

Chronic effects of aerobic exercise on panic disorder: a systematic review of randomized and non-randomized trials

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BACKGROUND: In general, most studies have supported an association between the acute effects of exercise and a reduced state anxiety, but failed to completely explain the relationship between the chronic effect of exercise and anxiety traits.

OBJECTIVE: The aim of this study was to systematically review the literature regarding the chronic effect of exercise on symptoms associated with panic disorder.

METHODS: The studies were retrieved from a MEDLINE/PubMed, ISI Web of Knowledge and SciELO. We adopted PICOS's strategy recommended to determine the eligibility criteria. The survey was conducted using an advanced search in the ISI Web of Science and MEDLINE / PubMed with MeSH terms and Entry Terms for the keywords "Panic Disorder" basis and "Exercise". Boolean operators "AND" and "OR" were used separately or in combination. Two independent researchers performed the selection of studies; in case of disagreement they sought a consensus on the selection.

RESULTS: A total of 265 articles were identified: 199 articles from PubMed/Medline, 63 articles from ISI Web of Science and 3 articles by manual searches. Thus, 31 articles were analyzed by the eligibility criteria and the exclusion criteria, a total of five studies included in the systematic review.

CONCLUSION: The regular practice of aerobic exercise seems to be an appropriate intervention to promote improvements in the severity of anxiety symptoms in PD patients.

KEYWORDS: Chronic effects, Aerobic exercise, Panic disorder.

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INTRODUCTION

Panic disorder (PD) is characterized by the presence of recurrent panic attacks, with at least one of them being sudden and followed by at least one month of persistent concern about a new attack or concerns about its effects.¹

Epidemiological data is scarce regarding the prevalence and incidence of PD, perhaps because until the nineteen eighties, the diagnosis of people suffering from anxiety attacks was anxiety neurosis. PD is about

twice as common in women as it is in men (DSM-V) and usually begins in late adolescence or early adulthood, with an average onset between 20 and 30 years.¹ Long term PD is associated with a decrease in productivity, well-being, social contact and self-realization.² In addition, comorbidities such as chest pain,³ coronary artery disease⁴ and other psychiatric comorbidities such as depression,⁵ substance abuse and suicide are common in these patients.⁶ In a review by Konnopka et al.⁷ it was found that most of the costs related with and anxiety disorders and their treatment were linked to PD and generalized anxiety disorder.

The most common forms of treatment in PD patients are pharmacotherapy and cognitive-behavioral

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therapy (CBT). In the acute phase of treatment, the combination of antidepressants and CBT appears to have better outcomes than the isolated treatment with either antidepressant or psychotherapy. The combined treatment gains seem to endure when compared to either monotherapy given alone. However, combined therapy may result in more dropouts than psychotherapy because of side effects.⁸ Despite the assumed superiority of combined therapy, no difference was found after seven months of interruption between a combination of benzodiazepine with CBT vs. the isolated use of CBT.⁹ Furthermore, although patients with PD present good pharmacological responses to treatment, approximately 20% of them remain symptomatic.¹⁰

Due to the chronic nature of anxiety disorders, new treatment strategies are being introduced, one of which is the use of physical exercise. Consequently, a growing number of studies have used exercise as a possible strategy to reduce anxiety. It seems that exercise is anxiolytic both for healthy subjects and for patients with PD, but, at the same time, it can induce panic attacks in these patients.¹¹ The possibility of physical exercise causing the patient to experience some symptoms of panic attack causes these individuals to avoid it and to exhibit low tolerance while exercising.^{12,13} This can be troubling, because some research has shown the anxiolytic effects of exercise, both acutely^{11,14} and chronically.^{13,15} Acutely, exercise seems to have an antipanic and anxiolytic protective effect in patients who are subjected to carbon dioxide inhalation¹⁴ and administration of cholecystokinin tetrapeptide.¹¹ This is possibly explained by the fact that the acute exposition to exercise increases the plasma concentration of atrial natriuretic peptide, which is known to have anxiolytic effects.¹⁶ However, few studies support the hypothesis that physical exercise has chronic anxiolytic effects.^{13,17} For example, in the study by Meyer et al,¹³ it has been demonstrated that aerobic exercise compared to placebo condition provided anxiolytic effects in the 6th and 10th week of treatment. However, some interpretations of the chronic effects of exercise may be inaccurate. This can be seen in the study published by Wedekind et al,¹⁸ where only the fourth week of the exercise intervention showed improvements in the Panic Agoraphobia Scale, compared to the condition without exercise. Nonetheless, this improvement may have been derived from the use of paroxetine, which improves outcome (as measured by the Panic Agoraphobia Scale) when compared with placebo and independently of exercise.

In general, most studies have supported an association between the acute effects of exercise and a reduced state of anxiety, but failed to completely explain the relationship between the chronic effect of exercise, physical fitness and anxiety traits.¹⁹ The short duration of the studies and the inconsistency in the selection of

patients with PD regarding adequate diagnosis weakens the results of several studies. The use of different anxiety measurements can further limit the generalizability of their findings. Moreover, the lack of valid control groups also occurs. Finally, for some disorders, such as PD, exercise can be helpful as a therapeutic alternative or add-on for the treatment of anxiety disorders.²⁰

The aim of this study was to systematically review the literature regarding the chronic effect of exercise on anxiety symptoms associated with PD. Although a consistent association between exercise and anxiety levels has been described, most authors emphasize that the causal effect of exercise decreasing anxiety is yet to be supported.

METHODS

Eligibility Criteria

We adopted PICOS's strategy ("Population", "Intervention", "Comparators", "Outcomes" and "Study design") recommended to determine the eligibility criteria.

1. Population: men and women, physically active or not, diagnosed with PD, according to DSM (III, IV and V) and to the tenth edition of the International Classification of Diseases (ICD-10), with or without other comorbidities associated.
2. Intervention: participants subjected to a chronic aerobic exercise intervention, associated or not with the use of drugs and other therapies (cognitive behavioral therapy).
3. Comparators: existence of a control group (placebo), which did not receive an aerobic exercise intervention for comparison purposes.
4. Outcomes: measurements that assess symptoms of PD included. These had to be divided into scales that assess global anxiety, frequency and intensity of panic attacks, phobic avoidance and cognitive distortions in relation to physical reactions of anxiety;
5. Study design: randomized controlled trials and non-randomized studies used to evaluate the chronic effect of exercise on symptoms of panic.

Exclusion Criteria

We excluded studies without any aerobic exercise intervention and/or without detailed statistical procedures and results of study outcome. The articles were not published in English were also excluded.

Sources

The studies were retrieved from MEDLINE/PubMed, ISI Web of Knowledge and SciELO. Experts on the subject of the present study were also contacted to indicate articles.

To find additional articles, all tables in retrieved articles were examined for evidence of previous systematic reviews; references to randomized controlled trials were examined. In addition, we analyzed the references of all selected articles. Searches were closed on the 15th of October of 2014.

Search

The survey was conducted using an advanced search in the ISI Web of Science and MEDLINE/PubMed with MeSH terms and Entry Terms for the keywords "Panic Disorder" basis and "Exercise". Boolean operators AND and OR were used in the following combinations: "Disorder", "Panic" OR "Disorders", "Panic" OR "Panic Disorders" OR "Panic Attacks" OR "Attack", "Panic" OR "Attacks", "Panic" OR "Panic Attack" AND "Exercises" OR "Exercise", "Physical" OR "Exercises", "Physical" OR "Physical Exercise" OR "Physical Exercises" OR "Exercise", "Aerobic" OR "Aerobic Exercises" OR "Exercises", "Aerobic" OR "Aerobic Exercise". All combinations necessary for the search were performed in SciELO database.

Selection of studies

Two independent researchers performed the selection of studies; in case of disagreement they sought a consensus on the selection. The evaluation consisted of a selection of studies by analysis of the title, followed by analysis of the abstract and then the analysis of the full text. When disagreement between the two researchers persisted, a third evaluator was called in to complete the process. Relevant articles were obtained and assessed for eligibility and exclusion criteria described in the methods.

Data collection

The data collected from the study were: numbers of participants, age, treatment performed, medication, study duration, frequency, duration and intensity of exercise, supervision in different treatments, diagnostic criteria and severity of the disease, instruments assessment, comorbidities, randomization of subjects and main results.

RESULTS

A total of 265 articles were identified: 199 articles from PubMed/Medline, 63 articles from ISI Web of Science and 3 articles by manual searches. No article was identified from ScieLO. After the duplicates were removed ($n = 10$), 255 articles were analyzed by title and/or abstract. After this analysis, 224 articles were removed for not corresponding to the studied topic. Thus, 31 articles were analyzed through the eligibility criteria, according to the model proposed by the "Prisma" and through the exclusion criteria. A total of five studies were included in the systematic review as shown in Figure 1.

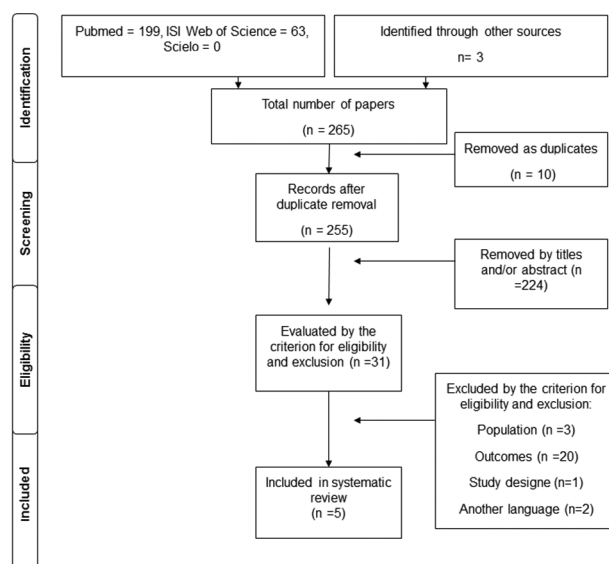


Figure 1- Flow of information through the different phases of Study selection

The treatments used in the five articles selected for systematic review were: CBT, drugs, physical exercise and control condition. The use of healthy individuals, educational programs, and relaxation exercises were used as a means of control; moreover, placebo pills was also used as controls. The drugs used in the treatment intervention during the studies were clomipramine¹⁵ and paroxetine.¹⁸

In one study it was reported that patients received benzodiazepines and selective serotonin reuptake inhibitors;¹⁷ two studies reported the use of promethazine in cases of panic attack.^{15,18} One study noted that the patients did not use medication during treatment¹⁹ and another study made no mention about the use of drugs during interventions.²¹ The treatment time ranged from eight to twelve weeks, except for one in which the follow-up period ranged from six to twelve months.¹⁷

On average, aerobic exercise was prescribed three times a week, between 30 and 60 minutes of total time. However, the intensities are not well established. In one study, subjects were instructed to keep a percentage of maximum heart rate ($60\% - 80\% HR_{max}$)¹⁷ and in another a percentage of 70% of maximum oxygen consumption (VO_{2max}).¹⁸

All interventions with CBT were administered by clinical psychologists with experience. Nevertheless, physical trainers,^{15,18,21} an experienced runner,¹³ physical therapists, occupational therapists and nurses¹⁷ supervised the interventions with physical exercise.

The diagnoses for panic disorder were conducted according to DSM-III, DSM-IV and ICD-10. Only two studies reported the values for the severity of PD.^{18,21}

For the assessment of PD the following instruments were used: "Mobile Inventory", "Agoraphobic Cognitions Questionnaire", "Body Sensations Questionnaire", "Hamilton

Anxiety Scale," "Panic and Agoraphobia Scale" and "Depression Anxiety Stress Scale".

Regarding the type of study, all the studies were randomized, with variability in control conditions, including the use of a placebo, of educational programs, or the absence of exercise or healthy subjects.

For the main outcomes, results were quite contradictory (see Table 1), as it will be explained in the discussion.

■ DISCUSSION

The aim of this study was to review systematically, the chronic effect of exercise on anxiety symptoms in associated with PD.

Data from our review showed some conflicting results. For example, in a recent study published in 2012, by Hovland et al,¹⁷ treatment with exercise provided a significant improvement in cognition (catastrophic thoughts associated with panic attack), physical symptoms and severity of agoraphobic avoidance, respectively measured by "Agoraphobic Cognitions Questionnaire", "Body Sensations Questionnaire" and "Mobile Inventory". However, with CBT better responses were obtained in cognition and physical symptoms.

The Wedekind et al.¹⁸ study compared treatment with aerobic exercise, with or without the use of drugs (paroxetine), with a control condition (relaxation), associated or not with paroxetine. The use of paroxetine was the key to the improved responses relating to anxiety. Indeed, in the fourth week of intervention, the group that performed aerobic exercise was superior compared to relaxation group. Considering that the difference in treatment occurred only after 4 weeks, it should be noted that the improvement might have been caused by the effect of the drug itself.

Corroborating these concepts, another survey, conducted by Brooks et al.¹⁵ compared three groups (aerobic exercise, clomipramine and placebo) for 10 weeks of intervention on the severity of PD with or without agoraphobia. Using the "Agoraphobia and Panic Scale", and the "Hamilton Anxiety Scale", the results showed that clomipramine was always superior to placebo and exercise conditions. Despite the superiority of clomipramine, aerobic exercise was superior to placebo condition. Thus, aerobic exercise alone may have some anxiolytic effect in PD patients in this study.

The hypothesis that aerobic exercise promotes anxiolytic effects has been corroborated in studies with acute PD patients.^{11,14} The explanation for this phenomenon may be associated to some acute physiological and behavioral changes caused by aerobic exercise. One suggestion relates to the fact that exercise increases the levels of atrial natriuretic peptide (anxiolytic action) and

promote anti-panic actions.^{11,14} Aerobic exercise has been shown to reduce generalized anxiety and may also reduce anxiety sensitivity.²² The anxiety sensitivity is a precursor of panic attacks and PD.²³ Taking this into account, protocols of 20 minutes of aerobic exercise with moderate (60% of HR_{max}) or high intensity (90% of HR_{max}) were performed, which caused reductions in the sensitivity to anxiety in both cases. However, the high-intensity exercise caused more abrupt reductions of a global measure of anxiety sensitivity.²² Thereby, it has been speculated that continuous exposure to aerobic exercise leads to a decrease in anxiety sensitivity, a fact observed in another study,²⁴ in which the active lifestyle in PD patients showed lower anxiety sensitivity.

On this basis, it appears that to provide the opportunity for PD patients to participate in regular aerobic exercise programs may be beneficial with regard to the severity of the disorder.

In spite of the lower effectiveness of exercise compared with clomipramine, aerobic exercise was better than control conditions in ten weeks of aerobic training.¹⁵ Using an aerobic training protocol (outdoor running) for 10 weeks (four miles, three or four times a week), significant improvements in specific scales that assess the severity of PD ("Panic and Agoraphobia Scale" and the "Hamilton Anxiety Scale") were reported.¹³ Meyer et al. also demonstrated that PD patients who performed aerobic exercise, when compared to control and placebo groups, had reductions in anxiety scores in the sixth and tenth weeks.¹³ However, in contrast to the evidence showing that aerobic exercises can produce anxiolytic effects in PD patients, another study did not show such improvements: Merom et al.²¹ compared a CBT intervention associated with aerobic exercise versus a CBT intervention associated with educational programs. The educational programs functioned as a control group, in which the subjects received information on healthy eating habits. These results showed that exercise had no influence on improvement of stress, anxiety and depression.

An important point in chronic studies of aerobic exercise with PD patients is the inadequate standardization of training prescriptions. According to our analysis, the control of the intensity, duration and frequency of training is not adequate. In addition, in two studies included in our review,^{13,17} there was no participation of a physical trainer in directing the training prescription. Thus, the lack of a structured protocol for prescribing aerobic training may be crucial to the adverse results. A case report showed that an effort interspersing two minutes of slow walking (73% of HR_{max}) with two minutes of brisk walking (83% of maximum heart rate), consisting of 12 training sessions, causes a reduction in cardiac anxiety.²⁵ In another study published by Broman-Fulks et al,²³ it has been shown that aerobic exercise performed in six sessions, for 20 minutes at

Table 1 - Chronic effects of aerobic exercise on panic disorder

Author, Year	N Patient (age)	Treatment	Medication	Duration	Supervision	Diagnostic/ severity	Measures	Comorbidity	Randomized	Main results
Hovland et al. ¹⁷	PE = 17 (38.1 ± 8.6 years) CBT = 19 (37.8 ± 8.9 years)	PE Day 1- aerobic exercise (walk and/or run), three weekly sessions, 60 minutes, and with 60%-80% of HRmax Day 2- circuit training (nine exercises, 15-second break between each exercises and 2-minutes break between each circuit) Day 3- sports and play with 60 minutes CBT Emphasis on cognitive restructuring and behavioural experiments, one weekly session, and two hours per session	PE 17.6% BZD 41.2% SSRIs CBT 10.5% BZD 31.6% SSRIs	12 week, and 6 to 12 months of follow-up	PE Physiotherapist, Occupational Therapist and Nurse; CBT specialist clinical psychologist	DSM-IV/ not mentioned	MI ACQ BSQ	80.6% agoraphobia 38.9% Major depression	Yes	MI-Alone, MI-Accompanied, and BSQ Interaction for group x moment for CBT group after treatment. Main effect to moment, revealed increased after treatment, and follow-up compared to baseline. ACQ Main effect to moment, with decreased compared to baseline
Wedekind et al. ¹⁸	GEF = 5 GEP = 5 GRP = 4 GRP/L = 1	Exercise Running, three weekly sessions, 45 minutes, and with 70% of VO _{2max} Drug 20 mg of paroxetine or placebo per day (two weeks); 40 mg of paroxetine or placebo per day (3* to 10* week) Relaxation Autogenic Training, once a week, and 5 to 20 minutes at the end of the study	Promethazine (25-50 mg) in cases of panic attack	10 weeks	Exercise Coach Relaxation Trainer	DSM-IV ICD-10/ PAS (minimum = 18 points)	P&A	Not mentioned	Yes	P&A The use of paroxetine was more efficient the fourth week compared to placebo; Compared exercise vs relaxation, after four week there was an improvement in the exercise group greater than relaxation
Broods et al. ¹⁵	GE = 11 Clom = 15 Control = 11	Exercise First week- three or four weekly sessions, and 4 miles Second week- short run (2 to 4 minutes), and 4 miles Third week- Gradual increase of running Fourth week- Encouraged to run Clomipramine First week- one capsules per day (37.5 mg); Second week- two capsules per day (37.5 mg); Third- 3 capsules per day (37.5 mg); Fourth week- 3 capsules per day (37.5 mg) Control Placebo pills	Promethazine (25-50 mg) in cases of panic attack	10 weeks	Exercise Trainer	DSM-III ICD-10/ not mentioned	HAMA P&A (Observer-Rated) P&A (Patient-Rated)	HAMA Not mentioned	Yes	HAMA Improvements in Clom vs Control (6 th , 8 th , and 10 th week) Improvements in GE vs Control (8 th , and 10 th week) P&A (Observer-Rated) Improvements in Clom vs Control (4 th , 6 th , 8 th , and 10 th week) Improvements in Clom vs GE (6 th , and 8 th week) Improvements in GE vs Control (8 th , and 10 th week) P&A (Patient-Rated) Improvements in Clom vs Contr (4 th , 6 th , and 8 th week) Improvements in Clom vs GE (6 th , and 8 th week) Improvements in GE vs Control (10 th week) DASS-21 No change in patients with PD
Merom et al. ²¹	CBT + Exercise = 38 (34% TP) CBT + ED = 36 (36% TP)	CBT 90 minutes Exercise 30 minutes, 150 minutes per week, and moderate intensity self-selected by individual Educational (Contr) Healthy eating guidance	Not mentioned	8 weeks	Exercise Trainer CBT Psychologist experienced	DSM-IV/ not mentioned	DASS-21	Not mentioned	Yes	
Meyer et al. ¹³	GPE = 15 GPC = 15 GPP/L = 15 HCG = 11	Exercise Running, 3x per week, 45 to 60 minutes, and not mentioned intensity	No medication	10 weeks	Exercise Experienced runner	DSM-III/ P&A (Patient-Rated) mean = 25 points PAS (Observer-Rated) mean = 25.4 points HAMA (mean = 22.6 points)	HAMA P&A (Observer-Rated) P&A (Patient-Rated) PAS (Observer-Rated) mean = 25.4 points HAMA (mean = 22.6 points)	Not mentioned	Yes	HAMA Improvements in GPC vs GPPL (6 th , and 10 th week) Improvements in GPE vs GPPL (6 th , and 10 th week) P&A (Observer-Rated) Improvements in GPC vs GPPL, and GPE (6 th week) Improvements in GPC, and GPE vs GPPL (10 th week) P&A (Patient-Rated) Improvements in GPC vs GPPL, and GPE (6 th week) Improvements in GPC e GPE vs GPPL (10 th week)

CBT: Cognitive Behavior Therapy; BZD: benzodiazepines; SSRIs: selective serotonin reuptake inhibitor; HRmax: maximum heart rate; DSM-III: Diagnostic and Statistical Manual of Mental Disorders (3^a edition); DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4^a edition); ICD-10: International Statistical Classification of Diseases and Related Health Problems (10^a edition); MI: Mobility Inventory; ACQ: Agoraphobia Cognitions Questionnaire; BSQ: Body Sensations Questionnaire; P&A: Panic and Agoraphobia Scale; ED: Educational; GEP: Group exercise + paroxetine; GEPL: Group relaxation + placebo; GRP: Group relaxation + placebo; GPPL: Group relaxation + placebo; VO₂ max: maximal oxygen consumption; Clom: clomipramine; Contr: control; HAMA: Hamilton Anxiety Scale; DASS-21: Depression Anxiety Stress Scale; PD: Panic disease; GPE: Group Panic + exercise; GPC: Group Panic + clomipramine; GPPL: Group Panic + placebo; HCG: healthy control group.

an intensity of 70% of HR_{max} was sufficient to decrease the anxiety sensitivity, when compared to conditions without exercise. We therefore suggest that a greater control in the aerobic exercise prescription, may bring responses that may clarify the effectiveness of exercise on PD symptoms.

■ CONCLUSION

The regular practice of aerobic exercise seems to be an appropriate intervention to promote improvements in the severity of anxiety symptoms in PD patients. However, the clinical trials reviewed here have shown a lack of adequate exercise prescription for this population. Therefore, we strongly believe that a greater level of standardization of standardization in the aerobic exercise prescription, a correct diagnosis of PD and an adequate assessment of the severity of PD in randomized controlled clinical trials, should produce better responses regarding the effectiveness of exercise on symptoms PD.

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■ CONFLICT OF INTEREST

The authors state none conflict of interest

EFEITOS CRÔNICOS DO EXERCÍCIO AERÓBIO SOBRE O TRANSTORNO DO PÂNICO: UMA REVISÃO SISTEMÁTICA DE ENSAIOS CLÍNICOS RANDOMIZADOS E NÃO-RANDOMIZADOS

INTRODUÇÃO: Em geral, grande parte dos estudos indicam a existência de uma associação entre os efeitos agudos do exercício aeróbio e um estado de ansiedade reduzida; no entanto, estes estudos não conseguem elucidar completamente a relação entre o efeito crônico do exercício aeróbio e traços de ansiedade.

OBJETIVO: O objetivo deste estudo foi revisar sistematicamente a literatura sobre o efeito crônico do exercício sobre sintomas associados com transtorno do pânico.

MÉTODOS: Os estudos foram recuperados de: MEDLINE/PubMed, ISI Web of Knowledge e SciELO. Adotamos a estratégia PICOS para determinar os critérios de elegibilidade. A estratégia de busca foi realizada utilizando uma pesquisa avançada no ISI Web of Science, MEDLINE/PubMed e SciELO com os seguintes termos: "Transtorno de Pânico" e "Exercício". Operadores booleanos

AND e OR foram utilizados para combinação dos termos. A seleção dos estudos foi realizada por dois pesquisadores independentes que, em caso de desacordo, procuraram um consenso sobre a seleção.

RESULTADOS: Foram identificados um total de 265 artigos: 199 artigos do PubMed/Medline, 63 artigos do ISI Web of Science e 3 artigos através de pesquisas manuais. Assim, 31 artigos foram analisados pelos critérios de elegibilidade e os critérios de exclusão, sendo que um total de cinco estudos foram incluídos na revisão sistemática.

CONCLUSÃO: A prática regular de exercício aeróbio parece ser uma intervenção apropriada para promover a melhoria da gravidade dos sintomas de ansiedade em pacientes com transtorno de pânico.

PALAVRAS-CHAVE: Efeitos crônicos, exercício aeróbio, transtorno do pânico.

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