Exercise as an Add-on Strategy for the Treatment of Bipolar Disorder: Systematic Review and Meta-analysis Protocol

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Protocol

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Abstract

Background: Bipolar disorder (BD) is a severe, recurrent and chronic disorder associated with cognitive impairment, reduction in quality of life and substantially reduction in psychosocial functioning. It presents high rates of comorbidity with cardiovascular and cerebrovascular diseases, diabetes and metabolic syndrome. Individuals with bipolar disorder need to focus their attention and treatment on mental and physical health. Physical exercise is often recommended in bipolar disorder, based on extrapolation from the major depressive disorder literature, theory and clinical expertise. However, studies tend to exclude individuals with BD or make no distinction between diagnostic groups, which leads to heterogeneity and difficulty in generalizing the results. The aim of this review is to evaluate the role of physical exercise as an intervention in bipolar disorder treatment.

Method: The study populations must be humans, aged 18 years or older, with a clinical diagnosis of Bipolar Disorder (BD) according to a recognised widely-used diagnostic classification approach, confirmed with a structured interview. We will evaluate two main outcomes (mood symptoms improvement and functioning) and an additional outcome (prevention of relapse/recurrence). The search strategy will be based on the PICOS framework, using medical subject headings, on the following databases: MEDLINE (via Pubmed), EMBASE, CENTRAL, SPORTDiscus (via EBSCO), PsycINFO (via APA) and OpenGrey Repository. Selection and data collection process will be carried out by two authors, independently. Risk of bias and quality of evidence will be graded acording ROB-2 and GRADE. We will present a narrative and quantitative synthesis of the results from the included studies. Regarding quantitative data, we will extract means (M) and standard deviations (SD), when available, to calculate the standardised mean difference (SMD). Effects size will be calculated using SMD and 95% confidence interval and heterogeneity will be assessed. Subgroup analysis will be conducted to explore heterogeneity across studies depending on quality and quantity of the data extracted.

Discussion: To date, there wasn't a systematic review with only randomized controlled trials on effects of physical activity on BD. Because of this, we will conduct this systematic review trying to estabilish the effects of exercise on mood, functionality and prevention of relapse.

Registration: submitted

Background

Bipolar disorder (BD) is a severe, recurrent and chronic disorder, which affect more than 1% of the world's population (1). The aggregate lifetime prevalences in a large cross-sectional survey were 0.6% for bipolar I disorder, 0.4% for bipolar II disorder, 1.4% for subthreshold bipolar disorder, and 2.4% for bipolar disorder spectrum (2). BD is associated with cognitive impairment, reduction in quality of life and substantially reduction in psychosocial functioning (1, 3). In addition to cognition and functioning, physical health is affected in patients with bipolar disorder (3) with loss of approximately 10–20 potential years of life and premature mortality (1).

People with bipolar disorder also presents high rates of comorbidity with cardiovascular and cerebrovascular diseases, diabetes and metabolic syndrome (4). They have almost 15-fold suicide mortality and 2-fold risk of cardiovascular disease mortality (4), dying of cardiovascular diseases approximately 10 years earlier compared to the general population (5). Most common death causes are cardiovascular diseases (38%), suicide/external causes (18%) and other diseases (44%) (5).

Because of this, individuals with bipolar disorder need to focus their attention and treatment on mental and physical health (6). Targeting medical and psychiatric comorbidity by adjunctive psychosocial treatments have been shown to improve health outcomes for people with bipolar disorders (1).

In that way, physical exercise is often recommended in bipolar disorder, based on extrapolation from the major depressive disorder literature, theory and clinical expertise (6, 7). Systematic reviews suggests that physical exercise has moderate-sized effect on depression (8) and should be regarded as an adjunctive strategy with antidepressants in people with depression (9). However, studies tend to exclude individuals with BD or make no distinction between diagnostic groups, which leads to heterogeneity and difficulty in generalizing the results. (7)

Some reviews have attempted to understand the relationship between exercise and mood symptoms in bipolar patients (10). Despite this, evidence was insufficient to infer a cause-effect relationship (10). There are promising data that exercise may be a viable and effective strategy to deal with bipolar depression (6). Althougth, there have been no reports of randomized clinical trials (RCTs) that have tested the impact of exercise on depressive, manic or hypomanic symptoms in the latest reviews (6). It was suggested that RCTs that use intention-to-treat analysis and robust assessor blinding procedures are needed to establish whether physical activity is effective in reducing symptoms of bipolar depression specifically (7).

The current literature has important limitations, such as: small samples, heterogeneous treatment groups, no control groups, no distinction between types of exercise, definitions of the amount (duration, frequency and intensity) of exercise (6). There is lack of empirical data on impact of exercise on mood symptomology for individuals specifically with bipolar disorder (6). Symptomatic episodes, reduction of affective symptoms, risk of relapse/recurrences and mood states are the most common outcome variables in intervention trials for BD (7, 12). Functional recovery following a mood episode consistently lags behind symptomatic and syndromal recovery, therefore it was suggested that functioning should be considered a primary outcome variable in any and all bipolar studies (12).

Systematic reviews are the first step in ensuring that an intervention has a significant effect (11). Therefore, the aim of this review is to evaluate the role of physical exercise as an intervention in bipolar disorders treatment. We will evaluate three outcomes: mood symptoms improvement (depressive, manic, hypomanic and mixed), functioning/functional recovery and prevention of relapse/recurrence.

Method

The systematic review will be conducted in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) Statement. Before undertaking this systematic review, preliminary searches were performed to check whether there are existing or on-going reviews regarding this topic.

Protocol registration and reporting

The present protocol has been registered within the PROSPERO database (submitted to register) and is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (13)

Population

The study populations must be humans, aged 18 years or older, with a clinical diagnosis of Bipolar Disorder (BD) according to a recognised widely-used diagnostic classification approach: i.e. the Diagnostic and Statistical Manual for Mental Disorders (DSM), or International Classification of Diseases (ICD), or Research Diagnostic Criteria (RDC). Diagnosis should be confirmed with a structured interview using one or more of the following: Mini International Neuropsychiatric Interview (MINI), Composite International Diagnostic Interview (CIDI), Structured Clinical Interview (SCID), or equivalent.

Intervention

For this review, exercise is defined as structured or repetitive physical activity that has an objective of improving or maintaining physical fitness (14). We will not restrictly specify the exercise parameters (type, mode, frequency, and duration) and the intervention characteristics (power generated; heart rate achieved; repetitions performed; duration of each session; number of total sessions; duration of the intervention programme).

Comparators

Control groups (i.e. not performing intervention) should include those diagnosed with MDD by the same standards as the participants, and treated with the same standard treatments (including antidepressant drugs, psychotherapy, no treatment, or placebo-control condition). Controls should ideally have the same amount of interaction time with the researchers.

Outcomes

We will evaluate two primary outcomes: mood symptoms improvement and functioning/functional recovery. Depressive and manic symptoms and severity should be scored using one or more standardized and validated scales. As example: Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS/HAM-D), Centre for Epidemiologic Studies Depression Scale Revised (CESD-R), Montgomery-Åsberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Hypomania Checklist-32 (HCL-32) or equivalent. Functioning should be scored using a validated scale, such as Global Assessment of Functioning (GAF) or equivalent, or another validated method. We will try to assess the effect of

exercise as a strategy for maintenance treatment (prevention of relapse or recurrence), if these data are available.

Information sources:

A literature search of the following electronic databases will be performed: MEDLINE (via Pubmed), EMBASE, CENTRAL, SPORTDiscus (via EBSCO), PsycINFO (via APA) and OpenGrey Repository (System for Information on Grey Literature in Europe). Searches will be supplemented by checking specialized registers and by reviewing the reference list from the studies found. The references of the assessed articles will also be further examined for relevant research studies. Trials Register of Promoting Health Interventions (TRoPHI; EPPI Centre), Current Controlled Trials, ClinicalTrials.Gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) will be searched for additional trials.

Search strategy:

The search strategy will be based on the PICOS (population, intervention, comparison, outcome, study design) framework and will involve the use of medical subject headings (MeSH or similar), such as: bipolar disorders, mania, bipolar depression, exercise, physical activity, sports, randomized controlled trial, clinical trials, or equivalent (see Appendix 1 for search strategy). No restriction for language and date of publication will be imposed. The PubMed search strategy was adapted according to the controlled vocabulary in each database

Data management (selection and collection process)

Articles will be searched independently by two authors (AR and RC). The selection will be carried out in steps independently by two reviewers (AR and RC). At each step, the following procedure will be undertaken to select papers that meet the inclusion criteria in terms of participants, intervention, control-group, outcome measures, and types of study components.

The review authors (AR and RC) will independently assess the relevant titles of the citations retrieved by the searches. Studies that meet the inclusion criteria when screening the titles will be included in the next step (screening the abstracts). Full texts of all studies that meet the inclusion criteria after reading the abstracts will be read. Studies that do not meet the inclusion criteria at any step will be excluded. If unsure, the paper will be included in the next step and the abstract or full text will be screened to determine whether it meets the inclusion criteria. At this step, two review authors (AR and RC) will independently check the full papers for eligibility; all discrepancies will be resolved via reviewer consensus or through consultation from a third reviewer.

Researchers of eligible trials will be contacted by e-mail to provide additional information on clinical/methodological aspects to their studies. Two reminders will be sent within a period of two weeks.

We will record all reasons for exclusion of studies for which we had obtained full copies and present them in a 'Characteristics of excluded studies' table. We will complete a PRISMA flowchart to summarise this process.

Data will be extracted independently by two reviewers (AR and RC) using a data extraction sheet that will be cross-checked and entered into a data management spreadsheet. Data collected will include the following, if it is available:

(1) Studies characteristics (author, country, publication date, sample size, date of collection of study data)

(2) Demographic data from participants: gender, age, socioeconomic issues, education, income.

(3) Modifiable characteristics related to intervention: frequency of exercise prescription, intensity of exercise prescription, type of exercise, length of individual intervention sessions and duration of intervention (number of total sessions ie. chronically or acutely performed).

(4) Characteristics of depression: number of episodes, severity, age of onset and serious events – suicidal ideation, suicide, self-harm and depression-related hospitalization.

(5) Type of usual treatment: antidepressants, mood stabilizers, psychoteraphy, combined, placebo.

(6) Supervision (Supervised or not-supervised)

(7) Outcome measures: mood symptoms improvement (depressive, manic, hypomanic and mixed), functioning/functional recovery and prevention of relapse/recurrence.

(8) Adherece (number of drop-outs)

(9) Adverse effects

Risk of bias (quality) assessment

We will assess risk of bias using the Cochrane risk of bias assessment tool (RoB-2) (15). Bias will be assessed in the following domains: 1) randomization process; 2) deviations from intended interventions; 3) missing outcome data; 4) measurement of the outcome; and 5) selection of the reported results. Each domain will be assessed for having either low risk of bias; some concerns; or high risk of bias. Two authors independent of each other will be perform the risk of bias assessment. To reduce the risk of bias in determining study quality, all discrepancies will be resolved via reviewer consensus or through consultation with a third reviewer.

We assessed and graded the evidence according to the Granding of Recommendations, Assessment, Development and Evaluation (GRADE) for high risk of bias, imprecision, indirectness, heterogeneity and publication bias.

Publication bias will be assessed by a funnel plot. In case of significant publication bias, the trim and fill statistical procedure was considered on the right and left side of the plot (16). This procedure adds or removes studies to balance an asymmetrical funnel plot and adjusts the effect-size accordingly. In this manner, an unbiased estimate of the effect is provided. If the number of studies is equal or greater than 10, Begg and Mazumdar rank correlation and Egger's test will also be performed.

Risk of bias and data quality for each study will be recorded in a spreadsheet and a table summarising the quality of assessment/evidence will be compiled and included in the systematic review and meta-analysis.

Strategy for data synthesis

We will present a narrative and quantitative synthesis of the results from the included studies. Tables will display the summary characteristics of all papers included in the systematic review. The tables will outline the following: characteristics of trials; risk of bias; quality assessment; analysis of subgroups; heterogeneity. After that, a table of summary of findings will be presented.

Two independent reviewers will insert quantitative data from each study twice into a data manangement software. If there are missing data that hinder effect size calculation, the authors will be contacted. If no response is received, the study will be excluded. Regarding quantitative data, we will extract means (M) and standard deviations (SD), when available, to calculate the standardised mean difference (SMD). We will use Comprehensive Meta-analisys V.3 to convert data into the desired format. Quantitative data will be analysed using Comprehensive Meta-analisys V.3.

If a study reported more than one post-treatment depression or manic/hypomanic score (e.g., midway, follow-up), only the assessment time-point immediately following the conclusion of the intervention phase was used. If a study reported depression scores on multiple outcome measures, only the most clinically relevant depression measure was used

Effects size will be calculated using SMD and 95% confidence interval (CI). A negative SMD will be interpreted as a greater reduction of depressive symptoms in the intervention group. Cohen's interpretation will be used—that is, 0.20, 0.50 and 0.80 as small medium and large effect size, respectively. We selected a random-effects model for our meta-analysis, under the assumption that the RCTs to be included in our study will have been performed in heterogeneous populations that may differ from each other.

Heterogeneity will be assessed using forest plots, Q statistics, p values and I^2 index values and their 95% CIs index values will be expressed as percentages and inter-preted as follows: unimportant heterogeneity (0%–40%), moderate heterogeneity (30%–60%), substantial hetero-geneity (50%–90%) and considerable heterogeneity (75%–100%). Sensitivity will be assessed during the first and last follow-up visit using fixed-effects model and Hedges' g. Some studies will be excluded from analysis (eg, studies with the highest risk of bias or causing the greatest increase in heterogeneity).

Subgroup analysis will be conducted to explore heterogeneity across studies depending on quality and quantity of the data extracted throughout the systematic review process, and if the meta-analyses allow such an approach to be undertaken. When available, the following data will be collected:

1. Risk of bias
2. Age (>18, 18-65 or > 65)
3. Number of past episodes (first episode or >1)
4. Type of usual treatment (antidepressants, psychoteraphy, combined, placebo)
5. Severity of depression (mild, moderate, severe)
6. Supervised or not supervised intervention

Discussion

BD is caracterized by high rates of relapse, comorbidities and functional impariment, even when treated with current treatment strategies (antidepressants, antipsychotic and mood-stabilizing medications) (3, 17). Because of this, psychosocial interventions are recommended according to treatment guidelines as an adjuvant strategy (17). As with other severe mental illness, interest has grown in the efficacy and effectiveness of exercise in BD.

Melo et al suggested that exercise was associated with improved health measures including depressive symptoms, functioning and quality of life, but a cause-effect relationship between mood and physical exercise could not be estabilished (18). Souza Sá et al suggests that aerobic exercise plays an important role in BD physiopathological mechanisms and it is a new way for it's treatment(19). Some evidence provides a rationale for empirically evaluating the neurocognitive benefits of aerobic exercise in BD (20).

Latest reviews concluded that exercise as a psychosocial adjunct for bipolar disorder should be assessed with rigorous randomized clinical trials (18, 21) and focus on the evidence for physical activity in regulating mood fluctuations and improving cognitive functioning(17).

To date, there wasn't a systematic review with only randomized controlled trials on effects of physical activity on BD. Because of this, we will conduct this systematic review trying to estabilish the effects of exercise on mood, functional and prevention of relapse. We believe that this step is crucial to the development of BD treatment.

Abbreviations

BD – bipolar disorder

MDD - major depressive disorder

RCT – randomized controlled trial

RCTs – randomized controlled trials

APA – American Psychiatry Association

AR – Andrey Rocca

RC – Rodolfo Campos

M – means

SD – standard deviation

SMD – standardised mean difference

CI – confidence interval

Declarations

Ethics approval and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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Supplementary Files

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- PRISMAPchecklist2.docx
- SearchStrategyBD.pdf