

Original Article

Impact of aerobic exercise on anxiety and neurobiological mechanisms in panic disorder: a mini-review

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Abstract

In the last few decades exercise has been explored as a potential tool to reduce symptoms experienced by patients with panic disorder (PD). This review aims to present the effects of exercise interventions on panic severity, and anxiety symptoms of patients with PD. A literature search was conducted using PubMed and ISI Web of Science databases, with the search terms panic disorder and aerobic exercise, exercise therapy, physical fitness, physical activity, aerobic training. Acute studies suggest that exercise immediately increases panic-related symptoms, but allows the reduction of artificially induced increase panic attacks and anxiety. There is still not clear evidence indicating that regular exercise programs reduce panic-related symptoms, but it seems that this intervention is effective to improve global anxiety measures. In addition, exercise seems to induce neurobiological effects that influence on several neural mechanisms related to anxiety disorders, such as increase of monoamine levels and brain-derived neurotrophic factor (BDNF). Both aerobic exercise and regular aerobic exercise seem to be an appropriate intervention to promote improvements in the severity of anxiety symptoms in PD patients. It is suggested a greater control in the prescription of aerobic exercise, to bring promising answers regarding the efficacy of exercise on symptoms in patients with PD.

Key-words: aerobic exercise, anxiety, cognitive behavioral therapy, neurobiological mechanisms, panic disorder

Introduction

Panic Disorder (PD) can be characterized by recurrent and unexpected panic attacks (PA), where at least one of the attacks was followed by a month (or more) of a persistent concern about new attacks and their consequences, in addition to generate behavioral change related to attacks (American Psychiatric Association, 2013). Epidemiological data indicate that women are more affected than men, with increase rates during adolescence, possibly after puberty, and reach their peak in adulthood, between 20 and 30 years old (American Psychiatric Association, 2013). The diagnosis of PD is performed in a clinical manner, which makes the judgment based on questions about what led the individual to the attack, and also by the individual himself, focusing on how much this panic attack occurred for no apparent reason (American Psychiatric Association, 2013). A PA is characterized by an abrupt outbreak of intense fear that lasts for a few minutes and presents four (or more) of the following psychosomatic symptoms: fear of dying, fear of losing control or going mad, derealization or depersonalization, paraesthesia, chills or chest pain or chest discomfort, nausea or abdominal discomfort, instability, dizziness/vertigo or fainting, feeling of shortness of breath or suffocation, choking sensation, tremors, sweating, palpitations and tachycardia (American Psychiatric Association, 2013).

The most used treatments in patients with PD are through pharmacotherapy and cognitive behavioral therapy (CBT). The combination of these two forms of treatment seems to present better results compared to anyone alone (Furukawa, Watanabe, & Churchill, 2007). Despite this, a study that found no difference after seven months of interruption of a benzodiazepine combination with CBT and CBT alone, was also found in the

literature (Watanabe, Churchill, & Furukawa, 2009). Combined therapy may also lead to greater treatment withdrawal compared to CBT alone (Furukawa, Watanabe, & Churchill, 2007). Although the patients have a good response regarding pharmacological treatment, approximately 20% of them remain symptomatic (Holt & Lydiard, 2007). New strategies are presented with the intention of contributing to the improvement of the clinical picture of patients with PD. A large number of studies have used physical exercise as an important tool within this process (Strohle, Feller, Strasburger, Heinz, & Dimeo, 2006; Strohle et al., 2009; Wedekind, Broocks, Weiss, Engel, Neubert, & Bandelow, 2010; Hovland et al., 2013). These researches has shown that exercise can provide great acute (Strohle et al., 2009) and chronic (Wedekind, Broocks, Weiss, Engel, Neubert, & Bandelow, 2010; Hovland et al., 2013) benefits. Despite the benefit that physical exercise can provide these patients, many of them avoid regular practice, because exercise can induce a PA (Strohle et al., 2009). This possibility, causes them to avoid exercise and present low tolerance for it (Meyer, Broocks, Bandelow, Hillmer-Vogel, & Rütger, 1998; Broocks, Meyer, Bandelow, George, Bartmann, Rütger, Hillmer-Vogel, 1997). In fact, these patients, compared to healthy subjects, presented low cardiorespiratory fitness and higher subjective perception of exertion during physical exercise, which did not seem to be related to the psychological variables (Caldirola, Namia, Miceli, Carminati, Bellodi, & Perna, 2011).

Thus, the objective of the present review was to present the main evidence related to the regular practice of aerobic exercise, as well as the acute effects of aerobic exercise, on anxiety symptoms in patients with PD.

Methods

A literature search was conducted using the following databases: PubMed and ISI Web of Science (Web of Science Core Collection). Search terms were defined accordingly to population (panic disorder) and intervention (exercise), based on previous systematic reviews on the field. The following search query was used: panic disorder, panic attack, aerobic exercise, exercise therapy, physical fitness, physical activity, aerobic training. Medical Subject Headings (MeSH) terms were removed from the query for the search using the Web of Science database. Included reports and important reviews regarding exercise and anxiety disorders were manually screened for additional relevant studies. Experts on the field, including authors from the included reports, were also requested to suggest any additional trials in order to ensure that the review was as comprehensive and up-to-date as possible. Only studies published in English were included.

Aerobic Exercise and Panic Disorder

As already observed in the literature, physical exercise present different modalities and expressions, where we can emphasize on aerobic exercise. The act of doing these exercises consistently and systematically, we classify as aerobic training. There is little evidence in the literature about the effects of exercise and/or training on the improvement of specific symptoms in patients with PD. Below, the acute and chronic effects of aerobic exercise on specific symptoms in patients with PD will be described and analyzed.

Effect of aerobic exercise on symptoms in patients with panic disorder

In general, the literature demonstrates that aerobic exercise can provide an anxiolytic effect in patients with PD (Strohle et al., 2009; Esquivel, Díaz-Galvis, Schruers, Berlanga, Lara-Muñoz, & Griez, 2008). In a study conducted by Esquivel et al.¹³, aerobic exercises were performed in a cycle ergometer, where the patients were divided into two groups: moderate /strong exercise (exercise group) and light exercise (control group). The exercise group underwent warm-up for three minutes (70 rpm and 100 watts (W) for women, 150 W for men) and after warming up they were required to reach between 80-90% of maximal heart rate and last for 15 minutes of total work or until the patient feels exhausted. In the control group, the procedures were the same, however with a load of 1W per kilogram body and a rotation between 20-70 rpm. After the conditions, both groups underwent a provocative PA test with inhaled carbon dioxide (CO₂) (35% CO₂ and 65% O₂). The results demonstrated that CO₂ panic reactions were lower in the exercise group (moderate/strong) compared with the control group (light exercise), suggesting that exercise may have an antipanic effect.

The intensity of exercise seems to contribute to the reduction of PA by a provocative test with inhalation of CO₂. Even with healthy subjects, after intense exercise, subjects had fewer panic symptoms when exposed to 35% CO₂ (Esquivel, Dandachi, Knuts, Goossens, Griez, & Schruers, 2012). When comparing again the exercise of a resting condition, 30 minutes duration on the treadmill and intensity of 70% VO₂max, this was enough to cause a significant increase of atrial natriuretic peptide (ANP). The results demonstrated that there is a positive correlation between exercise inducing a plasma increase in NP and exercise associated with a reduction in PA scores (Strohle, Feller, Strasburger, Heinz, & Dimeo, 2006). When considering the intensity of the effort, 20 minutes of aerobic exercises with moderate intensity (60% of HRmax) and high intensity (90% of HRmax) were performed, which showed sensitivity to anxiety reductions in both cases. However, high-intensity exercise caused sharper reductions in an overall measure of anxiety sensitivity (Broman-Fulks, Berman, Rabian, & Webster, 2004).

In the study conducted by Strohle et al. (2009), patients with PD and healthy subjects underwent a provocative PA test using the cholecystokinin tetrapeptide (CCK-4). The use of CCK-4 was performed after two experimental conditions, one at rest and the other with aerobic exercise, with a 30 minute run and 70% VO₂max intensity. The results showed that PA's were less frequent when the exercise was performed in advance (20.8%, four patients and one healthy) compared to rest (62.5%, nine patients and six healthy ones). Although the CCK-4 induced increase in PA, anxiety and somatic symptoms, in the exercise condition this effect was lower.

Effect of aerobic training on symptoms in patients with panic disorder

It can be observed in the literature that aerobic training has been prescribed at a frequency of 3 times per week, total duration between 30 and 60 minutes and the intensity prescribed as a percentage of maximal heart rate (60% - 80%) and maximal oxygen consumption % VO₂max).

For example, in a study published in 2012 by Hovland et al. (2013), subjects with PD were submitted to aerobic exercise (running and/or walking) three times a week, with 60-80% of maximum heart rate and a total duration of 60 minutes. In addition, patients also performed circuit-type exercises and sports activities. The results demonstrated that there was a significant improvement in cognition (catastrophic thoughts associated with panic attack), physical symptoms, and severity of agoraphobic avoidance.

The study by Wedekind et al. (2010) compared treatment with aerobic exercise, with or without the use of drugs (paroxetine), with a condition of control (relaxation), associated or not with paroxetine. The patients were submitted to running exercises, intensity of 70% VO₂max, three times a week with a total duration of 45 minutes. In the fourth week of intervention, the group that performed aerobic exercise presented better results regarding the severity of PD, being verified through the "Panic and Agoraphobia Scale".

A study conducted by Broocks et al. (1998) compared three groups: aerobic exercise, clomipramine and placebo. Aerobic training was done in a more periodized way. In the first week patients were asked to perform a walk of 6.4 kilometers (km) 3 or 4 times a week. In the second week they were asked to give "two-minute run" shots, completing the same distance (i.e., 6.4 km). In the third week, subjects gradually performed an increase in running time by the same distance. In the fourth week, the subjects performed the race during the whole course. The results showed that the medication was superior to the other conditions (exercise and placebo), using the Panic and Agoraphobia Scale and the Hamilton Anxiety Scale. Despite the superiority of clomipramine, aerobic exercise was superior to placebo. Thus, aerobic exercise may have some anxiolytic effect in patients with PD.

Meyer et al. (1998) also demonstrated that patients with PD who performed aerobic exercises, when compared to the control and placebo groups, had reductions in anxiety scores at the sixth and tenth weeks. In this study, aerobic exercise was a race, performed three times a week with a total duration of 40 to 60 minutes.

Broman-Fulks et al. (Broman-Fulks, & Storey, 2008) demonstrated that aerobic exercise performed in six sessions over 20 minutes at 70% HRmax intensity was enough to decrease anxiety sensitivity when compared to the non-exercise condition.

Thus, it seems that aerobic exercise being performed in a systematic and continuous way, provide benefits in relation to the severity of PD. However, despite the promising results demonstrated by the regular practice of aerobic exercise in patients with PD, a study by Merom et al. (Merom et al., 2008) did not show such results. In this study, the cognitive behavioral therapy (CBT) intervention associated with aerobic exercise was compared with a CBT intervention associated with educational programs. Educational programs served as a control condition. The results showed that exercise had no influence on the improvement of stress, anxiety and depression.

An important point in the chronic studies of aerobic exercise in patients with PD is the precarious prescription of training. There is no good control of the intensity, duration and frequency of training. Another relevant factor is that the prescription has not been performed by a physical education professional. Perhaps, the lack of a structured protocol for the prescription of aerobic training may be crucial for the adverse outcomes found.

Neurobiological Mechanisms

Exercise seems to induce neurobiological effects that influence on several neural mechanisms related to anxiety disorders (Fuss et al., 2010; Cassilhas, Antunes, Tufik, & De Mello, 2010). Studies showed that the effects of exercise are compared to the CBT or drugs in anxiety disorders (Wipfli, Rethorst, & Landers, 2008; Rossy et al., 1999). For example, monoamine levels may be increased with regular and systematic exercise training. Studies have shown that significant levels of noradrenaline and 5TH, as well as the expression of 5HIAA and 5-HT_{2C} receptors in the limbic system have been reported following exercise on a treadmill of chronic form (Acworth, Nicholass, Morgan, & Newsholme, 1986; Greenwood et al., 2012). Another important mechanism that suffers major adaptations is the hypothalamic-pituitary-adrenal system (HPA) subjected to chronic stress has great hyperactivity and elevated levels of glucocorticoids (Lupien, Buss, Schramek, Maheu, & Pruessner, 2005), which are harmful to the body. Thus, one of the main effects of endurance training is to alter the tissue sensitivity to glucocorticoids (Duclos, Gouarne, & Bonnemaïson, 2003), another effect of exercise is

the activation of the sympathetic nervous system that stimulate the secretion of glucocorticoids (Budde, Pietrassyk-Kendziorra, Bohm, & Voelcker-Rehage, 2010; Budde, Voelcker-Rehage, Pietrassyk-Kendziorra, Machado, Ribeiro, & Arafat, 2010).

Studies have shown that physically active people have different cortisol responses after acute exercise are attenuated and dissipate more quickly than less active individuals (Rudolph, & McAuley, 1998). Hence, exercise can reduce symptoms of anxiety due to their influence on the HPA system and glucocorticoid attenuated response to stressful stimuli. Factor that influences the HPA system is the peptide hormone ANP, which has been observed to inhibit the HPA system (Ströhle, Kellner, Holsboer, & Wiedemann, 1998). The physical activity also increases the plasma concentrations of ANP (Mandrourkas, Zakas, Aggelopoulou, Christoulas, Abatzides, & Karamouzis, 1995) and anxiolytic effects of exercise correlate with increased plasma concentrations of ANP (Strohle, Feller, Strasburger, Heinz, & Dimeo, 2006). Though, one of the mechanisms observed with CBT, tailored to the needs of each patient, is the power to produce volumetric changes in the amygdala, in the case of chronic anxiety (Neves-Pereira, Mundo, Muglia, King, Macciardi, & Kennedy, 2002). Human studies have shown that a deficiency in the availability of brain-derived neurotrophic factor (BDNF) is associated with vulnerability to depression (Hölzel et al., 2009) and this deficiency is reduced after 30 minutes of exercise in patients with panic disorder but not in healthy controls (Ströhle et al., 2012).

Final considerations

Both aerobic exercise and regular aerobic exercise seem to be an appropriate intervention to promote improvements in the severity of anxiety symptoms in PD patients. It is suggested a greater control in the prescription of aerobic exercise, to bring promising answers regarding the efficacy of exercise on symptoms in patients with PD.

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Conflict of interest

Authors declare have not conflict of interests.

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