Review article

Moderators of response in exercise treatment for depression: A systematic review

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ABSTRACT

Introduction: Exercise have antidepressant effects in people with Major Depressive Disorder (MDD). However, about to half of patients do not respond to exercise. The identification of factors that moderates the antidepressant effects of exercise in people with MDD may help researchers and health professionals to identify sub-groups of patients that would benefit more from exercise.
Methods: A systematic review was carried out using Medline(PubMed), EMBASE and psycINFO up to April 2015. Individual and composite moderators were summarized and the strength of the evidence was assessed.
Results: Eleven studies were included for review resulting in the identification of potential individual (two biological, three clinical, two psychological and two social individual) and two potential composite moderators (the interaction between BDNF and Body Mass Index (BMI) and between family history of mental illness and gender). Only the two biological features and the BDNF x BMI interaction provided confirmatory evidence.
Limitations: Due the different statistical approaches used in the studies, it was not possible to perform meta-analyses. The small number of studies and the exploratory nature of the evidence limits a wider generalization of the findings.
Conclusion: Potential clinical, psychological, social or biological moderators were identified. However, the small number of studies and the limited strength of the evidence requires further studies before drawn definitive results. Further trials should consider the inclusion of moderators analysis using an a-priori, theoretical/evidence based hypothesis in order to provide high quality evidence for the use of personalized medicine in exercise for depression.

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Contents

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1. Introduction

The use of Personalized Medicine is one of the strategic plans of the National Institute for Mental Health to improve treatment outcomes in the mental health (Insel et al., 2010). Personalized treatments in medicine and health area imply identification of the individual factors that predicts response or remission, resulting in better care outcomes and reduced costs (Kraemer et al., 2002; Wallace et al., 2013).

In Major Depressive Disorder (MDD), personalized medicine is particularly relevant because, at best, half of patients presents a acute clinical response (a decrease of 50% or more of the symptoms) to an initial pharmacological antidepressant treatment, and only one third presents remission (no longer meet criteria for depression diagnosis) (Sinyor et al., 2010). In this line, the identification of those subgroups of patients with increased, or decreased, likelihood of success in different treatments may play a key role in choosing the "best treatment" for each patient, and for improved treatment outcomes (Gvozdic et al., 2012; Kraemer et al., 2002; Malhi et al., 2013; Papakostas and Fava, 2008).

Recent guidelines suggested that exercise can be considered a therapeutic option for depression (Malhi et al., 2015) with consistent benefits to physical health, being a cornerstone to improve cardiorespiratory capacity (Stubbs et al., 2016) and decrease the risk of metabolic disorders (Stubbs et al., 2015a). On mental health, there are some discussion on the efficacy of exercise in depressive symptoms improvement. For example, a recent review found that clinical trials with good methodological quality does not support significant reductions on depressive symptoms (Cooney et al., 2013). It should be noted, however, that control groups used in clinical trials presents large and significant antidepressant effects (Stubbs et al., 2015b), decreasing the ability of detection of effects in exercise groups.

Despite the effect on symptom reduction remission rates in clinical trials are not optimal, ranging from 11% to 41%, for low and high doses of exercise, respectively (Dunn et al., 2005). In other words, about to half of people with depression will not experience significant improvements from exercise. One potential explanation to the heterogeneity in response rates can be due the heterogeneity of depression itself (Schuch and de Almeida Fleck, 2013). In this regard, the use of personalized medicine in exercise treatment for depression, identifying potential moderators (pre-treatment factors that modifies the magnitude or the direction of the effect of an intervention in an outcome (Kraemer et al., 2002)) can be of great interest for clinicians and researchers.

There is a wide range of factors that can potentially moderate response or remission of people with MDD to pharmacological treatment or psychotherapies, including clinical (e.g.: depression severity), demographical (e.g.: age, sex), psychological (e.g.: personal traits or characteristics), biological (e.g.: biomarkers), social and environmental factors (Button et al., 2015; Donker et al., 2013; MacPherson et al., 2014; Ozomaro et al., 2013; Papakostas and Fava, 2008). However, the potential moderators of the antidepressant effects of exercise remains poorly understood.

A previous study found initial evidence of the potential use of personalized medicine in physical activity and depression, identifying potential subgroups that are less likely to be engaged in physical activity (Vancampfort et al., 2015). In clinical trials, some studies have shown that neurogenesis and inflammation biomarkers, family history of depression, and severity of physical symptoms can moderate the effects of exercise on depression (Herman et al., 2002; Rethorst et al., 2013; Toups et al., 2011). However, to the best of our knowledge, no systematic review aimed to identify potential moderators of the antidepressant effects of exercise in people with MDD. The present review can be a hallmark for the creation and discussion of a body of evidence in the field, suggesting potential directions for investigation in further clinical trials.

The identification of potential moderators can suffer seriously from some issues such as the lack of an a-priori, evidence/theoretical based hypothesis, and the use of non-reliable or valid measures of moderators (Pincus et al., 2011). In this regard, the assessment of the strength of the evidence is required to provide an adequate comprehension of the generalization of the findings.

The objectives of the present study were to: (1) perform a systematic review of the potential moderators associated with treatment outcomes in randomized clinical trials evaluating the antidepressant effects of exercise in people with MDD; and (2) evaluate the strength of the evidence of the potential moderators of response.

2. Methods

The systematic review was carried out in three steps: literature search, study selection and data extraction, following the PRISMA guidelines (Moher et al., 2009).

2.1. Literature search

A comprehensive search of papers published up to April 2015 was carried out on Medline (PubMed), EMBASE and PsycINFO, using the following strategy: ((exercise OR physical activity) AND depress* AND (moderator OR predictor OR clinical trial OR