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SYSTEMATIC REVIEW

Can regular physical exercise be a treatment for panic disorder? A systematic review

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ABSTRACT

Introduction: In the last few decades, exercise has been explored as a potential tool to reduce symptoms experienced by patients with panic disorder (PD). This systematic review aims to assess the effects of regular exercise interventions on panic severity, global anxiety, and depression symptoms of these patients.

Areas covered: A search was conducted on PubMed, ISI Web of Science, and Cochrane Central Register of Controlled Trials using search terms related to PD and exercise. Eight trials were included, Furthermore, regular exercise programs presented different methodological characteristics. There is o clear evidence indicating that regular exercise programs (at least two 20-minute sessions per week for at least 6 weeks) reduce panic-related symptoms. Regular exercise is effective in improving global anxiety measures and depression.

Expert opinion: Continuous aerobic exercise is the main type of intervention in the literature, generally providing a limited prescription. Currently, it is recommended the interval training, with intense and shorter stimuli, and long-term duration trials. However, despite the use of self-selected intensities and control based on the internal load be interesting as recommendation to increase adherence, careful is needed regarding training prescription due to scarce evidence.

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KEYWORDS
Anxiety; exercise; depression; panic attack; panic disorder

1. Background

Panic disorder (PD) is characterized by 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 [1,2]. The estimated lifetime prevalence of PD is 1.7% and 80.4% of individuals with PD have a lifetime comorbid mental disorder [3]. PD is about twice as common in women than in men and usually begins in late adolescence or early adulthood, with an average age onset between 20 and 30 years old [1].

Long-term PD is associated with decreased productivity, well-being, social contact, and self-realization [4]. In addition, chest pain [5], coronary artery disease [6], depression [7], substance abuse, and suicide are common comorbidities in PD patients [8]. Most costs related to anxiety disorders and their treatment are linked to PD and Generalized Anxiety Disorder [9]. The most common forms of treatment in PD patients are pharmacotherapy and Cognitive-Behavioral Therapy (CBT). Drugs commonly used are tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective inhibitors of serotonin reuptake (SSRIs), and benzodiazepines (BZDs) [10]. CBT interventions include exposure (interoceptive and exteroceptive), cognitive restructuring, breathing training, and relaxation training [11–13]. The effects of CBT alone seem to be significant for PD, but when combined with aerobic exercise, the long-term effects of CBT appear to promote sustained improvement in PD patients [11,14]. Thus, greater prominence has been given to this new strategy for PD patients.

Due to the chronic nature of anxiety disorders, the introduction of physical exercise, especially aerobic exercise, has shown anxiolytic effects [15,16], mainly when considering regular exercise practice [11–13,17–20]. Despite the possible benefits of physical exercise, acute physical exercise can trigger brief panic attacks. However, PD patients display low levels of physical activity [21], health markers that worsen their symptoms and comorbidities, reinforcing the need for regular physical exercise among them. The specific effects of somatic anxiety symptoms experienced during exercise seem to be associated with a low level of physical activity [21].

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Article highlights

- Regular exercise seems to be effective to improve PD symptoms; however, this is still not clear;
- Comorbidities, such as depression, are positively affected by the effects of exercise;
- Patients with PD should be encouraged to practice regular physical exercise for health promotion;
- Exercise prescription based on self-selected and controlled intensities according to the internal physiological load can be adequate routes for adherence to regular exercise;
- New randomized controlled studies need to be carried out to determine state-of-the-art practices when using exercise for PD, allowing for better standardization of intervention and more adequate control groups.

Few studies support the hypothesis that physical exercise has chronic anxiolytic effects [12,19]. Most studies have generally supported an association between the acute effects of exercise and reduced state anxiety, but failed to completely explain the relationship between the chronic effects of exercise, physical fitness, and anxiety traits [22]. In recent reviews, exercise has been suggested as clinically effective, or at least an adjunct to established treatment, whether by psychotherapy or pharmacotherapy [23]. Moreover, there is a lack of valid control groups. Finally, for some disorders, such as PD, exercise can be helpful but is often falsely perceived as harmful to PD alone [24,25]. Therefore, this systematic review aims to assess the effects of regular physical exercise interventions on panic severity, global anxiety, and depression symptoms of adult patients with PD.

2. Methods

This systematic review was designed and reported accordingly to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26].

2.1. Eligibility criteria

The eligibility criteria for study inclusion were established according to the PICOS strategy:

- Population: participants must be primarily diagnosed with PD with or without agoraphobia using gold standard criteria such as the Diagnostic Statistics Manual of Mental Disorders [1,27,28], the International Classification of Diseases [29] or the Mini-International Neuropsychiatric Interview [30]. Participants may present secondary comorbid disorders (e.g. depression, social phobia, generalized anxiety disorder).
- Intervention: regular exercise intervention (i.e. aerobic, strength, or multimodal training) prescribed to reduce panic attacks and anxiety symptoms in patients with PD. Exercise interventions combined with other treatment procedures were also included.
- Comparators: exercise interventions must be compared to active or waiting control groups, treatment-as-usual or alternative interventions (e.g. pharmacotherapy, psychotherapy).
- Outcomes: primary outcomes were measures related to panic severity (frequency and intensity of panic attacks, standardized panic-related scales) and global anxiety (e.g. Hamilton Anxiety Rating Scale, Beck Anxiety Inventory). Measures related to depressive symptoms were defined as a secondary outcome (e.g. Hamilton Rating Scale for Depression, Beck's Depression Inventory).
- Study Design: randomized and non-randomized trials, using either cross-over or parallel-group designs, comparing an intervention(s) encompassing exercise with a group(s) without exercise. The non-blinded trials were included as patients and personnel participating in exercise programs are not expected to be blinded.

2.2. Search strategy and selection of studies

A systematic literature search was conducted through March 2021, using the following databases: PubMed, ISI Web of Science (Web of Science Core Collection), and Cochrane Central Register of Controlled Trials (CENTRAL). 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:

('anxiety disorders'[MeSH] OR anxiety disorder[All Fields] OR 'panic'[MeSH] OR 'panic'[All Fields] OR panic disorder*[All Fields] OR panic attack*[All Fields] OR agoraphobia*[All Fields] OR phobic disorder*[All Fields]) AND ('exercise'[MeSH] OR exercis*[All Fields] OR 'exercise therapy'[MeSH] OR 'physical fitness'[MeSH] OR physical fit*[All Fields] OR physical activit*[All Fields] OR aerobic training*[All Fields] OR resistance training*[All Fields] OR strength training*[All Fields] OR weight-lift*[All Fields] OR weight-bear*[All Fields] OR muscle stretch*[All Fields])*

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 in the field, including authors from the included reports, were also requested to suggest additional trials to ensure that the review was as comprehensive and up-to-date as possible. Only studies published in English were included.

After merging search results and discarding duplicates, two researchers (DM and EL) independently screened titles and abstracts to identify relevant studies. Full-text articles of the included reports were retrieved and independently assessed for eligibility by the two researchers according to the previously described criteria. In case of disagreement regarding any report, a consensus meeting was performed, and a third researcher (DM) completed the decision when required. When it was impossible to retrieve full-text articles, authors were contacted using e-mail and Research Gate to provide the required report. After three failed attempts to respond from the respective authors, the report was excluded from the analysis. Some reports were seemingly published based on data from the same trials. Corresponding authors were

contacted to confirm whether these reports were produced from different trials or not.

2.3. Data extraction and processing

Data extraction was independently completed in a standardized manner by two researchers (SM and EL), and a consensus meeting was held to review the collected data. Data extracted from the included trials included: general characteristics (title, authors and publication date), sociodemographic characteristics (age and gender), clinical information (diagnosis, symptom severity, duration of illness, medication), description of exercise intervention (exercise modality, length, frequency, duration, and intensity) and study design (sample size, control intervention, follow-up, drop-out rate, outcome measures).

Descriptive statistics regarding relevant outcome measures (mean change from baseline and standard deviation of the change, or post-intervention means and standard deviation) were extracted to compute effect sizes. If there was no information available, corresponding and senior authors were contacted by e-mail and Research Gate. If the authors could not provide the required information or if they did not reply after three attempts to contact them, descriptive statistics were obtained through the graphs provided in the full-text articles using the Plot Digitize software. This method to extract data has been proven reliable and accurate to extract data for systematic reviews [31]. In the trial of Wedekind et al. [20] there was no graphical data regarding the standard deviation of the change, and the baseline value was used to replace it and compute the effect size. In turn, some of the included trials encompassed patients with other primary psychiatric disorders in their analysis. Thereby, authors were contacted to provide descriptive statistics only regarding patients primarily diagnosed with PD. Although some of the authors accomplished to do so, other researchers did not reply to this request, which led to the exclusion of these trials.

The most commonly used formula to compute effect sizes is *Cohen's d*, but it slightly shows bias as it overestimates effect sizes in small samples. Thus, for studies with a small sample sizes, effect sizes were computed using the *Hedges' g*. It removes this bias using a simple correction (formula 1 & 2), yielding an estimation of the effect size [32].

$$Hedges'g = \left(\frac{\bar{X}\text{exercise} - \bar{X}\text{control}}{SDwithin}\right) \times J = \left(1 - \frac{3}{4df - 1}\right) \quad (1)$$

$$SDwithin = \sqrt{\frac{(n1-1)SD1^2 + (n2-1)SD2^2}{n1 + n2 - 2}} \quad (2)$$

SDwithin = within-groups standard deviation, pooled across groups; df = degrees of freedom; n1 = sample size exercise; SD1 = standard deviation exercise; n2 = sample size control; SD2 = standard deviation control

Hedges' g was individually calculated for every relevant outcome measure in each included trial. For trials with more than 2 groups, this calculation was performed to compare exercise and another condition. *Hedges' g* was preferentially calculated using change from baseline and standard deviation of the change. When the authors did not report or provide these measures, change scores and standard deviation of the change were calculated using baseline and post-intervention values, using the following formula:

$$\bar{X}change = \bar{X}pos - \bar{X}pre \quad (1)$$

$$SDchange = SEchange \times \sqrt{n} = \sqrt{\left(\frac{SDpre^2}{n} + \frac{SDpos^2}{n}\right) \times (1 - r)} \times \sqrt{n} \quad (2)$$

n = number of participants included for analyzes; r = within-individual correlation (between before and after condition)

Due to the lack of information regarding the within-group correlations, the *r*-value of 0.5 was used to compute the standard deviation of the change [33]. *Hedges' g* was computed so that positive values indicated superior treatment effects of exercise in comparison to the control or alternative treatment group. Furthermore, effect sizes were classified as trivial (d < 0.19), small (d = 0.20–0.49), moderate (d = 0.50–0.79), large (d = 0.80–1.29) and very large (> 1.30) [34].

2.4. Assessment of risk of bias in included studies

Risk of bias 2 (RoB 2) was judged based on the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions*, version 6 [35]. The following criteria were evaluated:

- D1: bias due to randomization (inadequate randomization procedures and inadequate concealment of allocations before assignment).
- D2: bias due to deviations from intended intervention (knowledge of the allocated interventions by participants and personnel).
- D3: bias due to missing data (amount, nature, or handling of incomplete data).
- D4: bias due to outcome measurement (knowledge of the allocated interventions by outcome evaluators).
- D5: bias due to selection of reported results (differences between reported and unreported findings).

Two researchers (SM and EL) independently assessed the included trials, rating each of the previously described factors with low, high, or some concerns according to the criteria defined by Higgins [35]. Again, a consensus meeting was performed to discuss rating disagreements, and a third researcher (DM) ensured the final decision when required.

3. Results

3.1. Study selection

The study selection flow chart is presented in Figure 1. A total of 3418 records were identified (2119 on PubMed, 990 on Web of Science, and 309 on CENTRAL), from which 805 duplicate citations were removed, leaving a total of 2613 records. After screening titles and abstracts, 2404 records were excluded because they did not meet the eligibility criteria. Thereby, a total of 35 full-text articles were assessed for eligibility. Twenty seven studies were excluded because they did not present any kind of comparator group. Four studies were not experimental research (commentary, cross-sectional, or retrospective), and 3 articles did not include participants with PD. One record was excluded because it was not written in English, and another 1 had no full-text available, even after contacting the authors.

It is important to notice that several trials included for full-text reading enrolled participants with other anxiety disorders rather than PD. Thereby, the authors were contacted to provide the required information only for patients with PD. Although 2 authors provided the necessary information, 4 trials had to be excluded as the authors could not provide the requested data or did not reply.

3.2. Participants

Sociodemographic and clinical characteristics of the participants in the included studies are described in Table 1. Regarding regular exercise programs, exercise groups had sample sizes between 5 and 39, among studies. Participants' average age was between 30 and 40 years old. The youngest group was the exercise plus placebo control group of Wedekind et al. [20], and the oldest was the traditional care control group of Ma et al. [18]. Regarding gender, most studies had more female participants than males (as expected) as only the clomipramine group from Broocks et al. [17] had more male than female.

Diagnostic procedures were quite consistent across studies, with every trial using some version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). However, some authors cross-validated the diagnosis with the *International Classification of Diseases* (ICD-10). Every trial also used some validated clinical interview, with 6 studies using the *Structured Clinical Interview for DSM* and three trials using the *Mini-International Neuropsychiatric Interview* (MINI). PD severity was not reported by three of the studies [13,18,36], as one trial did not use any sort of standardized procedures to report severity [12]. However, the remaining trials reported symptom severity at baseline using the Panic and Agoraphobia Scale (PAS), with average values from each group ranging from 20.5 to 29.4, suggesting moderate panic-related symptoms in the studied groups. It was also important to note that only three studies [36] reported illness duration, a factor that may play a role in treatment response. Finally, there were two different approaches to medication intake before and during the trial. There were two studies in which participants had to stop the medication before starting the trial [17,20]. Other authors chose to allow for medication intake during the trial (mainly

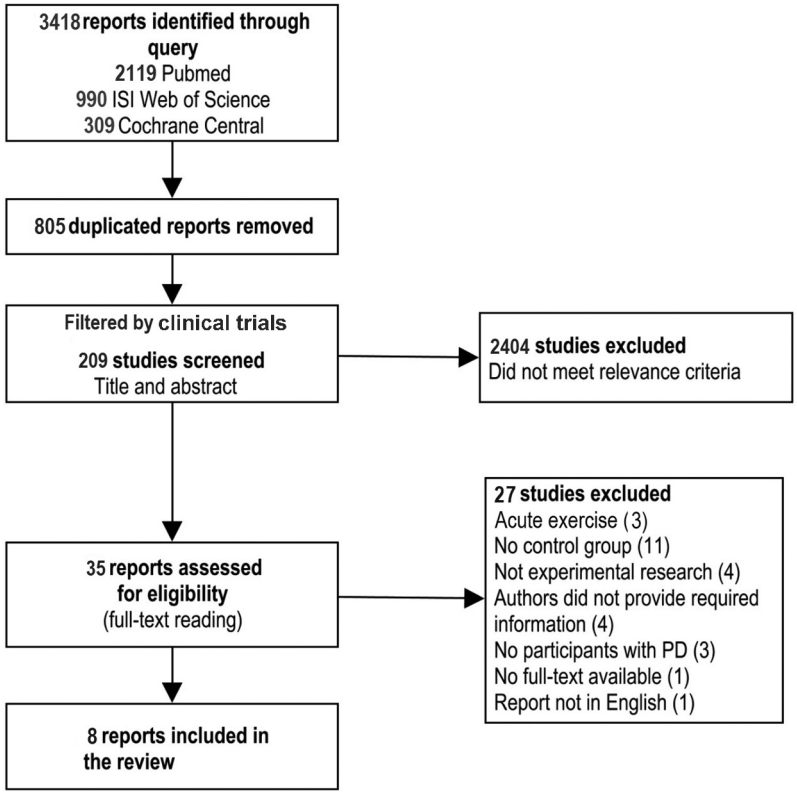

Figure 1. Study selection flow chart.

Table 1. Included studies description: sociodemographic and clinical characteristics of participants.

Study Authors	Sample Size	Drop-outs	Diagnosis	Age (Mean & SD)	Gender (% Male)	Panic Severity (Mean & SD)	Duration of Illness (Years/Mean & SD)	Medication
Gaudlitz et al. [11]	EX+CBT = 27 MV +CBT = 31	EX+CBT = 5 (19%) MV +CBT = 12 (39%)	DSM-IV ICD-10 (MINI)	EX+CBT = 35.4 (12.6) MV+CBT = 36.2 (8.9)	EX+CBT = 50% MV+CBT = 45%	*PAS* EX+CBT = 20.5 (9.0) MV+CBT = 20.62 (10.4)	No reported	*Antidepressants, beta-blockers or anxiolytics* EX+CBT = 7 MV+CBT = 8
Hovland et al. [12]	EX = 17 CBT = 19	EX = 0 CBT = 1 (5%)	DSM-IV-TR (SCID)	EX = 38.1 (8.6) CBT = 37.8 (8.9)	EX = 12% CBT = 26%	*Panic-related distress/ disability (0–8)* EX = 6.53 (1.42) CBT = 6.79 (1.32)	EX = 12.3 (10.7) CBT = 8.2 (8.1)	EX: SSRIs (7) and benzodiazepines (3) CBT: SSRIs (6) and benzodiazepines (n = 2)
Merom et al. [13]	EX+CBT = 13 ED +CBT = 13	EX+CBT = 6 (46%) ED +CBT = 5 (38%)	DSM-IV (SCID)	No specific information for PD participants	No specific information for PD participants	Not reported	Not reported	Not reported
Bischoff et al. [14]	EX+CBT = 39 LEX +CBT = 38	EX+CBT = 15 (38%) LEX +CBT = 11 (28%)	DSM-IV	EX+CBT = 37.2 (10) LEX+CBT = 36.2 (10.1)	EX+CBT = 38% LEX+CBT = 34%	EX *PAS* = 25.8 (8.2) LEX PAS = 24.2 (9.8)	Not reported	Antidepressants (n = 19) Beta blockers and benzodiazepine on demand prior to intervention
Broocks et al. [17]	EX = 16 CMP = 15 PLA = 15	EX = 5 (31%) CMP = 0 (0%) PLA = 4 (27%)	DSM-III-R & ICD-10 (SCID)	EX = 31.8 (9.5) CMP = 33.9 (9.2) PLA = 34.8 (6.8)	EX = 38% CMP = 73% PLA = 40%	*PAS* EX = 28.5 (9.1) CMP = 24.4 (6.4) PLA = 23.2 (7.4)	EX = 3.1 (2.1) CMP = 4.1 (4.6) PLA = 6.9 (7.9)	No medication for at least 3 weeks before the trial (only promethazine in case of panic attacks)
Ma et al. [18]	EX = 14 TC = 10	None	DSM-IV-TR (SCID)	EX = 39.86 (8.34) TC = 44.00 (8.45)	EX = 21% TC = 20%	Not reported	Not reported	No specific information for PD participants
Wedekind et al. [20]	EX+PAR = 21 RT +PAR = 17 EX +PLA = 20 RT +PLA = 17	EX+PAR = 5 (24%) RT +PAR = 4 (24%) EX +PLA = 5 (25%) RT+PLA = 1 (6%)	DSM-IV & ICD-10 (SCID)	EX+PAR = 31.3 (9.1) RT+PAR = 36.0 (9.7) EX+PLA = 29.8 (7.8) RT+PLA = 30.3 (5.8)	EX+PAR = 40% RT+PAR = 46% EX+PLA = 27% RT+PLA = 12%	*PAS* EX+PAR = 26.3 (8.1) RT+PAR = 27.4 (9.2) EX+PLA = 29.4 (8.9) RT+PLA = 25.7 (5.4)	No reported	No medication for at least 2 weeks before the trial (only promethazine in case of panic attacks during the trial)
Lattari et al. [36]	Ex = 5 Rest = 5	None	DSM-IV PDSS	EX = 36.4 (3.5) Rest = 42 (8.4)	Ex = 0% Rest = 0%	*PAS* EX = 13.8 (2.4) Rest = 13.2 (3.4)	> 5 years	Serotonin inhibitor Benzodiazepine

EX: exercise; LEX: light exercise; DSM: Diagnostic and Statistical Manual of Mental Disorders; MINI: Mini-International Neuropsychiatric Interview; R: Rest; SCID: Structured Clinical Interview for DSM; ICD: International Classification of Diseases; PAS: Panic and Agoraphobia Scale; CMP: clomipramine group; PLA: placebo group; MV: Movement Group; CBT: cognitive-behavioral therapy; SSRI: Selective Serotonin Reuptake Inhibitors; TC: Traditional Care; PD: Panic Disorder; ED: education group; PAR: paroxetine; RT: relaxation training

antidepressants), but the participants could not change medication until they finished the intervention period [11,12]. The remaining three trials did not provide information regarding the medication of patients with PD.

3.3. Exercise protocols and control groups

The characteristics of the included exercise protocols and respective control groups are described in Table 2. Studies with regular (at least 2 20-minute sessions per week for at least 6 weeks) exercise programs also presented different characteristics between each other. Interestingly, four out of eight studies [13,17,18,20] developed home-based exercise programs mainly requiring walking and running, although Ma et al. [18] also used other activities (dance, tai-chi, yoga). Furthermore, most programs developed aerobic training activities, although only two studies [12,18] utilized multimodal programs encompassing other procedures such as strength training, sports, dance, among others. Intervention length was quite similar among studies, ranging from 6 to 12. The session duration was either 30 or 45 minutes, except in the program of Hovland et al. [12], where each session lasted 90 minutes. Most programs included 3 sessions per week, although Ma et al. [18] and Merom et al. [13] home-based programs stimulated participants to work out 5 times per week. Finally, exercise intensity was labeled as moderate or vigorous in all included trials, although only two trials clearly defined aerobic training intensity [11,12].

It is also important to highlight that in three of the included trials, exercise was combined with other treatments procedures such as group CBT [11,13] and paroxetine or placebo pills [20]. Furthermore, there was a wide range of control interventions in the studies included, namely traditional care, clomipramine treatment or placebo pills, CBT, relaxation training, educational meetings, and movement sessions. In six studies patients were individually supervised during exercise sessions [11,12,14,17,20,36], however both supervised and non-supervised [13,18] studies showed significant results. All supervised studies had significant results for panic-related outcomes as well as global anxiety outcomes. The non-supervised studies just used global anxiety measures, and showed significant results for those outcomes.

3.4. Effects of regular exercise in patients with PD

Main findings and effect sizes regarding regular exercise programs are presented in Table 3. Six of the regular exercise trials included some sort of measure of panic-related symptoms. Only one trial reported clear effects of exercise on panic symptomatology, with large effects compared to placebo pills [17] (*Hedges' g = 1.33 and 1.35*). Other authors only reported small effect sizes of exercise [11,20] (*Hedges' g =* 0.25 and 0.29 respectively), and Broocks et al. [17] described that clomipramine treatment was marginally superior to exercise (*Hedges' g = 0.37 and 0.49)*. Finally, the study from Hovland et al. [12] comparing CBT and exercise had discrepant findings on several panic-related measures. CBT was slightly more effective than exercise on panic-related distress (clinician and patients ratings) and panic frequency (patients ratings) immediately after training (*Hedges' g = -0.18 and -0.37)* and on the follow-up periods (*Hedges' g = -0.20 and -0.65*). However, exercise was somewhat more effective on panic frequency (clinician ratings; *Hedges' g = 0.23 and 0.28*), suggesting no significant difference in treatment effects between these interventions.

Every included regular exercise trials included some measure of anxiety symptoms. Seven studies suggest that exercise effectively reduces anxiety in patients with PD [11–14,17,18,36], with effects ranging from trivial to very large (*Hedges' g = 0.01 and 1.61)*. Furthermore, three of these trials [11,18] reported small to moderate effects of exercise even after the follow-up assessment (*Hedges' g = 0.38 and 0.77)*. Conversely, Wedekind et al. [20] did not find significant differences between the exercise and controls. In addition the difference between exercise and clomipramine on anxiety-related symptoms also seems to be trivial (*Hedges' g = –0.11 and 0.22*) [17], and CBT seems to be slightly more effective immediately after the intervention [12] *(Hedges' g = -0.19 and -0.52)* and after the follow-up period [12] *(Hedges' g = -0.15 and -0.41)*.

Six of the included studies used regular exercise programs also had depression-related outcome measures, and results were quite discrepant across trials. Wedekind et al. [20] found no significant differences between groups using exercise intervention and relaxation training, and Gaudlitz et al. [11] only reported trivial effects of exercise plus CBT compared to the control group (*Hedges' g = 0.18; Follow-up = 0.14)*. Conversely, one trial also suggested moderate to large effects of exercise in the depressive symptoms of patients with PD (*Hedges' g* = 0.79–1.06) [17]. It is also interesting to compare the effects of exercise with other interventions on depressive symptoms. Both CBT and clomipramine treatment seem to be slightly more effective than exercise [17], although effect sizes favoring these interventions are small or trivial (*Hedges' g = -0.38 and -0.26*). Finally, Lattari et al. [36] showed significant improvements in anxiety symptoms after training compared to the control group (*BAI: Hedges 'g = 1.04 and 0.01, respectively*), with a significant effect on symptoms of depression (*BDI II: Hedges' g = 1.06 and 0.21, respectively for exercise group and control group.)*

3.5. Risk of bias assessment

The risk of bias assessment for each included trial is presented in Figure 2. Only three trials provided sufficient information about the randomization and were classified with a low risk of bias [12,14,36]. Thereby, there is a significant risk of selection bias on most of the included trials in this systematic review.

Regarding deviation from intended intervention, six studies have a high risk of bias [11–13,17,18,20], as it is impossible to assure blinding of participants and personnel in trials using exercise interventions. However, there was a low risk of bias regarding outcome measurement in many of the included trials. Some authors had evaluators blinded to group allocation [11,16], and others only included self-report scales as outcome measures [17,18]. There was a high risk of bias concerning outcome measurement for Hovland et al. that included clinician ratings and self-report measures. In this sense, the evaluators were not blind to the experimental

Table 2. Included studies description: interventions characteristics.

Study Authors	Exercise Modality	Intervention Length	Frequency (sessions per week)	Session Duration	Intensity	Control Intervention(s)
Gaudlitz et al. [11]	Aerobic Exercise (Treadmill) combined with Group CBT	8 weeks	3x/week	30 min.	70% VO_2Max	**Group CBT** (one weekly 90 min. session) combined with **Movement Group** (e.g. light stretching)
Hovland et al. [12]	Group-Based Multimodal Exercise	12 weeks	3x/week	90 min. (including introduction, warm-up, stretching)	**3 Session Types** *Walking/Running* (60–80 HR_{max}) *Strength Circuit Training* *Sports & Games*	**CBT** (one weekly 2-hour session)
Merom et al. [13]	Home-Based Aerobic Exercise (Walking) combined with Group CBT	8 weeks	At least 5x/week	30 min.	Moderate (participants educated on HR and exercise intensity)	**Group CBT** (one weekly 90 min. session) combined with **Educational Meetings** (healthy eating)
Bischoff et al. [14]	Aerobic Exercise (Treadmill)	7 weeks	Aerobic exercise prior to five exposure sessions within a Standardized seven week CBT.	30 min.	EX 70% VO2 Máx	LEX 30% VO2 Máx
Broocks et al. [17]	Home-Based Aerobic Exercise (Outdoors Walking/Running)	10 weeks	3x/week	45 min.	**Outdoors Route** *Week 1*: Walking *Week 2–6*: Short Running Periods *Week 7–10*: Running	**Clomipramine Group** (*Week 1*–37.5 mg; *Week 2*–75 mg; *Week 3-10* – 112.5 mg) **Placebo Group**
Ma et al. [18]	Home-Based Multimodal Exercise Program	12 weeks	5x/week	30 min.	Moderate to Vigorous (tai-chi, yoga, aerobic dance, 30-min. walking)	**Traditional Care**
Wedekind et al. [20]	Home-Based Aerobic Exercise (Outdoors Walking/Running) combined with Paroxetine or Placebo	10 weeks	3x/week (one group session with trainer)	45 min.	**Outdoors Route** *Week 1*: Walking *Week 2–6*: Short Running Periods *Week 7–10*: Running	**Relaxation** (one weekly session of autogenic training and home-based relaxation) combined with **Paroxetine (***Week 1-2* – 20 mg; *Week 3-10* – 40 mg) or **Placebo**
Lattari et al. [36]	Aerobic Exercise (Treadmill)	6 weeks	2x/week	2.5 min warm up + 20 min at target intensity + 2.5 min return to calm	50–55% HHR	**Rest** (20 min.)

HR_{max}: maximum heart rate; VO_2Max: maximum oxygen uptake; CBT: Cognitive-Behavioral Therapy;

Table 3. Major findings and effect size analysis (Hedges' g).

Study Authors	Exercise Condition	Control Condition	Follow-Up	Panic-Related Outcomes	Global Anxiety Outcomes	Depression Outcomes
Gaudlitz et al. [11]	Aerobic Exercise plus CBT (n = 22)	Control (Movement) plus CBT (n = 19)	5 months	PAS Patient Rating (0.25/FU: 0.32)	HARS (0.01/FU: 0.38) BAI (0.35/FU: 0.40)	HRSD (0.18/FU: 0.14)
Hovland et al. [12]	Multimodal Exercise (n = 17)	Group CBT (n = 18)	6 and 12 months	Panic-related Distress – Patient (−0.37/FU1: −0.31/FU2: −0.65) Panic Frequency – Patient (−0.34/FU1: −0.24/FU2: −0.60 Panic-related Distress – Clinician (−0.18/FU1: −0.20) Panic Frequency – Clinician (0.23/FU1: 0.28)	BAI (−0.52/FU1: -0.41/FU2: -0.33) STAI State (−0.19/FU1: -0.30/FU2: 0.08) STAI Trait (−0.23/FU1: -0.15/FU2: -0.26)	BDI-II (−0.38/FU1: -0.31/FU2: -0.35)
Merom et al. [13]	Home-Based Walking plus Group CBT (n = 7)	Education plus Group CBT (n = 8)	None	None	*DASS-21 Anxiety (0.91)*	*DASS-21 Depression (0.90)*
Bischoff et al. [14]	Moderate intensity exercise (n = 39)	Low intensity exercise (n = 38)	6 months	MI-E vs LI-E PAS (0.25 / FU1: 0.01)	HAM-A (0.01 / FU1: 0.08)	None
Broocks et al. [17]	Home-Based Aerobic Exercise (n = 11)	Clomipramine (n = 15) Placebo (n = 11)	None	*EG vs Placebo* PAS Observer Rating (1.35) PAS Patient Rating (1.33) *EG vs Clomipramine* PAS Observer Rating (−0.37) PAS Patient Rating (−0.49)	*EG vs Placebo* HARS (1.61) BAI (1.40) *EG vs Clomipramine* HARS (−0.11) BAI (0.22)	*EG vs Placebo* MADRS (1.06) BDI (0.79) *EG vs Clomipramine* MADRS (−0.26) BDI (0.11)
Ma et al. [18]	Home-Based Exercise (n = 14)	Usual Care (n = 10)	3 months	None	STAI State (0.45/FU: 0.55) STAI Trait (0.72/FU: 0.77)	*None*
Wedekind et al. [20]	Home-Based Exercise plus Placebo (n = 15) Home-Based Exercise plus Paroxetine (n = 16)	Relaxation Training plus Placebo (n = 16) Relaxation Training plus Paroxetine (n = 13)	None	EG plus Paroxetine vs RT plus Paroxetine PAS Observer Rating (−0.14) EG plus Placebo vs RT plus Placebo PAS Observer Rating (0.29) PAS Observer & Patient Rating No significant differences between exercise and relaxation groups	*HARS & BAI* No significant differences between exercise and relaxation groups	*MADRS & BDI* No significant differences between exercise and relaxation groups
Lattari et al. [36]	Aerobic Exercise (n = 5)	Rest (n = 5)	None	EG vs Rest PDSS No significant differences between exercise and control groups	BAI (1.40)	*BDI-II* (EG: 1.06/ CG:0.21)

EG: exercise group; CG: control group; PSL: DSM-IV Panic Symptom List; VAAS: Visual Analogue Anxiety Scale; PAS: Panic and Agoraphobia Scale; HARS: Hamilton Anxiety Rating Scale; BAI: Beck Anxiety Inventory; MADRS: Montgomery-Asberg Depression Rating Scale; BDI: Beck Depression Inventory; CBT: Cognitive-Behavioral Therapy; FU: Follow-Up; HRSD: Hamilton Rating Scale of Depression; State and Trait Anxiety Inventory; DASS-21: Depression Anxiety Stress Scale; RT: Relaxation Training; MG: Moderate Intense Exercise Group; LG: Low Intense Exercise Group; ES: Effect Size. FU1: first follow-up; FU2: second follow-up; PAS: Panic and Agoraphobia Scal; PDSS Panic Disorder Severity Scale.

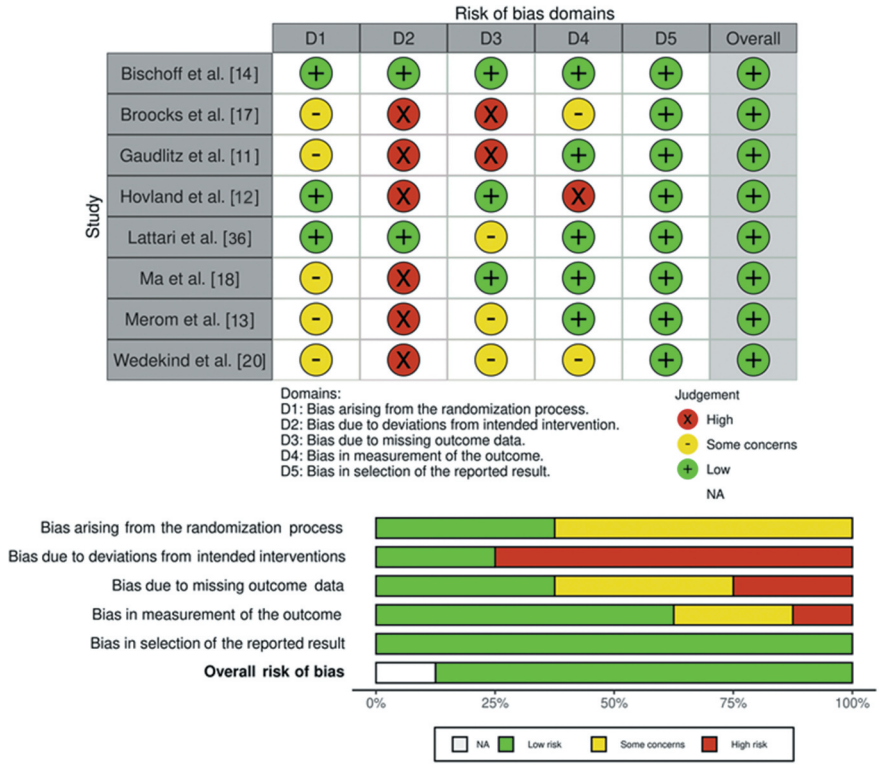

Figure 2. Risk of bias assessment.

conditions [12]. Still, regarding outcome measurement, some results should be carefully interpreted, as self-report measures can also lead to bias. For example, self-report measures are inherently biased by the person's feelings when they filled out the questionnaire. If the person feels bad when filling out the questionnaire, the answers will be more negative as well as the contrary is true.

All studies were judged as being at low risk of selection of reported results. Although none of the trials had a protocol, it seems unlikely that any authors did not report relevant outcome measures. The risk of missing data was low in three trials [12,18,14]. Attrition rates were not significantly different between groups in most trials, ranging from 0% to 46% in the exercise condition and from 0% to 39% in the control groups. However, two studies showed high risk due to substantial differences in drop-out rates [11,17], and other studies where studies did not clearly describe why participants dropped out.

4. Discussion

This study aimed to assess the effects of regular exercise interventions on panic severity, global anxiety, and depression symptoms of adult patients with PD. Results from chronic studies suggest that although the positive effects of exercise compared to control in patients with PD, the usual analyses carried out in this study show that it is impossible to clearly state such an outcome. However, the body of evidence leads us to believe that physical exercise seems to improve global anxiety measures and depression, as already evidenced [37].

This review showed that evidence about the effects of physical exercise on PD is scarce. Despite, patients with PD should be encouraged to practice regular physical exercise, as for any population, direct or indirect positive effects can be pointed out (cardiovascular, metabolic, and hemodynamic) [38]. However, the ability to adhere to regular practice is questioned because anxiety scores can rise due to exercise [36]. The literature proposes that adherence is determined by how the individual perceives and modulates perceived exertion (interoceptive stimulus) during the activity performed. Pleasure or displeasure, and consequently the engagement, is dependent on past experiences and cardiorespiratory fitness [39]. Low cardiorespiratory competence makes it difficult to maintain effort in areas of intensities where pleasure can be expressed. Lattari et al. [36] demonstrated that patients with PD had elevated anxiety scores after exercise, possibly transiting into areas of displeasure, but not after training (chronic effect), with a marked improvement in anxiety scores [36]. Perhaps this is the main factor for the smaller involvement of PD patients with exercise. Compared to healthy subjects, these patients presented low cardiorespiratory fitness and higher ratings of perceived exertion during physical exercise, as seen in some studies [11]. Corroborating with our hypothesis, patients with high somatic anxiety showed a significantly low level of physical exercise compared to those with low somatic anxiety. Somatic symptoms of anxiety were the critical predictors of a low level of physical exercise [21]. We believe that exercise can expose the individual to the physiological symptoms of panic, as it has been called in some studies, the interoceptive exposure mechanism [11,14].

Concerning the proposed mechanisms, some studies suggested an influence of the atrial natriuretic peptide [37], brain-derived neurotrophic factor (BDNF) [40], and the serotonergic system [41]. BDNF appears to play an essential key role on the nervous system, particularly on the serotoninergic system, as well as the HPA axis through its cortisol (stress-related) co-regulation [42]. Moreover, the BDNF appears to be potentially induced by aerobic exercise, being strongly associated with reduced levels of depression and anxiety [37].

The study by Brooks et al. [17] was the only one that demonstrated a reduction in the severity of panic symptoms observed by effect size (very large) [17]. In addition, the authors found that aerobic exercise performed for 45 minutes, 3 times a week, for 10 weeks, compared to placebo (i.e. pill) was effective in reducing overall anxiety levels (HAM-A and BAI) [17]. Exercise intensity was not controlled during training, and this may be a limiting factor in the results.

The differences observed in the methodological configuration of the studies can make it difficult the interpretation of results. Ma et al. compared a home-based multimodal exercise program to usual care [18]. The home-based multimodal exercise program consisted of tai-chi, yoga, aerobic dance exercises, and a 30-minute walk 5 times a week for 12 weeks. Results showed a reduction in state and trait anxiety for the exercise group. However, despite the beneficial results of exercise on anxiety levels found by Brooks et al. [17] and Ma et al. [18], no benefit was demonstrated in the study by Wedekind et al. [20], whose training prescription was similar to the study by Broocks et al. [17].

It is premature to speculate that exercise intervention alone will improve the severity of panic symptoms, as well as anxiety and depression symptoms in PD patients. Corroborating our hypothesis, PD patients who were treated with clomipramine had greater reductions in anxiety and disease severity compared to those who underwent exercise intervention [17]. CBT was also more effective in reducing anxiety and severity of illness than those who underwent exercise intervention [12]. However, exercise intervention associated with CBT has been an excellent option as adjunctive therapy to improve anxiety symptoms. Gaudlitz et al. examined the combination of aerobic exercise plus CBT compared to stretching exercises plus control CBT, with favorable results for aerobic exercise plus CBT with a reduction in anxiety levels and severity of disease [11]. Merom et al. investigated the effects of walking plus CBT compared to educational sessions and control plus CBT. They found it favorable to walking plus CBT to reduce anxiety and depressive symptoms [13]. Both studies with similar training prescriptions.

Given the amount of evidence in this work, it seems clear that physical exercise reduces some episodes of panic attacks and global anxiety. It seems to follow the previous hypothesized idea of the exercise-anxiety relation and corroborates decades of contextual evidence in exercise-related contexts.

Despite the study's strengths, some limitations should be acknowledged. We can highlight the following limitations: a) The small number of studies about the same topic; b) the different types of study design; c) several studies report different analyses or outcomes from the same trials; d) data not provided by the authors; e) the diversity of types of physical exercise; and f) the heterogeneous samples prevented us from performing a meta-analysis. In this context, the lack of standardization of the control group and the use of strategies that can create a confounding factor and interfere with psychophysiological responses should also be pointed out. This situation reinforces our caution in stating that exercise is medicine for panic patients. Finally, variations in exercise intensity, type of exercise, and instruments to assess anxiety, demonstrate difficulties in reaching more definitive conclusions. General practitioners, mental health nurses, and mental health managers also frequently cited barriers to the prescription of exercise such as lack of training (14.7%), and client's disinclination (12.6%) need to be addressed to overcome challenges that restrict the prescription of exercise as a therapeutic intervention [43]. The literature still needs to establish the exercise modality, duration, frequency, and intensity of the physical exercise required to promote positive effects in individuals with PD.

5. Conclusion

In conclusion, although exercise has shown positive effects on panic symptoms, methodological limitations and the number of qualified articles available prevent us from asserting that it is efficient as an adjuvant to PD treatment. However, regular exercise programs showed that this intervention is effective in improving global anxiety measures and depression. Evidence was insufficient to infer a cause-effect relationship, and new randomized controlled trials are suggested.

6. Expert opinion

We know that there is a fine line between the practice of physical exercises and the triggering of panic events, and this conception may lead us to question the real relevance of implementing this strategy as an adjunct to other main treatments. However, because of health precepts, comorbidities are developed through a sedentary lifestyle risk factor, with a high risk of mortality from any cause, in addition to functional disability. Therefore, this opinion is premised on the understanding that despite the chronic effects on panic symptoms are not well understood, physical exercise would promote greater aggregate benefits [44]. According to the American College of Sports Medicine (ACSM) [45], the accumulation of at least 150 min.week^{-1} of moderate aerobic exercise would constitute an effective form of health maintenance and, therefore, the reduction of outcomes associated comorbidities derived from chronic non-communicable diseases, common in patients with different mental disorders.

The increase in cardiorespiratory fitness in patients with different mental disorders could favor the reduction of the severity of symptoms, including those of anxiety and panic [46]. In this context, there seems to be an inverse relationship between $VO^2_{max.}$ levels and the symptoms [47]. Therefore, the relationship between physical exercise and PD patients emerge some questions: a) it is suggested to improve cardiorespiratory capacity in PD patients; however, we know that

light and moderate exercise can be strategies not as effective in achieving this result [48,49]; b) the adherence of these patients diagnosed with panic to physical exercise is low, due to the possibility of triggering a panic event; however, low cardiorespiratory capacity makes it very difficult to remain in a comfortable condition since there is no amplitude to move at different intensities; c) no intervention could lead to the appearance of comorbidities that would harm both the physical and produced conditions of the patient's life as well as the reactivity to the symptoms.

Solving such an equation is not simple and requires a greater depth of knowledge on issues related to physical training. For example, it is appropriate to think of a shift in focus from a prescription based on the external load setting (i.e. rigid work intensities), where a physiological response is manifested as a prescription product. The prescription based on the patient's own internal physiological perceptions could be a path that would implement multiple prescribing scenarios more acceptable [50–52]. Although studies point to an overestimation of the perceived exertion performed in patients with PD [53], this could be of important application. In studies related to how intensity is interpreted by our brain (with pleasure or displeasure), self-selected intensities seem to promote higher total work or average intensity when compared to an imposed prescription [54].

In another view, the continuous aerobic exercise model is the main form of work instituted in research procedures, generally providing a limited prescription. Currently, it is recommended the interval training [55], with intense and shorter stimuli, and long-term duration trials. In this way, it is possible to explore greater work ranges and obtain a controlled internal load from the patient. Since the internal charge is a product of stimulus intensity x stimulus time, we can create a greater physical and muscular demand without necessarily creating a perception of significant discomfort. The study conducted by Plag et al. [56] reproduces exactly this perspective. The authors used short periods of stimuli (77–95% of HRmax for 1 minute) intercepted by a 1-minute recovery on moderate to low exertion. The effects on the severity of panic, depression, and agoraphobia were significantly reduced and improved resistance capabilities. This conception is in line with current ideas in the literature related to exercise. However, there is still a need for more robust, randomized, and controlled studies to better understand.

Declaration of interests

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

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