relationship between physical activity and bipolarity, suggested change mechanisms, limitations, and suggestions for prescription in the clinical management of patients are reviewed in this work.

Keywords: *physical activity, exercise, bipolar, sport.*

INTRODUCTION

For several years now, there is knowledge that physical activity is recommended for the maintenance of health in a global way, with progressive development in increasingly precise recommendations in terms of frequency, duration, intensity, and type of exercise. There is a history that physical activity has been integrated since ancient times to the vision of health and well-being. Around 600 AD, Susruta, a renowned doctor from Benares (India), already mentioned the importance of physical activity in his university classes, in addition to recommending it to his patients at a specific intensity and time of execution, with an evaluation complete medical prescription prior to prescription, and alerting them to the risks of excessive physical activity. Since then, there are medical records in different civilizations perfecting the indication of physical activity for the maintenance of health and the treatment of diseases. Hippocrates is recognized as the first doctor on record to indicate, as a detailed written prescription, physical activity to a patient.[1]

Currently, the World Health Organization suggests the performance of 150 minutes of moderate aerobic activity or 75 minutes of intense aerobic activity per week for the maintenance of the health of the population at a global level[2]. On the other hand, the American College of Sports Medicine, in conjunction with the American Heart Association, suggests the practice of 150 minutes of moderate aerobic exercise per week, in sessions of 30 minutes for five days a week for individuals between 18 and 65 years of age[3]. These recommendations have been linked to a favorable and important impact on morbidity and

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mortality in the general population, mainly in metabolic, cardiovascular, mental, and oncological diseases, and general well-being, among others.[3]

When we approach the relationship between physical activity and mental health, it is possible to observe how there is a growing interest in the medical literature to know the dimension of its impact on the appearance, course, and treatment of mental illnesses, as well as the specific profile of recommended activity according to patient and pathology in terms of quality, time and intensity. Additionally, it is suggested that clinicians work in a very structured manner when prescribing physical activity to their patients. An example of this is the 5A model —Evaluate, Advise, Agree, Assist and Organize— a model developed to program physical activity in a health context.[4]

Within this growing concern for physical activity in healthcare, the interest in studying and knowing its impact in multiple dimensions in Bipolar Disorder (BD), its actual effect, its probable mechanisms, the best ways to prescribe it from a clinical practice standpoint, in addition to its problems and limitations in relation to current knowledge and other aspects associated with it, on which this text will be focused.

Exercise and bipolarity, multidimensional relationships

There has been a growing interest regarding the impact of physical activity on BD; this due, among other reasons, to the good results published concerning other mental illnesses studied, such as major depression and different anxiety disorders[5].

It is important to note the absence of multicenter and randomized clinical studies exploring the impact of physical activity on the symptomatic course of BD[6]. Despite this, some international guidelines, such as the Bipolar Disorder guide of the *National Institute for Health and Clinical Excellence*[7], already mentions physical activity as a recommendation for this group of patients. However, it appears in a general way and with little operational clarity. Instead, it focuses on lifestyle changes and the management of comorbidities, without mentioning the impact or indication of its scope in relation to the symptomatic nuclei of the disease and without references in terms of frequency, type, and intensity of exercise, thus imprecise its use in medical practice. In the previous version of this same guide, the following reference was also made: “Although exercise can be a healthy way to use excess energy in a person with mania and a helpful distraction, it could further awaken the body physiologically, increasing energy, social contact, and self-efficacy, exacerbating manic symptoms and potentially increasing cardiovascular stress “, suggesting that the practice of physical activity could even have a deleterious effect in specific phases of the disease[8].

In the context of this multidimensional relationship, a potential bidirectionality could also be deduced. An example of this is the relationship between groups of athletes who practice certain types of sports, particularly extreme or high-risk sports, with a higher prevalence of bipolarity, as suggested by a study by Dudek et al., where one-third of male and female athletes women surveyed had high scores on *the Mood Disorder Questionnaire.* The performance response in high-performance athletes, according to mood phases, has also been documented[9]. It is in this same group where it has also been pointed out that sports practice and high-demand training could hinder the correct diagnosis due to the tendency to normalize behavior and the high level of energy they display, also posing that the amount of energy could be an indicator of the course of the disorder[10].

Regarding the possible effects of exercise on the course of BD, physical activity

has been referred to as a “double-edged sword”, mentioning, as previously stated, some possible harmful effects of exercise in specific cases. This is due to publications that postulate a certain relationship between increased physical activity and the facilitation of manic or hypomanic phases in some groups of patients through qualitative studies that analyze patients’ individual experience around physical activity[11]. It is noteworthy to mention that, in these same qualitative analyzes, it is indicated that exercise has also produced a calming effect in the same mood phase (mania or hypomania), which has suggested that the prescription of exercise in bipolar patients should be individualized, such as in other diseases, considering the patient’s previous experience with physical activity. Its follow-up and compliance could provide significant value in the evolution of BD.

In the relationship between mood phase and physical activity, the interaction between this and the trigger of depressive phases has also been studied. Interestingly, a decrease in physical activity has been reported in bipolar patients with a history of frequent physical activity: it could facilitate the appearance of depressive episodes, as published by Proudfoot et al., where, through a semi-structured interview in 209 people with a clinical diagnosis of BD between 18 and 30 years of age, different triggers were sought according to mood phase, describing among the triggers of depressive episodes, the reduction or cessation of physical activity[12].

Various scientific publications have surfaced in recent years studying another aspect that has an impact on the indication of physical activity in bipolar patients, that is, the essential somatic comorbidity associated with this group, where excess malnutrition and metabolic and cardiovascular pathologies appear in the first plane of diseases, and where, also, the practice of physical activity already has greater validity and strength of recommendation[13][14]. It is interesting to consider that some of these aspects, such as excess malnutrition, have been linked to worse treatment outcomes in patients with BD[15]. It is also known that bipolar patients have a mortality rate two to three times higher compared to the general population[16].

Additionally, there is more evidence regarding lifestyle and treatment in bipolar patients. It has been reported that bipolar patients may show higher indicators of a sedentary lifestyle than the general population, as well as other problems related to lifestyle, which are added to the side effects of various drugs widely used for the control and management of the disease, such as mood stabilizers and antipsychotics, which are associated with metabolic and cardiovascular alterations, especially if they are considered to be indicated for prolonged periods, reinforcing the indication to consider the prescription of physical activity as routine in this group of patients[17][18].

Concerning the impact of physical activity on the symptoms of BD and its phases, one of the first studies to address this issue was conducted by Ng et al. in 2007, wherein a retrospective study performed in a small sample of hospitalized patients with the diagnosis of BD who were invited to participate in a walking group during their hospital stay voluntarily. The study compared the results with the group of patients who did not participate and observed a favorable impact on those who participated in the intervention, measured through a scale that evaluated anxiety, depressive and stress-related symptoms, obtaining an improvement in all the evaluation subscales[19]. Despite the methodological limitations of the study, these results stimulated interest in knowing the scope of physical activity in the disease beyond the indications

associated with comorbidities and general recommendations for well-being in health.

The importance of individual perception regarding the benefit according to the type and scenario of physical activity chosen has also been pointed out. Suto and collaborators, in a qualitative study, evaluated different strategies used by patients with a diagnosis of BD to maintain adequate control of their disease, highlighting physical activity as a widely used strategy, where the participants also referred to how the scenario where they practiced sports (for example, outdoor sports) and the type of exercise was important to achieve that goal according to their experience[20].

Another aspect studied is the regulatory effect of physical activity on sleep, with an improvement in sleep quality[11], also establishing a two-way relationship between physical activity and sleep quality, influencing positive or negative one over the other[21]. It is also known that poor sleep quality is related to the appearance of somatic comorbidities (coronary heart disease, cerebrovascular disease, diabetes, obesity, among others[22] frequent in bipolar patients. Therefore, the intervention of physical activity could improve both aspects related to comorbidities and factors that influence or manifest changes in bipolarity itself.

In addition to the intrinsic effect proposed on mood and comorbidities, continuous physical activity can provide structure to the day and motivation, especially when finding a type of physical activity in which they feel committed, and its practice is gratifying, with the appearance in short-term exercise, pleasant sensations linked to well-being. As it has been indicated in some reports in the general population[23][24], this allows integrating it in such a way that it helps to organize the day better, optimize community networks, and maintain motivation for the future, often with a new argument to advance recovery.

Physiological and neurobiological mechanisms proposed in the interaction between physical activity and bipolarity

Multiple physiological and neurobiological mechanisms have been studied to understand the multidimensional scope that physical activity could have in bipolar patients. One of them is the serotonergic system, which is due to evidence suggesting a decrease in the central activity of this neurotransmission system in depressive phases and also in euthymia[25]. Additionally, a study conducted by Drevets et al. using Positron Emission Tomography observed a decrease in the binding potential of the 5HT1A receptor in the raphe, hippocampus, and amygdala, which was more significant in the group of bipolar patients and patients with major depressive disorder with a history of a bipolar family[26]. In addition, in relation to the same serotonergic system, it is proposed that muscle activity requires the absorption of branched-chain amino acids. They usually compete with tryptophan, the precursor to serotonin, which is transported across the blood-brain barrier. By reducing the number of competitive amino acids through muscle absorption, aerobic exercise increases the chances that tryptophan will cross the blood-brain barrier and, therefore, can increase serotonin in the brain.[27]. It has also been observed, through studies with the intracerebral dialysis technique, an increase related to the physical activity of extracellular serotonin and its acid metabolite indoleacetic 5- hydroxy in various brain areas, including the hippocampus and cerebral cortex[28].

In the dopaminergic system, a state of hyperdopaminergia has been hypothesized in manic states, specifically elevations in the availability of D2 and D3 receptors and an overactive reward processing network. In the case of depressive states,

although there is abundant literature on the importance of the dopaminergic system in Major Depression, there are no consistent findings in the depressive states of bipolar patients, as published by Ashok et al. in a systematic search of postmortem, pharmacological, and in-vivo neuroimaging studies.[29] Aerobic exercise has shown, in different animal studies, an increase in dopamine levels in the striatum, hypothalamus, midbrain, and brainstem, which reinforces the idea of the positive effect of physical activity, especially aerobic activity in mood and cognition.

The role of phenylethylamine, an endogenous neuroamine, has also been studied. It is selectively metabolized by monoamine oxidase B into phenylacetic acid, which is measurable in urine and has been associated with physical energy, mood, attention, and possesses an action in noradrenergic and dopaminergic synapses. Additionally, it has been observed that it tends to decrease its values in urine in unipolar and bipolar depressed patients. In a study conducted by Szabo and collaborators, they measured phenylacetic acid levels in men with a history of previous regular physical activity, after 30 minutes of moderate physical activity to 70% of the total cardiac capacity, observing a significant increase of this in urine in relation to the same group when they did not perform physical activity[30].

In the hypothalamic-adrenal pituitary axis, significant abnormalities are reported in bipolar patients and patients with unipolar psychotic depression. It has been determined that up to half of depressed bipolar patients fail the cortisol suppression test with dexamethasone, suggesting an altered relationship in negative axis feedback. Also, in postmortem studies, a reduction in glucocorticoid receptor messenger RNA expression has been observed in brain tissue samples from bipolar patients[31]. In addition, it has been published that regular physical activity allows the possibility of reducing the rise in cortisol in situations of high psychosocial stress[32].

A possible role for endocannabinoids has also been studied, due to their similar psychological effects, such as anxiolysis, sedation, and feelings of well-being. There is a high density of type 1 endocannabinoid receptors in the frontal cortex, amygdala, hippocampus, and hypothalamus. A single session of physical activity at 70% - 80% of maximum heart rate delivers an optimal increase in endocannabinoids. One of the most critical endocannabinoids in relation to exercise would be Anandamide. This endocannabinoid easily crosses the blood-brain barrier and is central to the benefit of aerobic activity on mood. It is produced both centrally and peripherally, tends to decrease under psychosocial stress and to increase after physical activity, and it would also have an essential role in anxiety and depression given its regulatory effect on amygdala hyperactivity[27].

Another molecule studied is the Brain-Derived Neurotrophic Factor (BDNF), which has an essential role in the neuroplasticity of patients with BD. Its tendency to decrease in the maniacal and depressive phases of the disease has been observed[33]. One of the difficulties that could occur associated with the decrease in BDNF in hippocampal cells is the reduction of the so-called “cellular resilience”, that is, a lower capacity for resistance to noxas, such as excess glucocorticoids secondary to hyperactivity of the hypothalamic-pituitary-adrenal axis and other injuries, especially in hippocampal neurons[28]. It has been reported that an isolated session of physical activity increases BDNF levels. Likewise, in the case of those who perform continuous physical activity, this effect is more significant, and also, in this group, it tends to increase BDNF values even in repose. Preliminarily, it has been pointed

out that the amount of the positive effect of aerobic physical exercise on BDNF would be smaller in women than in men and more clearly reported at moderate to high intensity of exercise[34].

The change in the inflammatory response has also been explored, this due to a pro-inflammatory profile pattern present in bipolar patients, with a predominance of pro-inflammatory cytokines such as TNF a, Interleukin 6 and 8, in addition to a reduction of Interleukin 4, which has anti-inflammatory activity in both in manic and depressive phases. However, the role of terlequine 6 is more complex since its action could be pro or anti-inflammatory depending on the receptor to which it binds. Physical activity could cause an activation of the binding of Interleukin 6 to mainly anti-inflammatory receptors, which would have a secondary, favorable impact on the levels of BDNF and somatomedin. This is associated with the possible mechanism of reduction of cognitive damage through the reduction of hippocampal inflammation[28]. In addition, it is proposed that there could be a close relationship between physical exercise, an increase in the endocannabinoid Anandamide, and an increase in BDNF; there has been an attempt to show this by blocking cannabinoid type 1 receptor in rats, generating, as a result, a lower response to increase BDNF in them post-exercise[35].

Among the mechanisms, the positive impact of physical activity on the probable mitochondrial dysfunction present in BD is suggested, as it occurs in other diseases with mitochondrial involvement, where physical activity has shown benefit through this mechanism[36]. This mitochondrial dysfunction is proposed due to the observed alterations in brain energy metabolism, the impact of mood stabilizers on the mitochondria, the increase in deletions of mitochondrial DNA in neural tissue of bipolar patients, and the association of mutations and polymorphisms of mitochondrial DNA with bipolarity[37]. It has also been suggested that exercise could be related to the activation of a protein kinase activated by AMP, which would cause positive effects on learning, memory, neurogenesis, and gene expression associated with mitochondrial function in the hippocampus[38].

CONCLUSIONS

There is a long medical tradition that integrates the indication of physical activity as a treatment for diseases, and the case of BP should not be the exception. Although conclusive studies have not been published in this regard, there is a significant amount of literature that recommends the practice of continuous or frequent physical activity, mainly moderate or high-intensity aerobic activity, which is possible to make operative in adult patients without somatic impairment that contraindicates it, and, with the knowledge of its limitations, through the training of the patient in the measurement of their heart rate during exercise and estimating, using some highly diffused formulas in sports, such as those of Fox[39] or Tanaka[40], suggested heart rate parameters for the patient's training session, always considering a previous general medical evaluation, and investigating the absence of contraindications to performing physical exercise.

According to the information currently available, it is possible to say that it is highly suggestive that regular physical activity has a favorable impact on the control of different aspects of BD, such as the attenuation of mood and cognitive symptoms, a decrease in risk or of the impact of somatic comorbidities, as well as favoring community contact, sense of agency, and motivation regarding personal development.

The clinician must make an effort, in

light of the patient's mental history, to perform a general medical evaluation of possible comorbidities and specific medical conditions of the patient, as well as the patient's previous experience with physical activity, to recommend it in a structured way, considering that frequency, intensity, time of day, relationship with food, duration and type of exercise, among other aspects, must be carried out in a personalized way, and subsequently collecting the experience, tolerance, and adherence to what is prescribed, as well as the patient's relationship with physical activity as a possible influence to mood swings. Despite the existence of certain recommendations where the appearance of favorable mechanisms for both the disease and comorbidities is explained through neurobiological and physiological theories, the prescription must be conducted in such a way as to not hinder the patient's access to it, knowing that the greatest benefits in general morbidity and mortality, they appear when passing from a completely sedentary life to initiating small changes in the sense of improving physical activity[41].

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