# PHYSICAL EXERCISE AS A NON-PHARMACOLOGICAL AID IN THE TREATMENT OF ANXIETY DISORDER

## EXERCÍCIO FÍSICO COMO AUXÍLIO NÃO-FARMACOLÓGICO NO TRATAMENTO DO TRANSTORNO DE ANSIEDADE

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**Received:** 05/13/2023. **Accepted:** 05/25/2023

## ABSTRACT

**Anxiolytics such as with selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and benzodiazepines are often used to treat anxiety disorders. However, up to a third of patients do not respond to them, and they can have side effects. Regular physical activity, on the other hand, can improve cardiovascular, urinary, and brain functions. Exercise increases nitric oxide production in endothelial cells, relaxes smooth muscle cells, inhibits platelets, and lowers low-density lipoprotein while increasing high-density lipoprotein. It also increases dopamine receptor affinity, leading to anxiolytic effects, and may link to noradrenaline levels in the brain, which also have anxiolytic effects. Exercise intensity can also regulate neurotransmitter release in the brain, which may have a role in anxiety. Meta-analyses and systematic reviews show the benefits of physical activity in treating anxiety disorders. Practicing physical activity reduces anxiety scores compared to sedentary individuals. Physical activity regulates anxiety through systemic and intracellular pathways, making it a potential alternative or complementary strategy for treating anxiety disorders. It has multiple benefits for both physical and mental health and has fewer side effects than anxiolytics.**

**KEYWORDS:** Anxiety disorders; Exercise; Anxiolytics; Treatment.

## 1. INTRODUCTION

Anxiety disorders are a common mental health condition, and pharmacological treatments such as anxiolytics are frequently used to manage the symptoms of anxiety. The gold standard treatment options for anxiety include Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) as well as benzodiazepines[1].

However, while these medications can be effective for reducing symptoms of anxiety, they also have several side effects that can impact a patient's quality of life. These side effects include psychiatric side effects, such as an increased risk of suicidal ideation with SSRIs, as well as physical side effects like nausea, weight gain, decreased libido, and sexual dysfunction in both men and women[2,3].

Additionally, up to a third of patients may not respond to these treatments. Therefore, it is important for healthcare providers to consider both the benefits and potential risks of pharmacological treatments for anxiety and explore alternative options for patients who do not respond to these medications[4].

## 2. METHODS

This comprehensive literature review search was conducted to identify all peer-reviewed original and systematic manuscripts that investigated the effects of physical exercise treatment on anxiety.

We searched the PubMed and Scopus databases from the inception of each electronic database to 14 March 2022.

We used the following search terms (adapted according to the format required by each database: (physical exercise) *OR* (exercise) *AND* (anxiety) *OR* (anxiety disorder).

## 3. RESULTS AND DISCUSSION

### Benefits of Exercise

It is widely known the benefits of physical exercise in the cardiovascular system. The benefits of exercise are mainly mediated by its effects on the production of nitric oxide in endothelial cells in the vessels, which leads to improvement of endothelial function, relaxation of vascular smooth muscle cells[5], inhibition of platelets[6] and decrease of Low-Density Lipoprotein (LDL) and increasing High-Density Lipoprotein (HDL)[7].

Previous studies[8,9] showed that hypertensive individuals subjected to physical conditioning and resistance training for 45 minutes three days a week

over three months had significant improvements in their physical fitness and metabolic tests, such as fasting glucose, high-density lipoprotein, and low-density lipoprotein. Rats continuously trained for five days a week for 1 hour per 2 months had greater relaxation compared to the sedentary animals. When trained in an accumulated manner 4 bouts of 15 minutes/day in the same period, no differences were reported in the vascular function compared to the sedentary rats[10].

Although physical exercise benefits the cardiovascular system, other effects were reported in several organs, for instance, restoration of erectile function in patients with erection dysfunction in obese[11] and subjects with metabolic syndrome[12], ameliorating of symptoms of the overactive bladder[13]. In mental diseases, such as dementia[14] and schizophrenia[15,16], physical exercise showed: i) neuroprotective effect; ii) attenuation of cognitive decline; and iii) improvements of their symptoms.

## Physical exercise and brain

The benefits of physical exercise on psychiatric disorders have been addressed in several pathways as illustrated in Figure 1. Among these effects, the secretion of neurotransmitters is the most described in the literature, especially monoamines, which have been linked to exercise-induced neuronal adaptation.

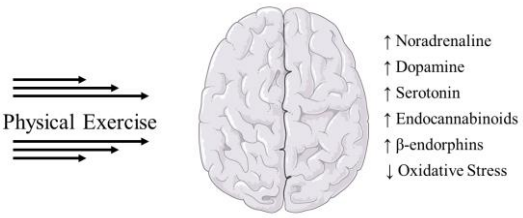


**Figure 1.** Physical exercise and the release of neurotransmitters and other molecules.

Rats subjected to running-wheel exercise 5 days per week for 8 weeks had higher dopamine levels in the brain, resulting in significant antidepressant effects compared to sedentary animals[17]. Besides the higher levels of dopamine induced by physical exercise, another important effect of exercise is to lead to the increased affinity of dopamine receptors, causing anxiolytic effects[18].

Noradrenaline is an important mediator that participates in memory consolidation and retrieval, emotional memories and anxiety[19]. Rats trained for 8 weeks on a treadmill and wheel showed a significant increase of noradrenaline in the brain compared to sedentary rats[20]. In addition, with the increased levels of noradrenaline in the brain, there is a higher production of endogenous noradrenaline in the peripheral nervous system and endothelium basally [21–23] and when exercise-induced[24], these effects may be a potential link of exercise-anxiolytic effect.

In the animal model, the reduction of serotonin in the brain has been addressed to learned helplessness[25,26]. Interestingly, moderate exercise, such as treadmills and running-wheel decreased the levels of serotonin in the brain[27,28]. However, high-intensity training on the treadmill significantly increased the levels of serotonin[29]. Altogether, these results indicate that the intensity of the exercise regulates the neurotransmitter release in the brain and has a potential role in anxiety.

Meta-analyses and systematic reviews have shown the benefits of physical activities in adults with anxiety disorders[30]. A previous study[31] quantified the anxiety scores in a sample of healthy individuals who practiced physical activities. A previous study[31] compared those who did not practice exercises, called sedentary individuals. The results showed that practitioners of physical activity have lower anxiety scores. Active individuals presented a prevalence of 9,4% intense anxiety and sedentary participants presented 25,4%[32].

Anxiety is modulated by two components, the frontal cortex, and the hippocampus. Having this in mind, it is important to notice that physical activity involves effects in so many ways, and again, there are two specific and important ones: both systemic and intracellular pathways[32].

The kynurenine pathway (a metabolic pathway and tryptophan needed) plays an important role in the regulation of anxiety leading to picolinic acid as a metabolite. In a running mice experiment, high levels of this acid were increased in their hippocampus, which led to an increased turnover of the kynurenine pathway. Meanwhile, tryptophan levels were not changed between the running and inactive mice, and it can be said that picolinic acid plays an important role in the regulation of glucose metabolism because there is a high level of picolinic acid and so it can be involved in the regulation of hippocampal metabolism during exercise as well[32].

## Acute physical exercise in anxiety

Consistently, several studies[19,33] showed that moderate aerobic exercise acts similarly to anxiolytic medication, increasing serotonin and noradrenaline in the brain. According to the World Health Survey, which includes 47 countries, indicated that sedentary lifestyle increases the odds of anxiety symptoms by about 32%[34].

A previous study[35] showed that a single bout of aerobic exercise over 30 minutes can lead to a small-significant reduction of anxiety symptoms compared to stretching exercises in healthy subjects. When compared to the high- with low- or moderate-intensity resistance exercise with weightlifting machines, the single boat of 20 minutes lower and moderate-intensity has effectively decreased the effectiveness of anxiety symptoms, whereas the high-intensity increased the anxiety symptoms[36].

Focht & Hausenblas, (2001)[37] showed that cycling, rowing, and Stairmaster machines lead to decreasing state of anxiety and increasing tranquility in young women. Similar studies[38–40] showed that acute moderate aerobic exercise demonstrated small to

moderate effects reducing temporarily the anxiety symptoms in non-clinically anxious subjects. Interestingly, one trial showed that subjects diagnosed with panic disorder showed that higher intensity aerobic exercise led to greater antipanic effect compared to moderate- and low-intensity exercise [41].

In subjects with a high state of anxiety, acute physical exercise mediated greater effects decreasing the anxiety symptoms[42]. The treatment with acute aerobic exercise had greater improvements in the anxiety symptoms in subjects with higher trait anxiety compared to the lower trait[43,44]. Altogether, the reports available in the literature show that acute physical exercise mediates as a potential treatment of anxiety symptoms with greater effects in subjects with higher anxiety states.

## Chronic physical exercise in anxiety

Continuous physical exercise has been recommended as a prevention tool for many disorders, e.g., cardiovascular[45], diabetes[46], insomnia[47], dyslipidemia[48], and erectile dysfunction[49]. This part of the review aimed to understand the effects of long physical exercise practice on anxiety symptoms.

Stroke is associated with functional impairments and cognitive dysfunction, e.g., depression and anxiety[50,51]. A previous study[52] showed that aquatic exercise during 12 weeks with patients who suffered an ischemic stroke had improvements in functional capacity and anxiety and stress levels. In subjects diagnosed with anxiety and/or stress aerobic exercise showed to be an effective treatment for anxiety symptoms[53].

In a previous study[54], regular physical exercise has been suggested as the most potent tool for the prevention and early treatment of anxiety symptoms and mood disorders. Confinement in prison increases the odds of mental health, e.g., the suicide rate in prison inmates is three to eight times higher compared to non-incarcerated subjects[55]. Legrand *et al*., (2020)[56] showed elevated anxiety symptoms in first-time prisoners and 6-week physical exercise had a greater reduction of anxiety compared to the sedentary inmates.

Higher levels of anxiety are closely associated with worse prognosis and increased mortality rates in coronary heart disease[57]. Recent studies have shown that exercise increases serum concentrations of endocannabinoids, which produces sedation and anxiolysis. A study with trained male college students running on a treadmill or cycling on a stationary bike for 50 minutes, considered to be moderate intensity, increased concentrations of anandamide in blood plasma. Anandamide is an endogenous ligand of cannabinoid receptors BC1. Both BC1 and BC2 receptors can be found in the skin, endothelium, and brain, explaining why endocannabinoids effects anxiety and the cardiovascular event vasorelaxation[58].

A previous study[59] conducted a study with females with Major Depressive Disorder (MDD) where it was shown that moderate, but not preferred-intensity exercise resulted in increased endocannabinoid anandamide serum. This finding supports the idea that after moderate sessions of exercise, physical activities play an important role in changing feelings, like depression and anxiety. Endocannabinoid signaling also can act out the behavioral and biological effects of the antidepressant.

Physical activities act out on monoamine levels and can also change the levels of the stress hormone cortisol. Physical activities can be compared with pharmacological treatment or cognitive behavioral therapy. It is known that activation of the HPA (hypothalamic–pituitary–adrenal) axis is an adaptative mechanism in mood change, and its prolonged high activation can lead to a health risk. In a state where the patient has chronic stress, there is a hyperactivity of the HPA axis and elevated levels of glucocorticoids, and a reduced thalamic 5-hydroxytryptamine (5-HT) transporter biding potential has been associated with increased cortisol response and with increased state anxiety. Stated this, it can be suggested that there is an interaction between 5-HT and stress hormone response when humans behave themselves in a negative mood period. It is observed a reduced Adrenocorticotropic Hormone (ACTH) and cortisol secretion in anxiolytic patients compared to healthy control, where secretions are increased. In animals, studies have shown that diminished stress-induced releases of ACTH and cortisol lead to reduce anxious behavior[60].

Endurance activity alters tissue sensitivity to glucocorticoids. When exercising or in other stressor environments, the sympathetic nervous system is activated, resulting in glucocorticoid secretion. However, individuals who practice physical activity show different cortisol responses after acute exercise that are attenuated and dissipated more quickly than in less active individuals. Animals that practice exercise facing demanding stressors show increased glucocorticoid response and mild psychologically stressful stimuli result in an attenuated glucocorticoid response showing less anxious behavior in the novelty situation[60].

Therefore, exercise might reduce symptoms of depressive and anxiety disorders by its influence on the HPA axis and attenuating glucocorticoid response to stressful stimuli. The peptide hormone Atrial Natriuretic Peptide (ANP) can influence the HPA axis, by its inhibition and exhibit anxiolytic activity after central or peripheral administration. ANP plasma concentrations are increased by physical activity, leading to anxiolytic effects. Studies suggest that exercise interacts with the HPA axis to a reduction of depressive and anxiety-related symptoms by its attenuated response to stress stimuli[60]. A study with 60 male college students (30 for the study group and 30 for the control group) shows a significant difference in anxiety levels in the group who did the exercise to the group who did not exercise. Doing physical activity once a week can decrease the individual's anxiety and

stress[61].

## 4. CONCLUSÃO

In conclusion, the available literature consistently shows that acute physical exercise acts as a potential treatment for anxiety symptoms. Moderate aerobic exercise has been found to increase serotonin and noradrenaline in the brain and to act similarly to anxiolytic medication. The effects of acute physical exercise on anxiety symptoms are greater in individuals with higher anxiety states. Chronic physical exercise has also been suggested as a potent tool for preventing and treating anxiety symptoms and mood disorders.

Physical activities can act on monoamine levels and change the levels of the stress hormone cortisol, and they can be compared with pharmacological treatment or cognitive-behavioral therapy. These findings suggest that physical exercise should be considered as a complementary or alternative treatment for individuals with anxiety symptoms.

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