University of Trás-os-Montes and Alto Douro

Exercise as a complementary treatment of pharmacotherapy in patients with clinical depression

ACADEMIC DISSERTATION OF PHILOSOPHY DOCTOR IN SPORT SCIENCES

Lara Sofia Rodrigues de Sousa Fernandes Carneiro

Supervisors:

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O Heterónimo *Alberto Caeiro*,

Para além da curva da estrada

Para além da curva da estrada

Talvez haja um poço, e talvez um castelo,

E talvez apenas a continuação da estrada.

Não sei nem pergunto.

Enquanto vou na estrada antes da curva

Só olho para a estrada antes da curva,

Porque não posso ver senão a estrada antes da curva.

De nada me serviria estar olhando para outro lado

E para aquilo que não vejo.

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Por ora só sabemos que lá não estamos.

Aqui há só a estrada antes da curva, e antes da curva

Há a estrada sem curva nenhuma.

To my **CHERISHED**, Lovely Family, for their love and unconditional support!

To my Grandfather **MANUEL**

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ABSTRACT

Depressive disorders represent a considerable burden for society due to increased costs imposed on the health care system and higher productivity losses, even when treated with pharmacotherapy and psychological interventions.

Non-pharmacological treatments for depressive disorders have been explored and the anti-depressive and anxiolytic effects of exercise have been described in the literature. Although there is evidence supporting the role of exercise in reducing depressive symptoms, not only the optimum dose-response remains uncertain but also the mechanisms underlying the psychological and biological effects of exercise among subjects with depressive disorders.

The general purpose of this research was to assess the role of exercise as a complementary therapy of pharmacotherapy on the treatment of patients who suffer from depression, as well its association with psychological variables and physiological biomarkers.

In order to establish recommendations for exercise practice in the treatment of depression, a systematic review was conducted in the first study. The exercise programs of randomized controlled trials, which analyzed the effect of exercise on depressive symptoms, were studied between 2003 and 2016. Secondary analyses were explored for data relating to fitness levels, aerobic capacity and placebo groups, aiming to optimize the prescription. Thirteen trials were identified and the results have demonstrated that there is evidence that aerobic exercise performed for at least a nine-week period, of three times weekly, 30-45 minutes/session is the minimal dose required to achieve the decrease in depressive symptoms. Defining guidelines, specifically in relation to intensity, still remains to be early to establish due to inconsistent and poor description of exercise protocols. Indeed, the methodological limitations and the heterogeneity presented within trials make it unfeasible to achieve consistent conclusions with the aim to define the optimum dose-response.

To address the aim of determining the impact of exercise as a complementary treatment of pharmacotherapy, a randomized controlled trial (**HAPPY BRAIN**) was conducted in the second study. A total of 26 patients were randomized to receive antidepressant medication, or antidepressant medication plus exercise. Depressive scores in the exercise group significantly reduced in comparison to the control group. In addition, physical capacity in the intervention group increased when compared to the control group. There were no significant differences on the variables of weight, body mass index (BMI), waist circumference and self-esteem. The efficacy of exercise in depressive disorders is

classically attributed to its impact on changing neurobiological mechanisms including the monoaminergic metabolism.

Thus, to clarify the molecular mechanisms, which can be involved in the antidepressant effects of exercise, a third study was carried out. The catabolic enzyme catechol-O-methyltransferase (COMT) responsible for the inactivation of catecholamines and one of the main modulators of the dopaminergic levels, was analyzed pre-post exercise intervention in fourteen patients diagnosed with clinical depression. Results demonstrated that in the intervention group (antidepressant medication plus exercise) the peripheral levels of COMT had decreased significantly comparatively to the control group (antidepressant medication). Hence, this study offers evidence that exercise interferes with peripheral levels of COMT.

The understanding of this molecular mechanism could be an important step to clarify the molecular mechanisms underpinning the efficacy of exercise in depressive disorders. However, these data are preliminary results from a small sample (n=14 patients) and should be replicated. There is evidence in the third study that exercise may act to decrease COMT activity, and in turn lead to dopamine availability.

Therefore, in the fourth study, in order to increase our understanding of biological mechanisms underpinning the effects of exercise on depressive disorder, levels of monoamines (dopamine, noradrenaline, adrenaline, serotonin) and cortisol were analyzed. For this purpose, these physiological variables were compared between exercise and control groups, pre and post exercise intervention. This study was developed in conjunction with the **HAPPY BRAIN** study. However, its goal was to assess biological parameters. Results have shown that exercise when combined with pharmacotherapy has not led to changes in the analyzed biomarkers, that is, in monoamines and cortisol plasma levels.

Thus, the overall findings of this investigation demonstrated that exercise could be an adjuvant therapy for patients with clinical depression and the positive effects are not limited to the decrease of depressive symptoms, but psychological mechanisms could mediate this relationship. There are several potential biological mechanisms that explain or are linked with the antidepressant effects. Nevertheless, findings should be further explored, as they are controversial.

Keywords: Depression, Exercise, Mechanisms, Psychological, Biological.

RESUMO

As patologias depressivas representam um peso considerável para a sociedade, devido ao elevado custo imposto ao sistema de saúde e elevadas perdas de produtividade, mesmo quando sujeitas ao tratamento com farmacoterapia e intervenções psicológicas.

Tratamentos não farmacológicos para as perturbações depressivas têm sido explorados e os efeitos antidepressivos e ansiolíticos do exercício têm sido descritos na literatura. Apesar de existirem evidências que suportam o papel do exercício na redução da sintomatologia depressiva, continua por clarificar a dose-resposta ótima e quais os mecanismos subjacentes aos efeitos psicológicos e biológicos do exercício entre indivíduos com desordens depressivas.

O propósito geral desta investigação consistiu em avaliar o papel do exercício como terapia complementar da farmacoterapia no tratamento de pacientes que sofrem de depressão, assim como a sua associação com variáveis psicológicas e biomarcadores fisiológicos.

Com o intuito de estabelecer recomendações para a prática de exercício no tratamento da depressão foi realizada uma revisão sistemática no primeiro estudo. Os programas de exercício dos estudos randomizados que verificaram os efeitos do exercício na sintomatologia depressiva foram conduzidos entre 2003 e 2016. Análises secundárias foram exploradas para os dados relacionados com os níveis de aptidão física, capacidade aeróbia e grupos placebo, com o objetivo de otimizar a prescrição. Treze estudos foram identificados e os resultados demonstraram que há evidências que o exercício aeróbio, realizado no mínimo por um período de nove semanas, três vezes por semana, 30-45 minutos/sessão é a dose mínima recomendada para obter uma diminuição da sintomatologia depressiva. Definir recomendações, especificamente em relação à intensidade, continua a ser prematuro, dado que há uma descrição inconsistente e deficitária dos protocolos de exercício. Na verdade, as limitações e a heterogeneidade metodológica apresentadas nos estudos, inviabilizam conclusões consistentes com o objetivo de definir a dose-resposta ótima.

Com o objetivo de determinar o impacto do exercício como tratamento complementar da farmacoterapia, foi conduzido um estudo controlado e randomizado (**HAPPY BRAIN**) no segundo estudo. Um total de 26 pacientes foram randomizados para receber medicação antidepressiva, ou medicação antidepressiva mais exercício. Os valores da depressão no grupo de exercício reduziram significativamente em comparação com o grupo de controlo.

Além disso, a capacidade física no grupo de intervenção aumentou quando comparada com o grupo de controlo. Não se verificaram diferenças significativas para as variáveis peso, índice de massa corporal (IMC), perímetro da cintura e autoestima. A eficácia do exercício nas desordens depressivas é classicamente atribuída ao seu impacto nos mecanismos neurobiológicos, incluindo o metabolismo monoaminérgico.

Assim, para clarificar os mecanismos moleculares que podem estar envolvidos nos efeitos antidepressivos do exercício, foi conduzido o terceiro estudo. A enzima catabólica catecol-O-metilttransferase (COMT) responsável pela inativação das catecolaminas, e uma das principais modeladoras dos níveis dopaminérgicos foi analisada antes e após a intervenção do exercício em catorze pacientes diagnosticados com depressão clínica. Os resultados demonstraram que no grupo de intervenção (medicação antidepressiva mais exercício), os níveis periféricos de COMT diminuíram significativamente, comparativamente ao grupo de controlo (medicação antidepressiva). Assim, este estudo evidencia que o exercício interfere com os níveis periféricos de COMT. O entendimento deste mecanismo molecular poderá ser um passo importante para clarificar os mecanismos moleculares subjacentes à eficácia do exercício nas desordens depressivas. No entanto, estes dados são os resultados preliminares de uma pequena amostra (n=14 pacientes) e deverão ser replicados. Há evidência no terceiro estudo, de que o exercício pode atuar para diminuir a atividade da COMT e levar à disponibilidade de dopamina.

Consequentemente, no quarto estudo, com o intuito de aumentar o entendimento dos mecanismos biológicos subjacentes aos efeitos do exercício nas desordens depressivas, foram analisados os níveis de monoaminas (dopamina, noradrenalina, adrenalina, serotonina) e cortisol. Com este propósito, estas variáveis fisiológicas foram comparadas entre o grupo de exercício e o grupo de controlo, antes e após o programa de exercício. Este estudo foi desenvolvido conjuntamente com o estudo **HAPPY BRAIN**. No entanto, o seu objetivo pautou-se pela análise dos parâmetros biológicos. Os resultados demonstraram que o exercício quando combinado com a farmacoterapia não induz alterações nos biomarcadores analisados, ou seja, nos níveis plasmáticos de monoaminas e de cortisol. Assim sendo, as conclusões gerais desta investigação demonstraram que o exercício poderá ser uma terapia adjuvante para pacientes com depressão clínica, que os efeitos positivos não estão limitados à diminuição dos sintomas depressivos, mas os mecanismos psicológicos podem mediar essa relação. Existem inúmeros mecanismos biológicos potenciais que explicam ou estão associados aos efeitos antidepressivos. No entanto, os resultados deverão ser explorados no futuro, dado serem controversos.

Palavras-chave: Depressão, Exercício, Mecanismos, Psicológico, Biológico.

RÉSUMÉ

Les troubles dépressifs représentent une charge considérable pour la société en raison de l'augmentation des coûts imposés sur le système de santé et des pertes de productivité plus élevés, même lorsqu'ils sont traités avec la pharmacothérapie et avec des interventions psychologiques.

Les traitements non pharmacologiques pour les troubles dépressifs ont été explorés et les effets antidépressifs et anxiolytiques de l'activité physique ont été décrits dans la littérature. Bien qu'il y a des preuves appuyant le rôle de l'activité physique dans la réduction des symptômes dépressifs, la dose-réponse optimale reste incertaine et aussi les mécanismes qui soutiennent les effets psychologiques et biologiques de l'activité physique chez cette population.

Cette recherche a évaluée le rôle de l'exercice comme une thérapie complémentaire de la pharmacothérapie pour le traitement des patients et son association avec les variables psychologiques et les bio-marqueurs physiologiques.

Afin d'établir des recommandations pour l'activité physique dans le traitement de la dépression, une révision systématique a été menée dans la première étude. Les programmes d'exercice des essais randomisés contrôlés, qui ont analysé l'effet de l'exercice sur les symptômes dépressifs, ont été étudiés entre 2003 et 2016. Des analyses secondaires ont été explorées pour les données des niveaux de la condition physique, la capacité aérobie et les groupes placebo pour optimiser la prescription de l'exercice. Treize essais ont été identifiés, et les résultats ont démontré que l'exercice aérobie effectué pendant au moins, dans une période de neuf semaines, trois fois par semaine, 30-45 minutes / séance est la dose minimale pour obtenir la rémission des symptômes dépressifs. Définir des lignes directrices, en particulier l'intensité, reste à être tôt pour établir, en raison de la description incohérente et pauvre des protocoles de l'exercice.

Les limitations méthodologiques et l'hétérogénéité font-il irréalisable d'atteindre des conclusions cohérentes pour définir la dose-réponse optimale.

Pour déterminer l'impact de l'exercice comme un traitement complémentaire de la pharmacothérapie, un essai randomisé contrôlé (**HAPPY BRAIN**) a été conduit dans la deuxième étude. Un total de 26 patients a été randomisé pour recevoir un médicament antidépresseur ou un médicament antidépresseur et de l'exercice. Les scores dépressifs dans le groupe d'exercice ont réduit de façon significative par rapport au groupe témoin. En outre, la capacité physique dans le groupe d'intervention a augmenté par rapport au groupe témoin. Il n'y avait pas de différences significatives pour les variables de poids, índice de

masse corporelle (IMC), le tour de taille, et l'estime de soi-même. L'efficacité de l'exercice dans les troubles dépressifs est classiquement attribuée à son impact sur le changement des mécanismes neurobiologiques, en comportant le métabolisme monoaminergique.

Pour clarifier les mécanismes moléculaires qui peuvent être impliqués dans les effets antidépresseurs de l'exercice, une troisième étude a été réalisée. L'enzyme catabolique catéchol-O-méthyltransférase (COMT) responsable pour l'inactivation des molécules, aussi par les catécholamines et l'un des principaux modulateurs des niveaux dopaminergiques a été analysé avant et après l'intervention dans quatorze patients diagnostiqués avec la dépression clinique. Les résultats ont démontré que, dans le groupe d'intervention (médicament antidépresseur et l'exercice) les niveaux périphériques de COMT avaient diminué de façon significative comparativement au groupe témoin (médicament antidépresseur). Conséquemment, cette étude montre que l'exercice interfère avec les niveaux périphériques de COMT. La compréhension de ce mécanisme moléculaire pourrait être une étape importante pour clarifier les mécanismes moléculaires qui soutiennent l'efficacité de l'exercice dans les troubles dépressifs. Cependant, ces données sont des résultats préliminaires à partir d'un petit échantillon (n = 14 patients) et doivent être répliqués. Il y a des preuves dans la troisième étude que l'exercice peut agir pour diminuer l'activité de la COMT, et à son tour conduire à la disponibilité de la dopamine. Dans la quatrième étude, pour augmenter notre compréhension des mécanismes biologiques qui soutiennent les effets de l'exercice dans les troubles dépressifs, les niveaux de monoamines (dopamine, noradrénaline, adrénaline, sérotonine) et le cortisol ont été analysés. Ces variables physiologiques ont été comparées entre les groupes, avant et après l'intervention. Cette étude a été élaborée en collaboration avec l'étude **HAPPY BRAIN**. Cependant, son objectif était d'évaluer les paramètres biologiques. Les résultats ont montré que l'exercice lorsqu'il est combiné avec la pharmacothérapie n'a pas conduit à des changements dans les bio marqueurs analysés, cette à dire, dans les monoamines et dans les niveaux de cortisol plasmatique.

Les résultats globaux ont démontré que l'exercice pourrait être un traitement adjuvant pour ces patients, et les effets positifs ne sont pas limités à la rémission des symptômes dépressifs, mais les mécanismes psychologiques pourraient rendre compatible cette relation. Il y a plusieurs mécanismes biologiques potentiels qui expliquent ou sont liés à l'effet antidépresseur. Néanmoins, les résultats devraient être plus recherchés parce qu'ils sont controversés.

Mots-Clefs: Dépression, Exercice, Mécanismes, Psychologique, Biologique.

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LIST OF ABBREVIATIONS

?	Not reported
5-HT	Serotonin
A-NOVA	Analysis of variance
AD	Adrenaline
APA	American Psychiatric Association
BDI	Beck depression inventory
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CG	Control group
CI	Confidence interval
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
CR	Clinical response
CRP	C-reactive protein
DA	Dopamine
DASS-21	Depression anxiety stress scale-21
DSM	Diagnostic and Statistical Manual of Mental Disorders
e.g.	For example
ECG	Electrocardiography
ECT	Electroconvulsive therapy
EDTA	Ethylenediamine tetraacetic acid
EG	Exercise group
ESCI	Exploratory software for confidence intervals
EXSEM	Exercise and self-esteem model
F32.1	Depressive episode moderate
F33.1	Recurrent depressive disorder, moderate current episode
F34.1	Dysthymia
GDS	Geriatric depression scale
h	Hour
HAM-D	Hamilton rating scale for depression
HPA	Hypothalamic-pituitary adrenal

HPLC	High-performance liquid chromatography
HRmax	Maximum heart rate
HRR	Heart rate reserve
HRSD	Hamilton rating scale for depression
ICD	International statistical classification of diseases and related health problems
IL	Interleukin
Kcal/week	Kilocalories per week
KM	Michaelis-Menten
LD	Low dose
MANOVA	Multivariate analysis of variance
MB-COMT	Membrane bound, catechol-O-methyltransferase
MDD	Major depressive disorder
MeSH	Medical subject headings
Mets	Metabolic equivalent
N	Number of subjects
NA	Noradrenaline
NICE	National Institute for Health and Clinical Excellence
O_2pulse	Oxygen pulse
PASE	Physical activity scale for the elderly
PE	Physical exercise
PEDro	Physiotherapy evidence database
PFC	Prefrontal cortex
PHD	Public health dose
PhD	Doctor of Philosophy
PS	PEDro scale
R	Remission
RCTs	Randomized control trials
RM	Repetition maximum
RPE	Rate of perceived exertion scale
S-COMT	Soluble, catechol-O-methyltransferase
SD	Standard deviation
SMD	Standardized mean differences
SNRIs	Serotonin norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
TMS	Transcranial magnetic stimulation
TNF	Tumor necrosis factor

Vmax	Maximum velocity
VO_2max	Maximal oxygen uptake
VO_2R	Maximal oxygen uptake reserve
η^2p	Eta-squared

GENERAL INTRODUCTION

1. Depression: increased recognition as a major cause of disability

Depression is a serious public health, representing one of the leading causes of disability worldwide, which occurs in people of all ages, genders, and socioeconomic conditions across all world regions (Ferrari et al., 2013). This dysfunction has economic impact on the individual, family, employer, and on society (Lepine and Briley, 2011). According to the recent Global Burden of Disease Study (2010) there are five types of mental illness: major depressive disorder (MDD), anxiety disorders, schizophrenia, dysthymia and bipolar disorder, which appear in the top 20 causes.

The World Mental Health Survey demonstrated that the prevalence of mental disorders in Portugal (22.9% in 2008) was the highest of all ten European countries, included in the survey. One in five Portuguese suffer from mental health problems, 16.5% live with anxiety, and 6.8% suffer from MDD (Almeida et al., 2013).

Until the publication of the original Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association (APA) in 1952, the history of diagnostic classification systems for mental disorders was characterized by a lack of unification (Barlow and Durand, 2009).

The difficulties and the necessity for establishing an appropriate system to diagnose depression have been pointed out by several authors and resulted in a wide variety of psychiatric scales. In the early 1950s, the development of the first antidepressants led to the evolution of measurement scales including Hamilton rating scale, which became the gold standard for assessment of depression (Walker, 2008). However, clinicians remained critical about this and other instruments including Beck's depression inventory, which were individualistic with large areas of personal and social functioning inadequately addressed. Thus, a new specific model that allowed professionals to aggregate cases was formulated. This new diagnostic culture appeared in the 20th century. Consequently, categories to classify mental diseases were standardized in the first edition of DSM in 1952. Therefore, the term "major depressive disorder" was incorporated in the diagnostic classifications in the second edition of DSM-II, published in 1980 (Philipp et al., 1991).

There have been two widely used classifications of mental disorders, the ICD–10 (International Classification of Diseases, ten edition) and the DSM–V. Fundamentally, the criteria used to diagnose depressive episodes in ICD–10 and DSM–V overlap greatly, though there are some differences between them that should be emphasized. According to ICD-10, MDD patients must have two of the first three core symptoms in order to be diagnosed: depressive mood, loss of interest, and decreased energy. Additionally, at least two more of the remaining seven symptoms; (1) loss of confidence or self-esteem, (2) unreasonable feelings of self-reproach or inappropriate guilt, (3) recurrent thoughts of death or suicide, (4)

diminished ability to think/concentrate or indecisiveness, (5) change in psychomotor activity with agitation or retardation, (6) sleep disturbance, and (7) change in appetite with weight change. Whereas in DSM–V the patient must have at least one from the first two (depressed mood and loss of interest), plus five or more of the following symptoms: (1) fatigue/loss of energy, (2) excessive worthlessness or inappropriate guilt, (3) recurrent thoughts of death, suicidal thoughts or actual suicide attempts, (4) diminished ability to think/concentrate or indecisiveness, (5) psychomotor agitation or retardation (6) insomnia/hypersomnia, and (7) significant appetite and/or weight loss. Both DSM–V and ICD–10 include dysthymia, which is sub threshold for MDD but persists for more than 2 years.

Precise diagnosis has been a limitation in clinical psychiatry (Young et al., 2016). As a result, this is possibly the dominant issue of discussion and debate in the psychiatric scope (Alarcon, 2009). The diagnosis of depression, traditionally made by clinical criteria, is extensively used but depends on subjective interpretation (Smith et al., 2013). It has been a challenge to categorize exactly the spectrum of symptoms and its severity (Bilello et al., 2015). Additionally, it has been emphasized that diagnosis centered on these criteria may not distinguish sadness from a genuine clinical condition (Wolpert, 2008). Although sadness is considered to be a core symptom of depression, even if its presence is not requisite for diagnosis (Mouchet-Mages and Baylé, 2008), it is crucial to understand whether someone is disordered or normally sad in order to reduce potential false-positive diagnosis, i.e. subjects who meet the DSM´s diagnostic criteria but do not in fact have a mental disorder (Wakefield et al., 2010). Consequently, there is the risk to pathologize normal distress or sadness (Parker, 2007). Moreover, it is also essential to consider personal past history and family history of depression when undertaking a diagnostic assessment. Besides, barriers to diagnose depression include the frequent co-occurrence with medical or/and psychiatric disorders (Zbozinek et al., 2012). Therefore, depression could be underdiagnosed and overdiagnosed (Fiske et al., 2009). In this way, expertise in differential diagnosis and finding assertive diagnosis is essential as it is the diagnosis that will guide the therapeutic approach, and lead to achieve and sustain remission (Papakostas, 2009). The gold aim of MDD treatment comprises the whole resolution of depressive symptoms and acquires previous levels of mental and physical functioning (Trivedi, 2009).

The present thesis is based on the bio-psychosocial model of health that supports the fact that human beings should be seen as a complex system. This model reflects an attempt to include the psychological and the environmental factors into the traditional unipolar perspective of the biomedical model of health. This analysis allowed providing new insight to understand not only biological mechanisms underlying MDD´s etiology, but also an attempt to integrate social and environment risk factors that contribute to the vulnerability or

predisposition of MDD. Thus, both biomedical and psychosocial factors interact dynamically in the MDD´s etiology. Certainly, an integrative understanding of its mechanisms will help to open up new avenues for therapeutic strategies. Hence, in this thesis a closer look at biological mechanisms such as monoamines, hypothalamic-pituitary–adrenal (HPA) axis, inflammation, and neurogenesis (Stuart and Baune, 2012) will be present. As well, given this widespread disease burden it is crucial to identify underlying risk factors of the increasing prevalence and many risk factors have been described in the literature with focus on demographic variables (gender, socio-economic status, marital status). In addition, perceived life stress, sleep disturbance and low self-esteem have also been highlighted as important risk factors.

2. Biological Mechanisms

2.1 Monoamine hypothesis

The classical monoamine model of depression attributes depressive symptoms to changes in the metabolism or activity of the monoamine neurotransmitters: serotonin (5-HT), noradrenaline (NA), and dopamine (DA) (Schildkraut, 1965). This theory was sustained by the observation that all currently approved antidepressants for depression act in a similar way (Toups and Trivedi, 2012), i.e. they are designed to increase the availability of monoamines neurotransmitters in the brain (Dantzer et al., 2011). Indeed, currently they still continue to be a pharmacological treatment for MDD (Koenig and Thase, 2009), which supports the hypothesis. However, in spite of the monoamine hypothesis having long been accepted as a fundamental concept in the pathogenesis of depression (Jeon and Kim, 2016), it is over simplistic due to the fact that it cannot explain the time delay (2-3 weeks) of the therapeutic action of antidepressants (Nagayasu et al., 2013) even though the neurotransmitter concentrations are increased within hours (Brigitta, 2002).

Additionally, depression is a multifactorial illness with modifications in various different biochemical parameters that does not only involve monoamines (Pålhagen et al., 2010). More recent hypotheses on the pathogenesis, well beyond perturbations of traditional monoamine systems, include the HPA axis hypothesis, inflammation hypothesis, and the neurotrophin hypothesis, which will be discussed further on.

2.2 Hypothalamic-pituitary adrenal (HPA) hypothesis

The HPA-axis is described as a central control and regulatory system connecting the central nervous system (CNS) to the endocrine system (Kudielka and Kirschbaum, 2005),

and plays a role in regulating the physiological response to stress (Du and Pang, 2015). The hyperactivity of the HPA-axis is strongly implicated as a causal factor in MDD (Verduijn et al., 2015), and has been reported as one of the most reliable biological alterations in MDD (Pariante and Lightman, 2008). In this regard, approximately 50% of depressive patients exhibit an excessive activity of the HPA axis (Maric and Adzic, 2013), and the chronic treatment with antidepressant drugs is known to attenuate this hyperactivity and normalize the HPA axis function (Weber et al., 2006). Furthermore, repeated exposure to psychological stress has impact on peripheral immune response, which has been associated with neurobiological changes underpinning MDD (Wohleb et al., 2016). In fact, hyperactivity of the HPA axis is linked to an activation of the inflammatory response system in depression (Maes, 2011).

2.3. Inflammation hypothesis

There is great evidence indicating that patients who suffer from depression demonstrate immune deregulation and exhibit higher circulating cytokines (Felger and Lotrich, 2013). Two meta-analyses (Dowlati et al., 2010; Liu et al., 2012) corroborated the previous findings and revealed that interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) were consistently more elevated in depressed patients than in healthy subjects. According to this, several other studies documented a reduction in pro-inflammatory cytokines levels after treatment with antidepressants for TNF-α, IL-1β, IL-6, and IL-12 (Dahl et al., 2014) as well as an increase in the anti-inflammatory cytokines, such as IL-4 (Lotrich, 2015). Additionally, treatments that lead to a decrease in inflammatory cytokine activity have not always been successful in treating MDD (Raison et al., 2013). It is important to note that not all types of depression necessarily include cytokines but it may be one subtype of depression (Felger and Lotrich, 2013). There are several factors that include medical disorders, major life stressors, and sleep disturbance that may lead to inflammation and precipitate the development of depression (Berk et al., 2013).

2.4. Neurogenesis hypothesis

Interestingly, higher levels of glucocorticoids can decrease neurogenesis (Krishnan and Nestler, 2008), and this has been reported as a mechanism for decreasing the hippocampus volume in many patients with depression (Campbell and Macqueen, 2004). Indeed, stress and depression can cause neuronal atrophy, and cell loss in limbic areas involved in depression, such as the amygdala, the prefrontal cortex, and hippocampus (Duman and Monteggia, 2006).

Brain-derived neurotrophic factor (BDNF) is a neurotrophin responsible for the stimulation and control of neurogenesis, and is the most predominant growth factor in the CNS (Autry and Monteggia, 2012). The role of BDNF in depression has gained attention because it is also involved in the maintenance of neuronal plasticity in adult brain, comprising regulation of synaptic activity, and in neurotransmitter synthesis (Dwivedi, 2010). Likewise, analysis of postmortem hippocampus reveals that the expression of BDNF is decreased in depressed suicide victims (Karege et al., 2005).

In conclusion, the biological approach offering explanations of behavior in terms of neurochemical imbalances is frequently highlighted as a contributor to the cause of MDD. However, MDD is a multifactorial illness (Vavakova et al., 2015) and its etiology is often explained through more complex interactions of biological, psychosocial factors (Fakhoury, 2015).

3. Demographic Variables

The socio-demographic factors of gender, marital status, education, and income have constantly been recognized as key factors in elucidating the variability in the prevalence of depression (Akhtar-Danesh and Landeen, 2007).

3.1 Gender

The influence of gender on depression has been well documented in psychiatric epidemiological studies (Kessler et al., 2005). Consistent with this, women are twice as likely as men to experience depression, and this gender difference emerges in puberty (Kessler, 2003). The predominance in prevalence varies according to diagnostic sub-types and is significant for MDD, dysthymia, atypical depression and seasonal winter depression (Piccinelli and Wilkinson, 2000). Explanations underpinning this gender's prevalence may reflect the interaction of biological, social and psychological factors (Essau et al., 2010). The ABC model, which was originally developed by Hyde et al. (2008), describes the vulnerability in women to experience depression in adolescence via affective (emotional reactivity), biological (genetic vulnerability, pubertal hormones, pubertal timing and development), and cognitive (cognitive style, objectified body consciousness, rumination) factors. These interact with negative life events, leading to proneness to experience depression. Furthermore, somatic symptoms, comprising fatigue and insomnia, have been found to be twice as high in females than in males (Silverstein et al., 2013).

3.2 Socio-economic status and marital status

Understanding if low socio-economic status is linked with increased risk of a new episode of common mental disorder or with worse prognosis is crucial from an etiological perspective and a public health viewpoint (Skapinakis et al., 2006).

Previous researches propose that depression usually occurs among subjects in disadvantaged socioeconomic groups, as assessed through education level, occupational grade or income (Lorant et al., 2003). Clarifying who acquires a greater protective effect from higher education against depression is essential for understanding mental health disparities in population (Bauldry, 2015). For instance, higher educational level may help to safeguard against depression. Still, the mediators seem to be personal characteristics related to resilience to stress (Bjelland et al., 2008), attainment of the most fulfilling careers and superior earnings, and development of a sense of mastery and self-efficacy, which in turn help individuals deal with life's daily challenges (Bauldry, 2015). Additionally, long-term probability of depression seems to be related with a socioeconomic proneness, where the subjects in the lowest occupational groups (i.e. defined as not being promoted during the course of their career) are most likely to be depressed, in comparison with subjects in the highest occupational groups (Melchior et al., 2013). For instance, occupational class may be related with prestige and feeling of power in society.

One of the most prominent aspects of the impairment related with MDD is that the salaries and household income of individuals with MDD are significantly lower in comparison with individuals without depression (McMillan et al., 2010).

Regarding marital status, it has been well documented the high prevalence of MDD in subjects separated, divorced, or widowed (Bulloch et al., 2009). However, literature also shows that marital dissatisfaction is strongly associated to depressive symptoms (Kessler and Bromet, 2013).

Given the personal, social, and economic costs of MDD, researchers have attempted to identify possible factors that may underlie the development of depression (Muscatell et al., 2009). As a result, to experience stress over a prolonged period of time and sleep disturbance are thought to be critical risks factors for MDD.

4. Perceived life stress caused by negative life events

There are subjects under constant stress who do not present signs of depression, and sometimes depression develops without previous stress (Monroe and Reid, 2009). Thus, there are individual differences and sensibilities in reacting to stress and adversity (Krishnan

and Nestler, 2008), and psychological and cognitive determinants are crucial for the course of the process (Le Moal, 2007). In fact, research has recognized personality characteristics including negative cognitive styles and rumination as risk factors for depression (Robinson and Alloy, 2003). Therefore, there is evidence that subjects with negative cognitive styles are more prone to experience depression in comparison to subjects with a positive cognitive style (Alloy et al., 2006). At the same time, rumination involves repetitive focus on the causes and implications of negative feelings, and problems (Watkins, 2015). However, substantial evidence supports that stress and recent major life events are linked with the onset of clinical depression (Kumar et al., 2015). Researchers have focused particularly on adverse life circumstances, which precede and predict the onset of MDD (Muscatell et al., 2009). For instance, several negative daily life experiences including isolation, parental divorce, experiencing a frightening event in childhood, the death of a spouse, loss of an important job, poor working conditions, and financial difficulties contribute to increase vulnerability and predict depression (Kessler, 1997; Monroe, 2008).

5. Sleep disturbance

Sleep is a regulated process with a vital restorative function (Penzel et al., 2003), and sleep disrupt predicts functional and social impairment, which has a significant impact on quality of life (Kallestad et al., 2012).

Insomnia, characterized by an inability to initiate or maintain sleep (Doghramji, 2003) is the most frequent sleep disturbance in depressed patients, and has been identified as a potential risk factor for depression (Paunio et al., 2015). This is in line with a meta-analysis highlighting that non-depressed subjects with insomnia have 2-fold risk to develop depression than subjects with no sleep difficulties (Baglioni et al., 2011). Furthermore, sleep disturbance is one of the core symptoms of MDD (Kurian et al., 2009), and closely 90% of patients with depression experience sleep impairment (Tsuno et al., 2005). In fact, both insomnia and hypersomnia are diagnostic criteria in DSM-V, and insomnia as a residual symptom (Kurian et al., 2009) is also associated with poor response to treatment.

6. Self-esteem

Self-esteem is best characterized as the individual's assessment of self-worth (Rosenberg, 1965). Subjects with low self-esteem assess themselves negatively, and poor self-esteem can result in a cascade of diminishing self-appreciation, feelings of incompetence, being weak, and fragile (Rizwan and Ahmad, 2015). In contrast, subjects with

high self-esteem, rate themselves more positively, believe that they are socially approved, and experience feelings of self-worth.

It has been proposed that low self-esteem is related to the etiology, understanding and treatment of a broad range of psychiatric disorders (Silverstone and Salsali, 2003). In fact, the symptom criteria for MDD, as detailed in ICD-10 and DSM-V, include two symptom sets related to self-esteem. The first in ICD-10 is loss of confidence or self-esteem, and the second in DSM-V is feelings of worthlessness.

Likewise, improvement of self-esteem has been consistently reported as one of the main treatment goals for psychiatric patients (Knapen et al., 2005). Additionally, lack of self-esteem is suggested to play an important role in the recurrence of depressive episodes (Risch et al., 2010). Several factors are related to lowered self-esteem in these patients including patients' age, gender, educational level, income, and employment status (Salsali and Silverstone, 2003). Although it is well recognized that low self-esteem and depression are interrelated, the nature of the relation has been a topic of extensive discussion (Orth and Robins, 2013).

It is not yet clear if low self-esteem makes subjects vulnerable to depression, or if depression contributes to the development of low self-esteem, or if they are reciprocally related. At the same time, it is still a matter of discussion the trait vs. state nature of this interaction, that means, if it is an individual characteristic (trait self-esteem), or if it is a quality of a person in a particular time i.e. state self-esteem (Silverstone and Salsali, 2003).

7. Therapeutic approaches

The high heterogeneity of diagnostic criteria and limited understanding of its etiology (Krishnan and Nestler, 2008) leads to no uniformly effective treatment available to treat depression (Koenig and Thase, 2009). Subjects who suffer from depression vary in the pattern of symptoms they experience, family history, personalities, physical and psychiatric comorbidities, and social problems that interfere with individuals' response to treatment.

The modern classes of antidepressants selective serotonin reuptake inhibitor (SSRI), and serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants are currently used as first line therapies for MDD (Dale et al., 2015). These offer superior tolerability and safety in relation to older medication (tricyclic antidepressants and monoamine oxidase inhibitors) (Koenig and Thase, 2009). However, SSRIs and SNRIs antidepressants have similar secondary effects, which include gastrointestinal effects, such as constipation, diarrhea, dizziness, headache, insomnia, nausea, sleep disturbance, and sexual dysfunction (Renoir, 2013). The potential side effects, their therapeutic delays, low remission rates of

nearly 30% (Krishnan and Nestler, 2008), and the difficulty to treatment adherence (Morehouse et al., 2011) lead to a necessity to achieve other therapies as a monotherapy or as a complementary treatment. In fact, a range of psychotherapeutic interventions, including cognitive-behavioral psychotherapy, psychodynamic psychotherapy or interpersonal psychotherapy, has been shown to relieve the symptoms of MDD (Linde et al., 2015). A meta-analysis reported that the effectiveness of psychotherapy for mild to moderate depression is as effective as pharmacotherapy, and combining both in treatment is more effective than each one alone (Cuijpers et al., 2011).

For those patients who fail to respond to psychological and pharmacological therapies, electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) are two of those options. They are used for severe and treatment-resistant psychiatric disorders, in particular for MDD (Gaynes et al., 2014; Kerner and Prudic, 2014). The major concern in using ECT for the treatment of depression remains to be the cognitive side effects (Semkovska and McLoughlin, 2010).

All of these issues highlight the necessity for other non-pharmacologic, complementary therapies, which should be effective and safe for patients, and exercise is potentially one such therapy (Mura et al., 2014). Thus, despite traditional treatments including pharmacological interventions, psychotherapy or a combination of both depending on its severity (Krogh et al., 2015), there has been an increase in clinical interest in the role of exercise as a non-pharmacologic intervention to mitigate symptoms of depression and optimize recovery.

The acceptance of exercise as a therapeutic tool for the treatment of clinical depression has been reported on previous randomized control trials (RCTs), not only in participants with light-to-moderate levels of depression (Legrand and Neff, 2016) but also in ones with severe levels of depression (Schuch et al., 2015b).

Exercise is a safe and well-tolerated therapeutic strategy associated with significant improvements included in cognitive function (Hotting and Roder, 2013), cardiovascular risk factors (Kerling et al., 2015), functional capacity (Carneiro et al., 2015), and quality of life (Schuch et al., 2015b). Experimental studies have also supported that exercise distracts attention from negative thoughts and ruminations (Searle et al., 2011), brings a sense of mastery, improves self-esteem, and self-efficacy (Callaghan et al., 2011; Craft, 2005). Physical activity has been positively associated with self-concept and body image (Dishman et al., 2006). Nonetheless, exercise provides an effective way to increase feeling of mastery by the belief based on the task-efficacy being performed (White et al., 2009). Indeed, if people believe in their capability to perform tasks without constraints, they will be more likely to initiate and persist at exercise (Weibull et al., 2015).

However, the precise molecular and neurobiological mechanisms are not clear (Schuch et al., 2015a). Thus, it has been reported that physiological benefits include changes in central dopaminergic, noradrenergic and serotonergic systems (Meeusen and De Meirleir, 1995), decrease the activity of the HPA axis (Sousa e Silva et al., 2010), reduce levels of serum inflammatory cytokines including C-reactive protein (CRP) IL-6 and IL-18 (Eyre and Baune, 2012), and increase levels of neurotropic factors, namely BDNF (Medina et al., 2015).

Nevertheless, despite the value of supervised and individualized exercise in the treatment of mental disorders including depression (Stanton et al., 2015), the available literature demonstrates that the rates of exercise among those who have mental illness are lower compared to the rest of the population (Patten et al., 2009).

Additionally, in spite of the significantly recent advances in this area of treatment, scientific research on the impacts of exercise on depression has its gaps (Medina et al., 2015), and many questions need further clarification.

Firstly, Krogh et al. (2011) published a meta-analysis to evaluate the effectiveness of exercise in adults with clinical depression, and the results showed that exercise interventions were linked with a small to moderate effect on depressive symptoms. However, when only the studies with high quality were included, the estimated beneficial effect of exercise was non-significant (standardized mean differences (SMD) of −0.19; 95% confidence interval (CI) −0.70 to 0.31). Corroborating this, Rimer et al. (2012) conducted a meta-analysis and concluded that exercise improved depressive symptoms in individuals with clinical depression, indicating a moderate effect size. Nonetheless, after only assessing robust trials with high methodological quality, the effect size was small in favor of exercise (SMD, -0.31; 95% CI -0.63 to 0.01). Secondly, other reviews contained a number of trials that included non-clinical community volunteers, who were defined as being depressed on the basis of cut-off point of the scales (Krogh et al., 2015).

At the same time, it is essential to understand why starting or maintaining a regular exercise routine can be a challenge for subjects who suffer from depression (Stubbs et al., 2016). To prescribe exercise, previous physical activity history, a-motivation and lack of pleasure in daily activities as a component of depressive symptomatology should be analyzed (Knapen et al., 2014), as well as comorbidities with chronic physical diseases. It is also important to bear in mind that prescribing exercise “is not one for all” (de Souto Barreto, 2015). Therefore, when making decisions, it is essential to understand the exercise program variables that are likely to result in successful treatment outcomes. Moreover, the optimal dose-response has not yet been determined (Knöchel et al., 2012).

To overcome this limitation in study one, we carried out a systematic review with thirteen studies with the aim to improving prescription to achieve better results in the treatment of depression. Data relating to physical fitness levels, aerobic capacity, and placebo effects that could interfere with exercise efficacy were also examined.

Moreover, in the second study the effectiveness of exercise as a complementary treatment was assessed. To overwhelm some limitations reported previously in the **HAPPY BRAIN** study, inclusion and exclusion criteria were meticulously defined, patients were recruited directly during routine external consultations by a psychiatrist, and ICD-10 was used as a diagnostic criteria.

In addition to diagnosis, the severity of the symptoms was assessed using self-report scales, the Beck Depression Inventory (BDI) scale, and the Depression Anxiety Stress Scale-21 (DASS-21). In the **HAPPY BRAIN** study, only women composed the sample, a physical training teacher supervised all sessions, and strategies to increase compliance were defined before exercise intervention.

Furthermore professionals from diverse areas (psychiatrists, physical training teachers, professor of exercise physiology) composed the **HAPPY BRAIN** team. Hence, a total of 26 women (aged 50.16 ± 12.08) diagnosed with clinical depression were randomized either to a supervised aerobic exercise group (45-50 min/week three times a week for four months) plus pharmacotherapy (intervention group), or only antidepressant medication group (control group). Considering that self-esteem is considered a trustworthy indicator of mental health, and is linked with a wide range of psychiatric disorders (Vracotas et al., 2012), Rosenberg's global self-esteem scale was used to measure global self-esteem. As reported previously, there are several factors that might moderate the antidepressant effects of exercise, nonetheless the underlying molecular and neurobiological explanations are not yet clear. In order to identify biological mechanisms that might contribute to elucidate the exercise as a therapeutic tool, in the third study an RCT to evaluate the effects of chronic exercise on soluble catechol-O-methyltransferase (S-COMT) activity in women with depressive disorder was conducted. Thus, fourteen women (aged: 51.4±10.5) diagnosed with clinical depression were randomized to one of two groups: pharmacotherapy plus exercise or only pharmacotherapy.

The fourth study was carried out in conjunction with the **HAPPY BRAIN** trial and we hypothesized that the exercise group would have a significant increase in monoamine levels and a decrease in cortisol levels in comparison with the control group. Indeed, this was the first study developed in women with depressive disorder, which analyzed the influence of chronic exercise on monoamine responses and cortisol plasma levels.

Objectives

The main objective of the research was to investigate the efficacy of exercise intervention as adjunctive to antidepressant medication in the treatment of patients with depressive pathology. A variety of study methods was used to address this goal, including a systematic-review, and a clinical trial. The specific goals were to:

I. Undertake a systematic review, with the primary outcome to define optimal dose-response when prescribing exercise for patients with depression. Data relating to the parameters of exercise: type, duration, frequency, and intensity. As a secondary aim, explore clinical trials (data relating to physical fitness levels, aerobic capacity, and placebo effects) with the goal to improve the prescription (study 1);
II. Examine changes on symptoms of depression, anthropometric measures, physical fitness, and self-esteem, induced by 16 weeks of exercise plus pharmacotherapy (exercise group), and compare them with only pharmacotherapy (control group) (study 2);
III. Investigate the potential impact of exercise plus pharmacotherapy on S-COMT activity, and compare them with control group (study 3), and;
IV. Compare exercise group to control group in relation to monoamines neurotransmitters (DA; adrenaline, AD; NA and 5-HT), and cortisol levels (study 4).

STUDIES

STUDY 1

Better prescription to achieve better results in the treatment of depression: Beyond frequency, intensity and duration

Better prescription to achieve better results in the treatment of depression: Beyond frequency, intensity and duration

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Objectives: The purpose of this study was to define the dose-response of exercise, and analyze data relating to physical fitness levels, aerobic capacity, and placebo effects that could interfere with exercise efficacy.

Design: A systematic review was carried out on all randomized control trials conducted between 2003-2016 in adults with depression.

Methods: In all studies, exercise was examined in relation to type, duration, frequency, intensity (including methods to assess intensity and analysis of self-selected intensity), physical fitness levels, aerobic capacity, and placebo effects. PEDro scale was used to examine methodological quality of studies.

Results: Thirteen studies met the inclusion criteria. There is evidence that aerobic exercise can be beneficial, when carried out for at least a nine-week period with a minimum of three times weekly, 30-45 minutes/session. In relation to intensity, it remains premature to advance recommendations.
Few studies analyzed physical fitness levels and aerobic capacity as indicators of exercise intervention efficacy. Low frequency group, stretching, flexibility, and exercise advice were included as placebo exercise groups.

Conclusions: Recommendations in relation to dose-response are similar with previous systematic reviews. Defining minimum dose-response instead of optimal dose-response is the most realistic approach. There is still lack in literature to identify intensity dose and studies analyzing physical fitness levels and aerobic capacity. Overcoming these limitations is a step to understand if the intervention is effective or not, and if gains in both parameters are associated with changes in depressive symptoms. Furthermore, placebo groups demonstrating clinical response or remission rates should be carefully analyzed.

Keywords – Aerobic capacity, depressive disorder, exercise, physical fitness, placebo effects, randomized control trials.

1. Introduction

Major depressive disorder (MDD) is a worldwide, generalized mental health concern leading to severe morbidity and increasing mortality risk (Taylor, 2015). Patients with depression have a 20-time greater risk of suicide compared to the general population (Lepine and Briley, 2011). Several countries have carried out epidemiological surveys and the high prevalence and persistence of MDD confirm that this is a worldwide disorder of utmost importance (Kessler and Bromet, 2013).

First-line treatment guidelines for moderate MDD include antidepressant monotherapy, psychotherapy, and the combination of both. Severe depression may need the combination of an antidepressant and an antipsychotic, electroconvulsive therapy, or an antidepressant and psychotherapy (Davidson, 2010). Undoubtedly, an investment in the search of effective adjuvant therapies has been made to enhance the treatment of depressive disorders. In recent years, the evidence base for both physical and mental health benefits of physical activity and exercise has been well established in improving depressive symptoms (Stubbs et al., 2016). Exercise produces several advantages, such as benefits in terms of physical performance (Carneiro et al., 2015). It may also fill in the three-to four-week time lag that antidepressants require before showing therapeutic effects (Fornaro and Giosue, 2010), improve quality of life (Schuch et al., 2015), decrease the risk of metabolic disorders (Stubbs et al., 2015), have a positive impact on sleep quality (Rethorst et al., 2013), and distract from negative thoughts and ruminations (Searle et al., 2011).

Although pharmacological therapy is the current gold standard for the treatment of depression, a wide body of literature including systematic reviews and meta-analyses (Stubbs et al., 2016; Knapen et al., 2015; Krogh et al., 2011) mentions the importance of the role of exercise as a treatment. While the impact of exercise interventions among subjects with depression has been explored, the optimal dose that might prove effective remains non-consensual, yet (Ranjbar et al., 2015). In fact, one systematic review and meta-analysis that investigated only trials recruiting patients from a clinical setting has shown no evidence that exercise had a beneficial effect (Krogh et al., 2011). Another meta-analysis indicated that the effects of exercise were small when only methodological robust trials were included (adequate allocation concealment, intention to treat analysis and blind outcome assessment) (Rimer et al., 2012). However, a more recent meta-analyses and systematic review (Knapen et al., 2015) reports that exercise is moderately more effective in comparison to no therapy in reducing symptoms of depression. Moreover, exercise is as effective as antidepressants and psychological therapies in reducing symptoms of depression, although this conclusion is based on a small number of studies. In Cochrane´s most recent meta-analysis review

(Cooney et al., 2013), the authors sustain that when compared to psychological or pharmacological therapies, exercise appears to be no more effective, although this conclusion is also based on few small trials.

Three systematic reviews (Perraton et al., 2010; Stanton and Reabum, 2013; Nystrom et al., 2015) of randomized control trials (RCTs) have been published to set recommendations for exercise program variables in the treatment of patients with depression. According to Perraton and Colleagues (2010), there is evidence of supervised aerobic exercise, performed three times a week at moderate intensity (60–80% of maximum heart rate) during 30-minute sessions, for a minimum of eight weeks.

The other narrative review (Stanton and Reabum, 2013) also reported supervised aerobic exercise, three to four times per week at a moderate or self-selected intensity for 30–40 min, over a period of at least nine weeks. Nevertheless, both of them (Perraton et al., 2010; Stanton and Reabum, 2013) included only studies in which the exercise program had significant effects in the decrease of depressive symptomatology. Another review (Nystrom et al., 2015) described that individually personalized physical activity, for at least 30 minutes, supervised and with a frequency of at least three times per week, is recommended when treating depression. Nonetheless, in complement to the reviews (Perraton et al., 2010; Stanton and Reabum, 2013), the authors also considered studies that did not find significant treatment effects. Despite this progress and these reviews having been helpful, there is incomplete understanding of exercise effectiveness as a therapy to treat depression.

The present review uses the same tool (Physiotherapy Evidence Database, PEDro Scale) to assess the methodological quality of individual RCTs, which was used in Perraton and Colleagues (2010) and Stanton and Reabum (2013) reviews. However, in both only RCTs of patients aged between 18-65 were included, as well as comorbidity with psychiatric disorders.

In the present review no upper age limit (18 and over) was included and mixed psychiatric diagnoses were set as an exclusion criterion.

For trials which provided more than one intensity of exercise or when trials included more than one type of exercise, we will take into account the greatest remission rate due to the fact that the goal of MDD treatment is to achieve full remission (Trivedi, 2009). Whereas, trials do not report remission rates, clinical response rates will be considered. In the RCTs that do not report either remission or clinical response, the strongest dose of exercise will be analyzed.

Aerobic exercise (Perraton et al., 2010; Stanton and Reabum, 2013) or resistance training (Cooney et al., 2013) were eligible based on past research that suggested both types might have an antidepressant effect.

A total of thirteen papers was included in the present review, but five (Schuch et al., 2015; Sims et al., 2006; Chalder et al., 2012; Legrand and Neff, 2016; Siqueria et al., 2016) of them are different from other two previous reviews (Perraton et al., 2010; Stanton and Reabum, 2013).

The objectives of the present study were to: (1) perform a systematic review in regard to optimal dose-response when prescribing exercise for patients with depression. Data relating to the parameters of exercise: type, duration, frequency, intensity (methods used to assess intensity and analysis of self-selected intensity prescription); (2) explore clinical trials (data relating to physical fitness levels, aerobic capacity, and placebo effects) with the goal to optimize the prescription and set new directions for clinical research.

2. Methods

Searches on PubMed, CINAHL, MEDLINE, PsychINFO, PsycARTICLES and Cochrane databases (January 2003 to July 2016) were carried out using medical subject headings (MeSH) and the following text terms: “depressive disorder” or “unipolar depression” or “major depressive disorder”, and “exercise” or “exercise programs”, and “clinical trial” or “randomized controlled trial”. The main search for trials was updated for the last time on July 7, 2016.

The methodological evaluation was conducted using the PEdro Scale (Sherrington et al., 2000), an 11-point scale addressing external and internal validity, which considers various aspects of the study design: random allocation, allocation concealment, baseline similarity, blinding of participants, therapists, and assessors, key outcome measures obtained from at least 85% of the participants initially assigned to groups, the intention to treat the analysis performed, and between group statistical analysis carried out on at least one key outcome. Lastly, both point measures and measures of variability were performed for at least one key outcome.

External validity of this instrument is addressed by one item (1) and internal validity is addressed by two items (2 and 9) (Sherrington et al., 2000), but item one is not considered as part of the overall scoring. Furthermore, due to the nature of the intervention (i.e., physical activity or exercise) it is not possible to blind subjects. Consequently, in this systematic review the maximum possible score used in the PEdro scale was nine.

The participants were: adult men and women aged 18 and over (with no upper age limit) with clinical depression as defined by the Diagnostic or Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria, or a validated depression scale.

The intervention used was aerobic or a resistance training program or a combination of both. In relation to the comparison group, any intervention such as pharmacotherapy, psychotherapy, another exercise program, or no intervention (placebo or wait-list control) were analyzed.

Outcome measures validated depression-rating scales.

As for the inclusion criteria, all RCTs were included, whether exercise was beneficial or not in the treatment of depression; all RCTs were from peer reviewed journals; and the search was limited to English language RCTs published.

Regarding the exclusion criteria, all RCTs were excluded if trials included depressed population not diagnosed by the DSM-IV, ICD-10 criteria, or a validated depression scale; depression with co-morbid illness such as diabetes (insulin dependent), cancer, multiple sclerosis, and cardiovascular disease; mixed psychiatric diagnosis; trials of exercise intervention that did not include an aerobic or resistance training program or a combination of both components; and studies that measured outcomes immediately before and after a single exercise session.

Considering exercise parameters, studies have been included in accordance with the following data criteria:

Type - aerobic or a resistance training program or a combination of both

Duration - number of minutes per session

Duration of intervention - number of weeks

Frequency - days per week

Intensity - amount of energy expended measured in kilocalories per week (Kcal/week); percentage of maximum heart rate (%HRmax); percentage of heart rate reserve (%HRR); percentage of maximal oxygen uptake (VO_2max.); percentage of maximal oxygen uptake reserve (VO_2R); metabolic equivalent (Mets)

Adherence - number of percentage of completers

3. Results

As can be noticed in Figure 1, thirteen references met the broad inclusion criteria and the methodological evaluation. Among the included studies, one trial (Siqueria et al., 2016) scored the highest (9 out of 10), whereas one study (Legrand and Heuze, 2007) had the lowest score (6 out of 10).

Figure 1 – Study Selection Process.

In the present review, eight studies had two arms (Schuch et al., 2015; Sims et al., 2006; Chalder et al., 2012; Siqueria et al., 2016; Callaghan et al., 2011; Mota-Pereira et al., 2011; Schuch et al., 2011; Trivedi et al., 2011), three had three arms (Legrand and Neff, 2016; Legrand and Heuze, 2007; Chu et al., 2009), one had four arms (Blumenthal et al., 2007), and one had five arms (Dunn et al., 2005).

The analysis of the studies showed that the samples comprised mainly women (Schuch et al., 2015; Sims et al., 2006; Legrand and Neff, 2016; Siqueria et al., 2016; Legrand and Heuze, 2007; Mota-Pereira et al., 2011; Trivedi et al., 2011; Dunn et al., 2005); two studies only included females in the sample (Callaghan et al., 2011; Chu et al., 2009); one study (Schuch et al., 2011) did not provide sufficient information, and the other two (Blumenthal et al., 2007; Chalder et al., 2012) studies included more males than females. Patients´ mean age was 44.7 years.

All subjects were assessed using DSM-IV, ICD-10 or validated instruments. In eight trials, diagnosis of depression was done through DSM-IV (Schuch et al., 2015; Legrand and Neff, 2016; Siqueria et al., 2016; Mota-Pereira et al., 2011; Schuch et al., 2011; Trivedi et al., 2011; Blumenthal et al., 2007; Dunn et al., 2005), one by ICD-10 (Chalder et al., 2012), and four studies used a cut-off point of two depression scales: Beck Depression Inventory (Legrand and Heuze, 2007; Callaghan et al., 2011; Chu et al., 2009) and Geriatric Depression Scale (GDS) (Sims et al., 2006).

Out of a total of thirteen intervention studies, eleven obtained significant positive results in the reduction of symptomatology when using aerobic exercise. From the two studies that did not obtain significant results, one study opted for strength training (Sims et al., 2006), and another study (Chalder et al., 2012) assessed face-to-face coaching and telephone consultations, i.e. not structured exercise.

The majority of the studies opted for aerobic intervention; nevertheless, there was heterogeneity among the trial monitoring intensity. One aspect of heterogeneity concerns the diversity of measures to assess intensity as an indicator of effort control in the process of exercise prescription. Four studies used the quantity of energy spent on exercise sessions measured in kilocalories (Kcal/week) (Schuch et al., 2015; Schuch et al., 2011; Trivedi et al., 2011; Dunn et al., 2005). By contrast, three opted for the evaluation of the percentage of maximum heart rate (%HRmax) (Legrand and Neff, 2016; Siqueira et al., 2016; Legrand and Heuze, 2007), the percentage of heart rate reserve (%HRR) (Blumenthal et al., 2007), the percentage of the VO_2 reserve (%VO_2R) (Chu et al., 2009), the scale of subjective perception of effort by Borg (Sims et al., 2006; Callaghan et al., 2011; Mota-Pereira et al., 2011), and one study (Chalder et al., 2012) did not report intensity. All studies except one (Callaghan et al., 2011) prescribed intensity instead of preferred intensity.

Concerning the duration of sessions, six studies (Mota-Pereira et al., 2011; Trivedi et al., 2011; Chu et al., 2009; Blumenthal et al., 2007; Legrand and Neff, 2016; Legrand and Heuze, 2007) obtained improvement between 30-45 minutes per session, one study (Siqueria et al., 2016) between 20-60 minutes, and four studies did not specify the duration (Callaghan et al., 2011; Schuch et al., 2015; Schuch et al., 2011; Dunn et al., 2005). Studies that have not shown significant improvement as an anti-depressive lasted 30 minutes per session (Sims et al., 2006), and the other study (Chalder et al., 2012) only refers to 150 minutes per week in periods of at least 10 minutes per session.

Regarding the duration of exercise intervention programs, there is variability: studies reported improvements between 10 days and 16 weeks with a 9-week mean duration, excluding one study (Schuch et al., 2011) which did not report, as well as the study by Legrand, Neff (2016), which only lasted 10 days.

The studies that did not show significant improvements reported 10 (Sims et al., 2006) and 16 (Chalder et al. 2012) weeks of intervention program.

Regarding frequency, there is variability: studies reported significant improvements with 3 sessions per week (Callaghan et al., 2011; Schuch et al., 2015; Schuch et al., 2011; Dunn et al., 2005; Blumenthal et al., 2007), 4 sessions per week (Siqueria et al., 2016), 3-5 sessions per week (Legrand and Heuze, 2007), 4-5 sessions per week (Chu et al., 2009), 5 sessions per week (Mota-Pereira et al., 2011; Trivedi et al., 2011), and one study (Legrand and Neff, 2016) did not report any frequency. Two studies, which did not show improvements in depressive symptoms, one of them (Sims et al., 2006) opted for 3 sessions weekly, and the other one did not specify (Chalder et al., 2012).

Our aim was to evaluate changes in physical fitness and aerobic capacity, and to monitor the effectiveness of exercise. Therefore, the studies that only assessed them at baseline did not fit these criteria. In addition, the studies that did not specify the differences between groups and only the differences within groups did not comply with our criteria in order to be analyzed.

Thus, Table 1 shows that there are ten (Chalder et al., 2012; Legrand and Neff, 2016; Legrand and Heuze, 2007; Schuch et al., 2015; Callaghan et al., 2011; Mota-Pereira et al., 2011; Schuch et al., 2011; Trivedi et al., 2011; Chu et al., 2009; Dunn et al., 2005) studies that have not assessed physical fitness and aerobic capacity before and after exercise intervention. Among the three studies that reported these parameters, one study (Sims et al., 2006) assessed physical activity through a scale, another one (Blumenthal et al., 2007) evaluated both aerobic capacity and physical fitness, and the other study (Perraton et al., 2010) assessed only aerobic capacity.

Out of a total of thirteen studies, we will only analyze the studies (Sims et al., 2006; Legrand and Heuze, 2007; Chu et al., 2009; Dunn et al., 2005) that included placebo exercise conditions (i.e. low frequency group, stretching, flexibility, exercise advice) as a control group, and compare it to the exercise intervention. The studies that included placebo exercise conditions, as a complementary therapy, did not fit our inclusion criteria.

Thus, one study (Dunn et al., 2005) used flexibility as a placebo, another one (Sims et al., 2006) exercise advice, one (Legrand and Heuze, 2007) low-frequency exercise, and the last one (Chu et al., 2009) performed stretching plus flexibility (table 2).

Table 1 – Characteristics, results, and methodological quality of the studies meeting inclusion criteria for systematic review.

	Participants					Intervention – Exercise				Depressive Symptoms
Study	Pedro Scale	N	Sample	Mean Age	Baseline Depression	Intervention Type	Duration (wk)	Adherence (%)	Patients' fitness levels + aerobic capacity (Between-group differences)	Clinical Response (CR%) or Remission (R%)*
Dunn et al. (2005)	8	80 75% female	Diagnosed by DSM-IV	35.9	HRSD-17= 19.4 ± 2.3	<u>Aerobic-exercise groups:</u> LD/5: Treadmill or stationary bicycle; Individual supervised exercise, 7.0 kcal/kg/wk, 5 sessions/wk (n =18) LD/3: Treadmill or stationary bicycle; individual supervised exercise, 7.0 kcal/kg/wk, 3 sessions/wk (n =16) PHD/3: Treadmill or stationary bicycle; individual supervised exercise, 17.5 kcal/kg/wk, 3 sessions/wk (n =17) PHD/5: Treadmill or stationary bicycle; individual supervised exercise; 17.5 kcal/kg/wk, 5 sessions/wk (n =16) <u>Exercise placebo control group:</u> Flexibility exercise; 3 sessions/wk (n =13)	12	72 42	Not reported	6 (CR) 11(R) 38 (CR) 25 (R) 41 (CR) 41 (R) 44 (CR) 31 (R) 23 (CR) 15 (R)

Sims et al. (2006)	8	32 66% female	Geriatric Depression Scale	74.3	GDS-30=12.4±3.5	Strength–exercise group: Moderate-intensity; progressive resistance training (80% 1 RM); 30 min x 3 sessions/wk (n= 14) Control group: Exercise advice and information about local exercise options (n=18)	10	58	Physical activity scale for the elderly (PASE)	Not reported
Blumenthal et al. (2007)	8	202 23% female	Diagnosed by DSM-IV	52.0	HRSD-17=16.8±4.2	Supervised-exercise: Treadmill walking; 70%-85% of HRR (45 min x 3 sessions/wk) (n =51) Home-based exercise: Treadmill walking; 70%-85% of HRR (45 min x 3 sessions/wk) (n =53) Medication: (n =49) Placebo: Placebo pills provided daily (n =49)	16	83 94	Aerobic capacity Oxygen consumption The exercise groups showed ⇑ levels in VO_2 peak compared with placebo and medication **(p<0.0001)**	Fitness The exercise groups showed ⇑ levels in treadmill compared with placebo and medication **(p<0.0001)**	45 (R) 40 (R) 47 (R) 31 (R)
Legrand and Neff (2007)	6	23 70% female	Beck Depression Inventory	34.5	BDI=20.7±5.08	High frequency exercise: Treadmill, a stationary bicycle, or a rowing ergometer; 60%-80% of HRmax (30 min x 3-5 sessions/ wk) (n = 8) High frequency exercise + group-based intervention: Treadmill, a stationary bicycle, or a rowing ergometer; 60%-80% of HRmax (30 min x 3-5 sessions/ wk) (n = 8) Low-frequency: Brisk walking, running, cycling on a stationary bicycle; 60%-80% of HRmax (30 min x 1 session/wk) (n=7)	8	Not reported	Not reported		62.5 (RC) 75 (R) 62.5 (RC) 87.5 (R) 0 (RC) 14.3 (R)

Chu et al. (2009)	7	54 100% female	Beck Depression Inventory	26.4	BDI=22.5±5.2	<u>High-intensity:</u> Treadmill; 30–40 min; 4-5 sessions/wk; 65%-75% VO_2R (n =18) <u>Low-intensity:</u> Treadmill; 30–40 min; 4-5 sessions/wk; 40%-55% VO_2R (n =18) <u>Stretching:</u> 30 min yoga–based stretching exercise (n =18)	10	97 99 99	Not reported	Not reported
Callaghan et al. (2011)	8	38 100% female	Beck Depression Inventory	53.7	BDI=28.5±11.4	<u>Preferred intensity:</u> Treadmill; 3 sessions/wk Training at RPE-9.8, (n =19) <u>Prescribed intensity:</u> Treadmill;3 sessions/wk Training at RPE-12.2 (n=19)	4	66 50	Not reported	Not reported
Mota-Pereira et al. (2011)	7	29 70% female	Diagnosed by DSM-IV	47.0	BDI=21.3±2.0 HAMD-17=16.2±1.6	<u>Aerobic exercise + Pharmacotherapy:</u> Walking Home-based exercise; 30-45 min/day walks, 5 sessions/wk, (n =19) <u>Control group:</u> Pharmacotherapy (n=10)	12	91	Not reported	21 (CR) 26 (R) 0 (CR) 0 (R)
Schuch et al. (2011)	7	26 Not reported	Diagnosed by DSM-IV	42.3	HRSD-17=26.7±3.7	<u>Aerobic exercise + Pharmacotherapy</u>: Individual supervised exercise; stationary bicycle, a treadmill, or an elliptic; 16 kcal/kg/week in 3 sessions/wk (n=15) <u>Control group:</u> Pharmacological therapy and/or electroconvulsive therapy (n=11)	At time of discharge from hospital	100	Not reported	Not reported

Trivedi et al. (2011)	8	122 82% female	Diagnosed by DSM-IV	47.0	HRSD-17=18.0±3.8	16 kkw Exercise group + Pharmacotherapy: Individual supervised exercise + home-based sessions; treadmill, cycle ergometer or both, 16 kcal/kg/wk, 150 min (30min x 5 sessions /wk) to 210 min (30minx 7 sessions/wk) (n=64) 4.0 kkw Exercise group + Pharmacotherapy: Individual supervised exercise + home-based sessions; treadmill, cycle ergometer or both; 4.0 kcal/kg/wk, 75min/wk (n=62)	12	82	Not reported	28.3 (R) 15.5 (R)
Chalder et al. (2012)	7	361 34% female	Diagnosed by ICD-10	39.9	BDI= 32.1±9.3	Intervention group: Exercise coaching face to face and by telephone (n=182) Usual care group: Treatment usually available in primary care, including the use of antidepressants (n=179)	16	71	Not reported	Not reported
Schuch et al. (2015)	8	50 72% female	Diagnosed by DSM-IV	40.3	HAM-D=25 (severe)	Exercise + treatment as usual: 16.5 kcal/kg of weight/week, 3 sessions/wk, supervised stationary bike/treadmill/ "transport" machine (n=25) Control group: Usual care (n=25)	During hospitalization (about 3 wks)	90.7	Not reported	48 (R) 32 (R)

Legrand and Neff (2016)	7	35 72% female	Diagnosed by DSM-IV	49.1	BDI-II=29	<u>Drug therapy + Aerobic exercise:</u> 30 min Supervised brisk walking or jogging/outdoor 65–75% of HR max (n=14) <u>Drug therapy + Stretching:</u> 30 min Supervised stretching exercises/indoor (n=11) <u>Control-group:</u> Pharmacotherapy (n=10)	10 days	7	Not reported	57.1 (CR) 9.1 (CR) 10.0 (CR)
Siqueira et al. (2016)	9	57 72% female	Diagnosed by DSM-IV	38.8	HAM-D=15 (moderate to severe)	<u>Aerobic exercise + Pharmacotherapy (SSRI):</u> 20–60 min of continuous or intermittent aerobic exercise and exercise intensity being set at 60–90% of HRmax or 50–85% of VO_2Max (n=29); 4 sessions/wk <u>Control-group:</u> Pharmacotherapy (SSRI) (n=28)	4	<u>Aerobic capacity</u> <u>Oxygenation</u> Exercise groups showed ⇑ levels in O_2 pulse⇑ compared with control group **(p=0.05)**		?

Legend: BDI, Beck Depression Inventory; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; CR-Clinical Response, reduction of baseline score by 50% or more; R-Remission, defined as a HAM-D score < 8; HAMD17 score ≤7; BDI-II score of ≤13; Fourth Edition; GDS-15, 15-item Geriatric Depression Scale; GDS-30, 30-item Geriatric Depression Scale; HRR, Heart rate reserve; HAM-D or HRSD-17, 17-item Hamilton Rating Scale for Depression; ICD-10, International Statistical Classification of Diseases and Related Health Problems, tenth revision; LD, Low dose; HRmax, Maximum heart rate; O_2pulse; oxygen pulse; PASE, Physical Activity Scale for the Elderly; PHD, Public health dose; PS, PEDro scale; RM, Repetition maximum; RPE, Rate of perceived exertion scale; SSRI, Selective serotonin reuptake inhibitor; VO_2Max, Maximal oxygen uptake; VO_2R, Oxygen uptake reserve; VO_2-VT2,VO_2 at the second ventilatory threshold; ?, not reported.

Table 2 – Description of placebo interventions.

Study	Intervention Category	Intervention description	Described as 'Placebo group' by author
Dunn et al. (2005)	Flexibility	The exercise placebo control group was defined as 3 days/week of stretching flexibility exercise for 15 to 20 minutes per session.	Yes
Sims et al. (2006)	Advice	Exercise advice and information about local exercise options	No
Legrand and Neff (2007)	Low-frequency	Low-frequency exercise was defined as an exercise regime of one weekly session.	No
Chu et al. (2009)	Stretching	Stretching control group performed 30 min of supervised stretching and flexibility exercise	Yes

4. Discussion

There is a preference and a growing evidence for using aerobic exercise in treating depression, which is in accordance with previous and recent systematic reviews (Perraton et al., 2010; Stanton and Reabum, 2013; Nystrom et al., 2015).

In relation to the targeted intensity, there are some methodological limitations. Studies incompletely reported the intensity and have not detailed how intensity progressed during intervention. Thus, not planning progression could result in small and/or non-significant improvements in the outcomes, especially during a longer intervention (Wintesr-Stone et al., 2014). On the other hand, the three studies that used Borg´s scale of subjective perception of effort have not specified the intensity levels ranging from 6 (very, very light) to 20 (very, very hard) (Borg, 1974).

Despite the diversity of instruments to assess the prescribed intensity (and all of them could be considered valid to evaluate the effects of exercise intervention), it is yet premature to provide recommendations in relation to the intensity, which was also corroborated by one previous systematic review (Stanton and Reabum, 2013). Furthermore, the RCT that used self-selected intensity suggested that the possibility of self-selecting effort intensity is a variable that positively influences exercise in women with depressive disorders. One review (Stanton and Reabum, 2013) already published corroborated the previous study, and argued that an intervention using self-selected intensity appears to be effective in the treatment of depression. Moreover, Parfitt, et al. (2012) reported that prescribing intensities, which are less pleasant and/or imposed, can sometimes disregard motivational aspects. However, in spite of self-selected preferred intensity being a potential factor of argumentation, which according to the authors contributes to participants´ adherence to the exercise intervention, in the study by Callaghan et al. (2011) the preferred intensity group only showed 66% of adherence. As well, when we observed data from studies where preferred intensity was not prescribed but showed significant reduction in depressive symptomatology, three studies (Mota-Pereira et al., 2011; Trivedi et al., 2011; Blumenthal et al., 2007) presented high rates of adherence (80%-100%). To our understanding, the adhesion rate is an important factor; however, it could be achieved not by selecting the most convenient intensity, but by outlining other strategies of intervention (e.g. knowledge of subjects‘ daily and leisure activities, and preferences about the context).

Nonetheless, it should be noted that prescribed exercise is a dependent dose and should guarantee a sufficient stimulus to produce relevant benefits to health. According to the overload principle of training, exercise below a minimum intensity or threshold will not induce the body sufficiently to result in increased VO_2max and improvements in other

physiological parameters (Garber et al., 2011). Considering these, the initial stage of an exercise program, choosing self-selected comfortable exercise intensity seems to be the option for patients to induce intrinsic exercise motivation and adherence. Corroborating this, a recent research (Vancampfort et al., 2015) has established that it is important to develop future studies that promote feelings of autonomous motivation in subjects with severe mental illness (e.g. MDD), as they are associated with the adoption and maintenance of health promoting behaviors. However, we sustain that it seems clear that the principles of training should be applied to the exercise programs. Exercise intensity should be pleasurable, but it should also be gradually increased to guarantee a minimal level required to induce a training effect (principle of progression) (Winters-Stone et al., 2015).

In relation to session duration, six studies argued that a session duration ranging between 30-45 minutes is effective in reducing depressive symptoms. This is similar to previous 3 systematic reviews, which referred 30 minutes (Perraton et al., 2010), lasting 30-40 (Stanton and Reabum, 2013) minutes or at least 30 minutes (Nystrom et al., 2015).

Regarding the duration of exercise interventions, the majority of the studies reported positive outcomes to treatment with a duration of at least 9 weeks. This is a similar recommendation from past reviews, which have considered at least 8 (Perraton et al., 2010) or 9 weeks (Stanton and Reabum, 2013).

With reference to physical fitness and aerobic capacity, the studies presented in Table 1 show that there is a lack of studies that have evaluated and compared the changes in these parameters. Therefore, if subjects engage in less exercise throughout the intervention than prior to it, they may experience no fitness improvements. An intervention to improve fitness must be greater than the subject has already been engaging (appropriate application of the principle of overload) (Winters-Stone et al., 2014). On the other hand, it is important to understand, whether improvement in depressive symptoms is related with the improvement in physical fitness and aerobic capacity, as an effective indicator of exercise intervention.

One study (Sims et al., 2006) assessed physical activity levels via questionnaire, which is quite subjective due to its dependency on subjects‘ self-report.

One study (Chu et al., 2009) analyzed only the differences within groups and reported that after 10 weeks of exercise, subjects in high intensity group displayed a significant 7% increase in maximal VO_2 and there was no change in maximal VO_2 for stretching group. However, authors found that there has been no significant association between changes in aerobic capacity and changes in depressive symptoms ($p=0.491$).

These findings are corroborated by an other study, Siqueira et al. (2016), which showed that the changes in depressive symptoms were not correlated with those of aerobic capacity (VO_2max).

The strength of exercise intervention must be assessed relatively to the control groups (Stothart et al., 2014). Yet, there are studies that include an active control group that performs some form of physical activity, which at times is designed as a placebo group.

Based on the available evidence in the study by Dunn et al. (2005), three days per week of stretching and flexibility exercises for 15 to 20 minutes per session were sufficient to reduce symptoms of depression (remission=15%). In addition, another research (Chu et al., 2009) introduced a yoga-based stretching exercise in a placebo group, and this group showed a significant reduction in the depressive symptomatology.

This is not surprising, as a meta-analysis concluded that yoga was an effective adjunct treatment of major psychiatric disorders, particularly depression and anxiety (Cabral et al., 2011).

Clinical trials that used exercise as a placebo group must be carefully analyzed due to the fact that, many times the results do not show reduced depressive symptoms when both groups are compared. However, most often there are improvements when the differences between baseline and post intervention in each group are assessed. When an exercise group is compared to an active placebo group instead of a passive placebo group, the differences between the efficacy of exercise and active placebos are much less pronounced. It is expected that doing something is likely to induce greater expectations for improvements than doing nothing (Stothart et al., 2014). Accordingly, one meta-analysis (Josefsson et al., 2014) assessed the efficacy of exercise when comparing it with no treatment, placebo conditions, or usual care among clinically depressed patients. The main result showed a significant effect in favor of exercise intervention programs, and the effect size was even larger when it included trials that had used no treatment or placebo conditions. Moreover, the fact that participants in the control group exercised under the supervision of an experienced professional and within a group (Krogh et al., 2012) is reason enough to reduce depressive symptoms.

This review included studies between 2003-2016, and subjects who were not recruited through clinical settings, may limit the generalizability of our findings.

Furthermore, although the PEDro scale is a tool used to examine the methodological quality of RCTs, according to the principles for assessing risk of bias defined by Cochrane (Higgins et al., 2011), quality scales and resulting scores are not an appropriate way to value clinical trials. This is due to the fact that there is a proneness to combine assessments of quality reporting aspects, with aspects of trial conduct, and put some weight on different items in ways that makes it difficult to justify.

Conclusions

Due to the heterogeneity of the studies it is premature to define the ideal dose-response. Defining the minimum dosage instead of the consistent dose-response is more assertive. Thus, aerobic exercise, with duration of at least 9 weeks, and a minimum frequency of three times per week, between 30-45 minutes/session is recommended. A suitable intensity is missing as well as studies comparing different doses of exercise. Furthermore, it is fundamental to define and follow a consistent line aiming to simplify and make reliable the comparison between the studies. There are studies that have not reported remission or clinical response; others have described the differences between groups, and others within groups. Additionally, there is a lack of studies that assess and compare patients´ fitness levels and aerobic changes. Moreover, placebo exercise groups, which show benefits and clinical response or remission rates, should be carefully analyzed. Although in the last years there has been a consistent growth in this scope, it remains premature to define a steady and an optimum dose-response. Therefore, measures should be taken to overcome these shortcomings in order to improve methodological quality.

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References

1. Blumenthal, J.A., Babyak, M.A., Doraiswamy, P.M., Watkins, L., Hoffman, B.M., Barbour, K.A., Herman, S., Craighead, W.E., Brosse, A.L., Waugh, R., Hinderliter, A., Sherwood, A., 2007. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom. Med. 69, 587-596.

2. Borg, G.A., 1974. Perceived exertion. Exerc. Sport Sci. Rev. 2,131-153.

3. Cabral, P., Meyer, H.B., Ames, D., 2011. Effectiveness of yoga therapy as a complementary treatment for major psychiatric disorders: A meta-analysis. Prim. Care. Companion CNS Disord. 13, PCC.10r01068.

4. Callaghan, P., Khalil, E., Morres, I., Carter, T., 2011. Pragmatic randomised controlled trial of preferred intensity exercise in women living with depression. BMC Public Health 11, 465.

5. Carneiro, L.S., Fonseca, A.M., Vieira-Coelho, M.A., Mota, M.P., Vasconcelos-Raposo, J., 2015. Effects of structured exercise and pharmacotherapy vs. pharmacotherapy for adults with depressive symptoms: A randomized clinical trial. J. Psychiatr. Res. 71, 48-55.

6. Chalder, M., Wiles, N.J., Campbell, J., Hollinghurst, S.P., Searle, A., Haase, A.M., Taylor, A.H., Fox, K.R., Baxter, H., Davis, M., Thorp, H., Winder, R., Wright, C., Calnan, M., Lawlor, D.A., Peters, T.J., Sharp, D.J., Turner, K.M., Montgomery, A.A., Lewis, G., 2012. Facilitated physical activity as a treatment for depressed adults: Randomised controlled trial. BMJ 344, e2758.

7. Chu, I.H., Buckworth, J., Kirby, T.E., Emery, C.F., 2009. Effect of exercise intensity on depressive symptoms in women. Ment. Health Phys. Act. 2, 37-43.

8. Cooney, G.M., Dwan, K., Greig, C.A., Lawlor, D.A., Rimer, J., Waugh, F.R., McMurdo, M., Mead, G.E., 2013. Exercise for depression. Cochrane Database Syst. Rev. 9, CD004366.

9. Davidson, J.R., 2010. Major depressive disorder treatment guidelines in America and Europe. J. Clin. Psychiatry 71 Suppl E1, e04.

10. Dunn, A.L., Trivedi, M.H., Kampert, J.B., Clark, C.G., Chambliss, H.O., 2005. Exercise treatment for depression: Efficacy and dose response. Am. J. Prev. Med. 28,1-8.

11. Fornaro, M., Giosue, P., 2010. Current nosology of treatment resistant depression: A controversy resistant to revision. Clin. Pract. Epidemiol. Ment. Health 6, 20-24.

12. Garber, C.E., Blissmer, B., Deschenes, M.R., Franklin, B.A., Lamonte, M.J., Lee, I.M., Nieman, D.C., Swain, D.P., 2011. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. Med. Sci. Sports Exerc. 43,1334-1359.

13. Higgins, J.P., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A., et al., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928.

14. Josefsson, T., Lindwall, M., Archer, T., 2014. Physical exercise intervention in depressive disorders: Meta-analysis and systematic review. Scand. J. Med. Sci. Sports 4, 259-272.

15. Kessler, R.C., Bromet, E.J., 2013. The epidemiology of depression across cultures. Annu. Rev. Public Health 34,119-138.

16. Krogh, J., Nordentoft, M., Sterne, J.A., Lawlor, D.A., 2011. The effect of exercise in clinically depressed adults: Systematic review and meta-analysis of randomized controlled trials. J. Clin. Psychiatry 72, 529-538.

17. Knapen, J., Vancampfort, D., Morien, Y., Marchal, Y., 2014. Exercise therapy improves both mental and physical health in patients with major depression. Disabil. Rehabil. 37, 1490–1495.

18. Krogh, J., Videbech, P., Thomsen, C., Gluud, C., Nordentoft, M., 2012. DEMO-II trial. Aerobic exercise versus stretching exercise in patients with major depression-A randomised clinical trial. PLoS ONE 7, e48316.

19. Legrand, F., Heuze, J.P., 2007. Antidepressant effects associated with different exercise conditions in participants with depression: A pilot study. J. Sport. Exerc. Psychol. 29, 348-364.

20. Legrand, F.D., Neff, E.M., 2016. Efficacy of exercise as an adjunct treatment for clinically depressed inpatients during the initial stages of antidepressant pharmacotherapy: An open randomized controlled trial. J. Affect. Disord. 191,139-144.

21. Lepine, J.P., Briley, M., 2011. The increasing burden of depression. Neuropsychiatr. Dis. Treat. 7, 3-7.

22. Mota-Pereira, J., Silverio, J., Carvalho, S., Ribeiro, J.C., Fonte, D., Ramos, J., 2011. Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. J. Psychiatr. Res. 45, 1005-1011.

23. Mura, G., Moro, M.F., Patten, S.B., Carta, M.G., 2014. Exercise as an add-on strategy for the treatment of major depressive disorder: A systematic review. CNS Spectr. 19, 496-508.

24. Nystrom, M.B., Neely, G., Hassmen, P., Carlbring, P., 2015. Treating major depression with physical activity: A systematic overview with recommendations. Cogn. Behav. Ther. 44, 341-352.

25. Parfitt, G., Alrumh, A., Rowlands, A.V., 2012. Affect-regulated exercise intensity: Does training at an intensity that feels 'good' improve physical health? J. Sci. Med. Sport. 15, 548-553.

26. Perraton, L.G., Kumar, S., Machotka, Z., 2010. Exercise parameters in the treatment of clinical depression: A systematic review of randomized controlled trials. J. Eval. Clin. Pract. 16, 597-604.

27. Ranjbar, E., Memari, A.H., Hafizi, S., Shayestehfar, M., Mirfazeli, F.S. Eshghi, M.A., 2015. Depression and exercise: A clinical review and management guideline. Asian J. Sports Med. 6, e24055.

28. Rethorst, C.D., Sunderajan, P., Greer, T.L., Grannemann, B.D., Nakonezny, P.A., Carmody, T.J., Trivedi, M.H., 2013. Does exercise improve self-reported sleep quality in non-remitted major depressive disorder? Psychol. Med. 43, 699-709.

29. Rimer, J., Dwan, K., Lawlor, D.A., Greig, C.A., McMurdo, M., Morley, W., Mead, G.E., 2012. Exercise for depression. Cochrane Database Syst. Rev. 7, CD004366.

30. Schuch, F.B., Vasconcelos-Moreno, M.P., Borowsky, C., Zimmermann, A.B., Rocha, N.S., Fleck, M.P., 2015. Exercise and severe major depression: Effect on symptom severity and quality of life at discharge in an inpatient cohort. J. Psychiatr. Res. 61, 25-32.

31. Searle, A., Calnan, M., Lewis, G., Campbell, J., Taylor, A., Turner, K., 2011. Patients' views of physical activity as treatment for depression: A qualitative study. Br. J. Gen. Pract. 61, 149-156.

32. Schuch, F.B., Vasconcelos-Moreno, M.P., Borowsky, C., Fleck, M.P., 2011. Exercise and severe depression: Preliminary results of an add-on study. J. Affect. Disord. 133, 615-618.

33. Sherrington, C., Herbert, R.D., Maher, C.G., Moseley, A. M., 2000. PEDro. A database of randomized trials and systematic reviews in physiotherapy. Man. Ther. 5, 223-226

34. Sims, J., Hill, K., Davidson, S., Gunn, J., Huang, N., 2006. Exploring the feasibility of a community-based strength training program for older people with depressive symptoms and its impact on depressive symptoms. BMC Geriatr. 30, 18.

35. Siqueira, C.C., Valiengo, L.L., Carvalho, A.F., Santos-Silva, P.R., Missio, G., de Sousa, R.T., Di Natale, G., Gattaz, W.F., Moreno, R.A., Machado-Vieira, R., 2016. Antidepressant Efficacy of adjunctive aerobic activity and associated biomarkers in major depression: A 4-week, randomized, single-blind, controlled clinical trial. PLoS ONE 11, e0154195.

36. Stanton, R., Reaburn, P., 2013. Exercise and the treatment of depression: A review of the exercise program variables. J. Sci. Med. Sport. 17,177-182.

37. Stothart, C.R., Simons, D.J., Boot, W.R., Kramer, A.F., 2014. Is the effect of aerobic exercise on cognition a placebo effect? PLoS ONE 9, e109557.

38. Stubbs, B., Rosenbaum, S., Vancampfort, D., Ward, P.B., Schuch, F.B., 2016. Exercise improves cardiorespiratory fitness in people with depression: A meta-analysis of randomized control trials. J. Affect. Disord. 190, 249-253.

39. Stubbs, B., Vancampfort, D., De Hert, M., Mitchell, A.J., 2015. The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: A systematic review and comparative meta-analysis. Acta Psychiatr. Scand. 132, 144-157.

40. Taylor, J., 2015. Depression associated with five-fold increased mortality risk in heart failure patients. Eur. Heart J. 36, 1946.

41. Trivedi, M.H., 2009. Treating depression to full remission. J. Clin. Psychiatry 70, e01.

42. Trivedi, M.H., Greer, T.L., Church, T.S., Carmody, T.J., Grannemann, B.D., Galper, D.I., Dunn, A., Earnest, C.P., Sunderajan, P., Henley, S.S., Blair, S.N., 2011. Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. J. Clin. Psychiatry 72, 677-684.

43. Vancampfort, D., Stubbs, B., Venigalla, S.K., Probst, M., 2015. Adopting and maintaining physical activity behaviours in people with severe mental illness: The importance of autonomous motivation. Prev. Med. 81, 216-220.

44. Winters-Stone, K.M., Neil, S.E., Campbell, K.L., 2014. Attention to principles of exercise training: A review of exercise studies for survivors of cancers other than breast. Br. J. Sports Med. 48, 987-995.

STUDY 2

Effects of structured exercise and pharmacotherapy vs. pharmacotherapy for adults with depressive symptoms: A randomized clinical trial

Effects of structured exercise and pharmacotherapy vs. pharmacotherapy for adults with depressive symptoms: A randomized clinical trial

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Abstract

Objective: Physical exercise has been consistently documented as a complementary therapy in the treatment of depressive disorders. However, despite a higher prevalence among women compared to men, the trials developed in women are scarce. In addition, the optimal dosage of exercise capable of producing benefits that reduce depressive symptoms remains unclear. This clinical trial is designed to measure the effect of a structured physical exercise program as a complement to antidepressant medication in the treatment of women with depression.

Methods: From July 2013 to May 2014, we implemented a randomized controlled trial (**HAPPY BRAIN** study). A total of 26 women (aged 50.16 ±12.08) diagnosed with clinical depression were randomized either to a supervised aerobic exercise group (45-50 minutes/week three times a week for four months) plus pharmacotherapy (intervention group), or only antidepressant medication (control group).

Results: The exercise group presented a decrease in BDI-II and DASS-21 total score scales. Relatively to DASS-21, it showed a significant decrease in anxiety and stress. The exercise group when compared to a control group showed improvement in relation to physical functioning parameters between baseline and post-intervention. Moreover, anthropometric parameters presented only significant differences between groups in fat mass percentage. Nonetheless, no differences were found between groups in weight, body mass index, waist circumference, and self-esteem.

Conclusion: Our results showed that supervised structured aerobic exercise training could be an effective adjuvant therapy for treating women with depression, reducing depressive symptomatology and improving physical fitness. A key factor of this improvement included strict control of exercise workload parameters and adjustment to each subject's capacity.
In our study, due to the sample size there is an increase in the probability of type II errors.

Keywords: Major depressive disorder, Depression, Women, Aerobic exercise.

1. Introduction

Depression affects over 120 million people worldwide (Lepine and Briley, 2011) and is much more common among women than men, with female/male risk ratios roughly 2:1 (Kessler, 2003). Indeed, the increasing burden of depression makes it essential to search for an extended understanding of causes and for development of complementary effective treatments. The American Psychiatric Association has supported the inclusion of physical exercise (PE) treatment in patients with major depressive disorder (MDD) (American Psychiatric Association, 2010), and according to their practice guidelines, new research should include evaluation of benefits of PE in reducing side effects of other therapies and in improving health. Despite the current gold standard for the treatment for MDD including antidepressant medication and psychotherapy, data indicate that only 55% of individuals seek treatment (Lepine and Briley, 2011). Thus, PE has been proposed as a rehabilitation strategy and a complementary treatment to reduce symptoms of depression. Indeed, evidence from other studies including systematic reviews and meta-analysis of the literature (Knapen et al., 2014; Rethorst et al., 2009; Silveira et al., 2013), supports the efficacy of exercise in the treatment of depression. Therefore, several biological and psychological hypotheses have been posited to explain the mechanisms that mediate the impact of exercise on depression. For instance, PE has shown to have anti-inflammatory effects in non depressed subjects (Gleeson et al., 2011), and thus, in the long term, regular aerobic exercise leads to lower levels of several circulating pro-inflammatory biomarkers, including Interleukin-6 (IL-6) and C-reactive protein (CRP) (Kohut et al., 2006), which are increased in depressed patients (Dowlati et al., 2010). Furthermore, PE induces the release of proteins such as brain-derived neurotrophic factor (BDNF) (Heyman et al., 2012), which is a neurotrophin responsible for the stimulation and control of neurogenesis, and altering the hypothalamic-pituitary axis function through decreasing long-term basal levels of cortisol (Sousa e Silva et al., 2010). Additionally, PE increases self-esteem (Callaghan et al., 2011), reduces tendency to ruminate (Craft, 2005), and restores psychosocial function (Mota-Pereira et al., 2011).

Thus, PE remains an area of active investigation and raises questions regarding dose-response and the best type of exercise for various depressed patients. However, researches investigating this association in women are limited, with most focusing on postnatal depressed women (Teychenne and York, 2013) and others emphasizing observational studies that examined walking, yoga or recreational physical activity (Shahidi et al., 2011). In most of the studies women were not recruited by psychiatrists but by physicians, advertisements placed in local newspapers, posted fliers and university communities

(Callaghan et al., 2011; Chu et al., 2009). Regarding the limitations and importance incidences of depression in women, the aim was to evaluate the efficacy of four months of aerobic exercise intervention in a group of women referred by psychiatrists.

2. Methods

Recruitment for the trial took place from July to December 2013. A total of 26 women (aged 50.16±12.08) were randomized. This research protocol was performed according to the Declaration of Helsinki, and was approved by the Ethics Committee of Centro Hospitalar de São João (March 11, 2013) with ethics reference number 112/13.

2.1 Inclusion criteria

The inclusion criteria consisted of (1) women aged 18-65; (2) who were able and willing to provide informed consent and accept randomized group assignment; (3) with current diagnosis of ICD-10 (International Classification of Diseases, 10th revision): F32.1 (depressive episode moderate), F33.1 (recurrent depressive disorder, moderate current episode), F34.1 (dysthymia) and confirmed by a psychiatrist; (4) physical fitness to endure exercise confirmed in writing by general practitioners; (5) normal ECG; and (6) sedentary (engaged in sports activity for less than one hour per week).

2.2 Exclusion criteria

The exclusion criteria consisted of (1) psychiatric co-morbidities; (2) current participation in other clinical trials; (3) medical background indicating significant medical constraints; (4) current active alcohol/drug abuse or dependence; (5) pregnant or planning a pregnancy in the following year; (6) taking beta-blocking medications; (7) change of pharmacological therapy during PE program; (8) alteration of drug therapy in the past six weeks; (9) exhibiting significant exacerbation of symptoms; (10) minimal overall attendance of 60% of sessions; (11) undergoing complementary therapies (such as psychotherapy).

2.3 Trial design

This trial was randomized and two-armed. Due to the nature of the intervention none of the participants, physical training teacher, general practitioners, psychiatrists or researchers performing the outcome assessments were blinded in relation to treatment allocation.

If patients were considered eligible for inclusion and accepted participation in the study, they were referred for randomization. These were randomized following a 1:2 scheme to one

of two groups: control (N=10) and aerobic exercise (N=9). Randomization was implemented with sequentially numbered opaque, sealed envelopes.

3. Intervention

3.1 Exercise group

Nine individuals were assigned to moderately intense exercise in addition to their usual pharmacology therapy. Exercise consisted of 45-50 minutes per session, three times a week, for a total of 16 weeks (36 sessions). Sessions took place at the Faculty of Sport at the University of Porto, Portugal, between January and April 2013, in the presence of a physical training teacher. The intensity for each patient was based on the baseline fitness (physical fitness tests). All patients in the aerobic group wore a heart-rate monitor (Polar FT1, Finland) during every session to ensure they exercised in prescribed pulse intervals. Moreover, downloading was done after each session, which allowed for precise data from participants, and, consequently, they were informed of their goal achievement. Each individual began PE sessions at individually prescribed exercise intensity. A rate of perceived exertion was used (Borg scale) to have a measure of the subjective intensity of exercise. Participants maintained a diary of frequency and intensity of all sessions. Regarding guidelines for prescribing PE, the National Institute for Health and Clinical Excellence (NICE) (2009) suggests three sessions/week of 45-60 minutes. The frequency and duration sessions of the program fulfilled the NICE requirements. Regarding intensity, the average number for four months was 65%, 73%, 74% and 76% HRmax respectively (RPE=12-13).

The aerobic exercise program was designed to (1) improve physical fitness; (2) distract attention from worries and ruminations; (3) provide social support and reduce loneliness; (4) increase sense of control and self-esteem; (5) enhance a sense of achievement/mastery; and (6) promote behavioral change by acquiring a healthy lifestyle.

The program started with ten minutes of a general low-intensity warm-up. This was followed by 30 minutes of aerobics and a 5-minute low-intensity cool down period. The aerobic exercise included traditional games, indoor/outdoor natural circuit workouts with resistance bands, jump ropes, fitness balls, brisk walking, and dancing. These were all done at an intensity that would maintain the participant's heart rate in the assigned training target load. The general aim of a cool down period was to decrease post-exercise stress level; therefore, we included flexibility exercises. Aiming to maintain cohesion in the group, at least once per week the session ended with group choreography.

The objectives throughout the course of the PE intervention were for patients, during the first month, to work at intensity levels that corresponded to at least 65% of their percent

of the maximum HR (%HRmax), to increase to 70% in the second month and 80% in the third month. The exercise program was designed to optimize patients' adherence, and several strategies were included, as there is not only one effective strategy for all individuals. Therefore, motivational strategies were implemented. These included (1) multidisciplinary teams; (2) creation of a Facebook page **HAPPY BRAIN** to maintain an online interactive system that provided support/cohesion among exercise program patients; (3) adherence feedback from **HAPPY BRAIN** - Facebook and physical training teacher; (4) PE done in group as an effective way to enhance psychosocial behavior and social interaction; (5) multiple activity regimes, including outings in the sunlight and in pleasant settings (contact with nature); (6) PE adapted to each patient's functional capacity; (7) choice of enjoyable activities; (8) phone calls to patients whenever they missed exercise sessions; (9) wearing group tee shirts with logos chosen by participants; (10) having an experienced exercise leader to supervise; (11) exercising with patients' musical preferences; (12) setting realistic goals (possible goals can increase sense of self-esteem/helpfulness); (13) creating cheer choreography; (14) awarding monthly prizes for assiduity; (15) self-monitoring of daily performance (heart rate, RPE); and (16) encouraging patients to start exercising on their own at least once a week (brisk walking).

3.2 Control group

The control group consisted of ten patients who continued their usual pharmacological therapy but were not assigned to any exercise. Control subjects were instructed to maintain their habitual activities.

All participants were assessed for depressive symptoms, functional assessment and anthropometric parameters at baseline (time 0: before starting PE program), and at 16 weeks. Participants met with a psychiatrist throughout the study to assess symptomatology and medication tolerance. The medication dosage was kept constant in both groups. All patients were medicated with selective serotonin reuptake inhibitor (SSRIs); fluoxetine, escitalopram, sertraline and paroxetine. When convenient, benzodiazepines diazepam, lorazepam and estazolam were used as anxiolytic or hypnotics.

4. Assessment procedures

Patients underwent medical screening by a clinical physician before participating in the study. If a patient was found to have any significant medical condition that contraindicated safe participation, they were excluded.

4.1 Demographic questionnaire

Patients filled in a demographic questionnaire, which evaluated variables including age, marital status, education and occupational status.

4.2 Psychiatric evaluation

Patients were considered eligible if they were referred by a psychiatrist and fulfilled the ICD-10 criteria. Depression was assessed by self-report depressive symptoms, using the Portuguese Version of the Beck Depression Inventory-II (BDI-II), which is a questionnaire with 21 items (Campos and Gonçalves, 2011). Total scores ranged from 0 to 63 points, with a high score reflecting a higher level of depressive symptoms. In addition, the Portuguese version of the Depression Anxiety Stress Scale-21 (DASS-21) measured the severity of core symptoms of depression, anxiety, and stress (Vasconcelos-Raposo et al., 2013).

4.3 Self-esteem

The Portuguese Version of Rosenberg´s Global Self-Esteem Scale was used to measure global self-esteem (Vasconcelos-Raposo et al., 2012). The scale consists of 10 statements relating to feelings of self-worth. Total scores can range from 10 to 50, with a high score indicating a higher level of self-esteem.

4.4 Physical examination

Through the use of eight polar electrodes, the Tanita BC-418 Segmental Body Composition Analyzer showed a complete body composition profile in seconds including weight, body fat percentage, and body mass index (BMI). Moreover, waist circumference was measured at the end of a normal expiration, with a tape placed horizontally directly on the skin and reported as the mean of three measurements.

4.5 Physical functioning

To evaluate physical functioning, a short physical performance battery was used. Participants were assessed based on the distance walked in six minutes, the number of times they could sit and stand from a chair in 30 seconds, and a seated medicine ball throw.

4.6 Compliance

Overall compliance was calculated as the average adherence over the 16 weeks. Adherence was defined when at least 60% of sessions were completed.

4.7 Statistical analysis

All dependent variables were tested for normality according to the Shapiro-Wilks method. For baseline demographic and clinical characteristics of participants and differences between treatment groups in the change from baseline to endpoint (16 weeks), independent sample *t*-tests and multivariate analysis of variance (MANOVA) were used. Tests were considered significant at a $p<0.05$. Statistical analyses were performed using IBM SPSS Statistics 21. Data were also analyzed for practical significance using magnitude-based inferences (Hopkins et al., 2009). The effect size partial eta-squared (η^2p) was computed and reported for MANOVA, which is provided by statistical software packages SPSS. Cohen (1988) provided benchmarks to define small ($\eta^2= 0.01$), medium ($\eta^2= 0.06$), and large ($\eta^2= 0.14$) effects. The effect size Cohen´s d was performed using the software ESCI (Exploratory Software for Confidence Intervals) (Cumming, 2013a) and reported for independent sample *t*-tests. Cohen's d magnitude thresholds for difference in a mean were described using the following scale: 0-0.2 trivial, >0.2-0.6 small, >0.6-1.2 moderate, >1.2-2.0 large, and >2.0 very large (Hopkins, 2010). This qualitative approach refers to recommended practices, including estimation based on effect sizes and confidence intervals (Cumming, 2013b). If 95% confidence intervals overlapped small positive and negative values, the magnitude was deemed to be the observed magnitude (Hopkins et al., 2009).

5. Results

5.1 Study population and baseline values

From July to December 2013, 78 potential individuals were referred to the trial by their psychiatrists during routine external consultations at Psychiatry and Mental Health Clinic, Centro Hospitalar São João, Porto, Portugal. Out of these, 52 were excluded and 26 patients were enrolled and randomized; 13 were allocated to the aerobic exercise group versus 13 to the control group. The main reasons for exclusion were declining participation (N=9), psychiatric comorbidity (N=11) and age over 65 (N=12). Figure 1 presents the flow of participants in the **HAPPY BRAIN** study. Out of the 26 patients enrolled, 7 were excluded before completing the full 16 weeks, 4 from the exercise group (23%). One participant emigrated; one had medical contraindication after the assignment; one was noncompliant with 60% of sessions; one had worsening of symptoms. Three participants were excluded from the control group (31%). One detected lung cancer and two reasons were unknown due to difficulties in contacting patients.

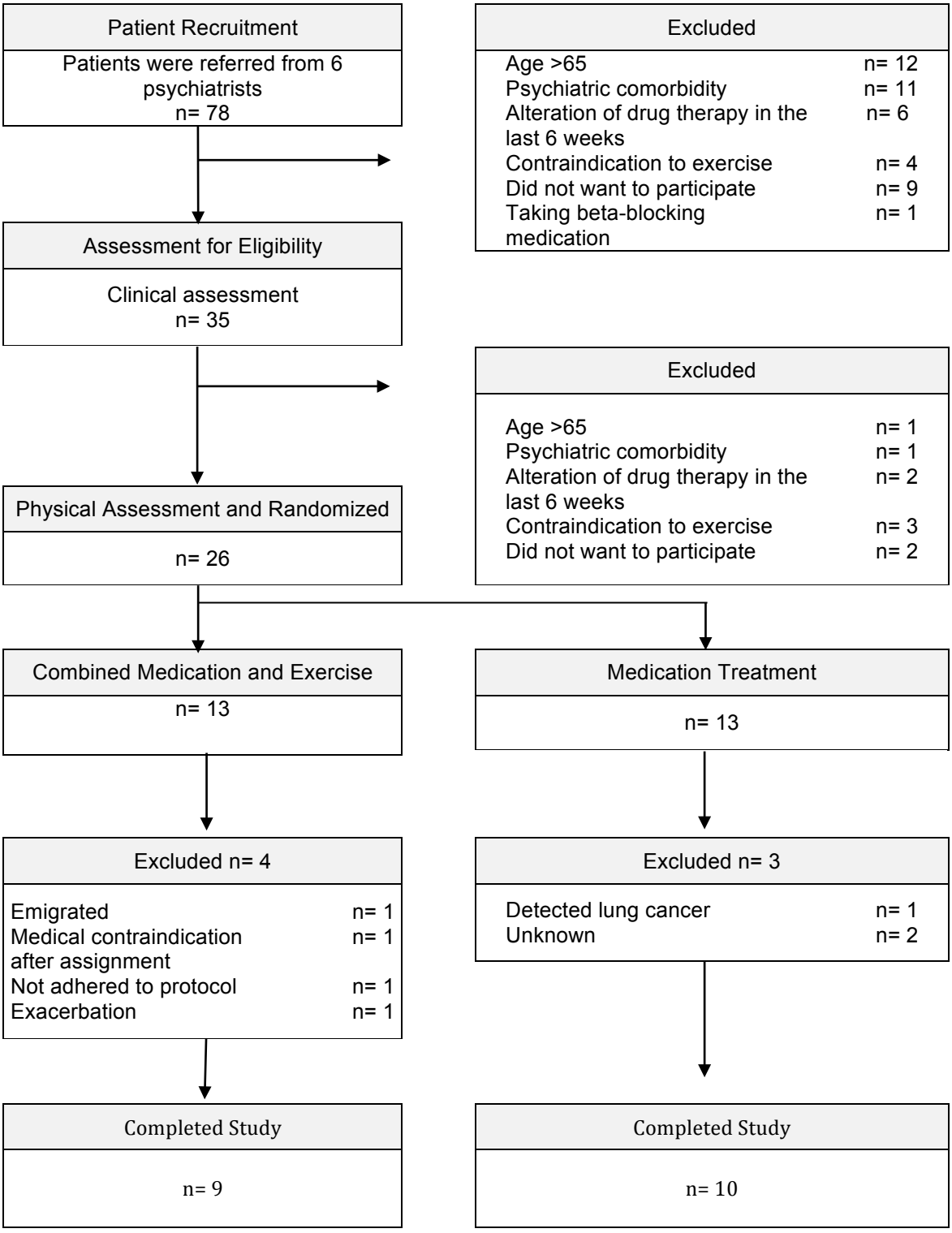

Figure 1 – Flow diagram for the **HAPPY BRAIN** trial.

Most patients were married (47.4%), the majority had elementary schooling, were unemployed and the mean age was 50.2 (SD= 12.1). In relation to weight and fitness, the average weight was 71.6 kg (SD=12.8), with 36.6% (SD=6.4) fat mass and a mean body mass index calculated as kg/m^2 of 29.3 (SD=5.7). Moreover, most patients (73.7%) had a

diagnosis of dysthymia. Fluoxetine was the most commonly used SSRI (66.7%), followed by escitalopram (22.2%). In baseline, the patients included in the exercise group did not differ significantly from individuals in the control group in the variables analyzed (Table 1).

Table 1 – Comparison between intervention and control group at baseline.

	Exercise (N=9)	Control (N=10)	Difference (95% CI)	p value	η^2p
Demographic			**Exercise vs Control**		
Age (years), mean (SD),	52.78±7.66	47.80±15.05	-0.42(-6.63, 16.59)	0.373	
Marital status, n (%)					
Married	3 (33.3)	6 (60)			
Divorced	3 (33.3)	2 (20)			
Single	2 (22.2)	2 (20)			
Widow	1 (11.1)	0 (0)			
Education, n (%)					
Elementary school	7 (77.8)	5 (50)			
Junior high school	1 (11.1)	3 (30)			
Secondary School	0 (0)	1 (10)			
Higher education	1 (11.1)	1 (10)			
Occupational Status, n (%)					
Student	0 (0)	1 (10)			
Employed	2 (22.2)	1 (10)			
Unemployed	5 (55.6)	2 (20)			
Retired	1 (11.1)	4 (40)			
Sick leave	1 (11.1)	2 (20)			
Weight and fitness, mean (SD),					
Weight, kg	74.08±11.58	69.31±13.99	-0.37 (-7.75,17.28)	0.433	
Body mass index, kg/m^2	31.10±5.84	27.72±5.37	-0.60 (-2.04,8.81)	0.205	
Fat mass, %	38.67±4.00	34.60±7.87	-0.65 (-2.35,10.49)	0.192	
Waist circumference, cm	95.67±11.68	92.60±14.24	-0.24 (-9.63,15.76)	0.617	
Functional assessment, mean (SD),					
Walk test, 6 minute	467.33±82.67	398.80±74.33	-0.87 (-743,144.50)	0.074	
Medicine ball throw, seated	2.74±0.30	2.94±0.26	0.71 (-047, 0.07)	0.134	
Chair stand test, 30 second	19.56±3.28	18.00±4.85	-0.38 (-2.50, 5.62)	0.430	
Depression characteristics, n (%)					
Moderate depressive episode	1 (11.1)	0 (0)			
Recurrent depressive disorder	1 (11.1)	3 (30)			
Dysthymia	7 (**77.8**)	7 (70)			
Symptom severity, mean (SD),					
BDI-II	45.56±9.65	46.10±11.52	0.05 (-10.90, 9.81)	0.913	
DASS-21	36.33±21.26	34.10±13.58	-0.13 (-14.84, 19.31)	0.786	
Depression	12.78±6.82	11.30±5.48	(9.06,15.0)	0.607	0.016
Anxiety	10.22±8.18	9.70±6.48	(6.41, 13.51)	0.879	0.001
Stress	13.33±7.09	13.10±4.25	(10.42,16.01)	0.931	0.000
Self-esteem, mean (SD),	28.89±2.57	29.90±2.33	0.41(-3.38, 1.36)	0.381	

Abbreviations: BDI=Beck Depression Inventory; DASS-21=Depression Anxiety Stress Scale-21.

5.2 Mean changes from baseline to last observation

At the end of the exercise intervention program, the exercise group when compared to the control group showed improvement in relation to depression and functioning parameters, by having lower BDI-II and higher physical fitness (Table 2). In relation to DASS-21, the exercise group showed a decrease in anxiety and stress when compared to the control group. Furthermore, anthropometric parameters showed only significant differences between groups in fat mass percentage.

Table 2 – Comparison between intervention and control group after 4 months of exercise intervention.

	Exercise (N=9)	Control (N=10)	Difference (95% CI)	*p* value	$\eta^2 p$
Weight and fitness, mean (SD),			**Exercise vs Control**		
Weight, kg	72.68±11.65	68.75±14.24	-0.30 (-2.12, 3.80)	0.557	
Body mass index, kg/m^2	30.54±5.98	27.44±5.24	-0.55 (-3.80, 2.12)	0.557	
Fat mass, %	35.32±5.61	34.50±7.18	-0.13 (-5.27,-1.22)	**0.004**	
Waist circumference, cm	91.89±11.31	91.80±13.29	-0.01 (-617, 0.22)	0.066	
Functional assessment, mean (SD),					
Walk test, 6 minute	600.56±61.56	395.90±69.79	-3.11 (-186.58, -85.67)	**<0.001**	
Medicine ball throw, seated	3.49±0.37	2.90±0.58	-1.21 (-1.13,-0.48)	**<0.001**	
Chair stand test, 30 second	26.11±3.30	17.00±5.68	-1.96 (-10.83, -4.29)	**<0.001**	
Symptom severity, mean (SD),					
BDI II	34.89±10.56	49.40±16.72	1.04 (-26.48, -1.45)	**0.031**	
Self-esteem, mean (SD),	29.78±1.64	29.80±1.62	0.01 (-3.19,1.21)	0.357	
DASS-21	20.33±19.15	35.60±16.43	0.94 (-31.92, -3.08)	**0.020**	
Depression	7.33±6.12	11.90±6.52	(-0.92, 5.76)	0.073	0.177
Anxiety	5.89±6.94	10.80±6.75	(-0.72, 3.95)	**0.025**	0.262
Stress	7.11±6.64	12.90±4.43	(0.95,5.48)	**0.012**	0.316

Abbreviations: BDI=Beck Depression Inventory; DASS-21=Depression Anxiety Stress Scale-21.

6. Discussion

The **HAPPY BRAIN** trial (implemented from July 2013 to May 2014), aimed to assess the efficacy of a four-month exercise intervention as complementary therapy in a group of patients referred by psychiatrists. Results suggest that 16 weeks of aerobic exercise improved functional functioning and reduced depressive symptomatology. These results are similar to several previous trials that described positive effects of aerobic exercise as

adjuvant treatment for patients with clinical depression (Mota-Pereira et al., 2011; Schuch et al., 2011). Corroborating these findings, PE has received considerable and growing attention, and a large number of studies have shown therapeutic benefits when used not only as adjuvant treatment but also as a first option (Dunn et al., 2005; Trivedi et al., 2011). However, according to the available literature, results have not always been so consistent. Indeed, Krogh et al. (2011) published a highly cited systematic review and meta-analysis that exclusively assessed trials recruiting patients from a clinical setting, and the results showed a small benefit in reducing depressive symptoms (standardized mean differences (SMD) of -0.4). Although there has been an increase of scientific productivity with better designed studies in this area, the authors that conducted the most recent review for the Cochrane database made an urgent call for higher quality trials (Cooney et al., 2013) obeying stringent criteria to sustain the effect of PE on depressive pathology. This review included 39 trials (2326 participants) and indicated a moderate clinical effect. The pooled SMD for the primary outcome of depression at the end of the treatment was -0.62 (95% confidence interval (CI) -0.81 to -0.42). However, when only six robust clinical trials (464 participants) with adequate allocation concealment, intention-to-treat analysis, and blinded outcome assessment were included, the pooled SMD for this outcome was not statistically significant (-0.18, 95% CI -0.47 to 0.11). These results are not surprising and seem to be similar to another review published by Cochrane (Rimer et al., 2012), which included only trials with rigorous criteria. In these trials the pooled SMD was -0.31 (95% CI -0.63 to -0.01), indicating a small effect in favor of exercise. Recently, some authors (Daley and Jolly, 2012; Rosenbaum et al., 2014) have reported similar arguments for this heterogeneity of results, which can be attributed to methodological limitations, such as different degrees of disease severity, different pharmacotherapy and study designs, different outcome evaluations and a lack of objective measurement of PE interventions, lack of measuring longer term outcomes and using standardized clinical interviews to diagnose depression, and a lack of psychometric pitfalls of depression assessment scales. Parker (2005) also argued that the MDD concept classifies a heterogeneous group of patients who may have different clinical symptoms (e.g. weight loss or weight gain) in a diagnosis.

In this study, baseline characteristics were compared between groups and their values did not differ (Table 1). After the PE intervention, we found that patients allocated to the exercise group showed significant reduction in BDI-II (p=0.031) and DASS-21 (p=0.020). The effect size for the BDI-II and DASS-21 outcome was moderate. When comparing exercise group versus control group, the treatment effect was 1.04 (95% CI -26.48 to -1.45) for BDI and -0.94 (95% CI -31.92 to -3.08) for DASS-21. This result is in accordance with similar studies that used the BDI scale to measure the severity of depression (Callaghan et al.,

2011, Mota-Pereira et al. 2011). When analyzing the three dimensions of DASS-21 in relation to treatment groups, we did not achieve a statistically significant result *F* (3, 15)=2.77, *p*=0.078; Wilk's Λ=0.643, partial η^2p=0.357. However, the reduced power of a statistical test (π)=0.550 and the small sample size (n=19) could explain the absence of statistical significance. In fact, a large effect size was observed (η^2p=0.357*).* From a clinical perspective, the presence or absence of statistically significant differences is of limited value. Indeed, a non-significant outcome does not automatically imply that the treatment was not clinically effective, as small sample sizes and measurement variability can influence statistical results (Batterham and Hopkins, 2006). When analyzing how dependent variables differ from independent variables, results showed that the treatment group had a statistically significant and large effect on both anxiety (*p*=0.025; η^2p=0.262) and stress (*p*=0.012; η^2p=0.316) scores. It is important to note that despite not finding a statistically significant result for variable depression (*p*=0.073), we did observe a large effect size (η^2p=0.177*).* In the present study after 16 weeks no significant statistical differences in self-esteem were found 0.01 (95% CI -3.19 to 1.21; p=0.357) between treatment groups. Nevertheless, within groups, the analysis indicated that only the exercise group showed slight enhancement in self-esteem. However, this improvement was very small, and all psychiatric patients had lower self-esteem. These results suggest that the decrease in depressive symptomatology observed at the end of the PE intervention was not a consequence of changes in self-esteem. Moreover, the PE training did not induce significant changes in anthropometric parameters. Results revealed only significant differences -0.13 (95% CI -5.27 to -1.22; *p*=0.004) in percentage of body fat mass. Considering that body image often influences self-esteem (Bolton et al., 2010), the absence of results in the anthropometric parameters could explain the lack of increase in self-esteem. PE may reduce depression through its impact on the perceptions on the physical self. A last justification, and probably the most plausible, pertains to the fact that the degree of low self-esteem in the psychiatric disorder varies with psychiatric diagnosis and gender (Silverstone and Salsali, 2003), and lower self-esteem is one of the diagnosis criteria for dysthymic disorder (Silverstone and Salsali, 2003).

In the study by Krogh et al. (2012) a tendency for improved metabolic parameters (lower waist circumference, lower fasting plasma glucose and insulin) as a result of aerobic exercise was observed. Thus, present findings suggest that reductions in symptoms of depression cannot be explained by changes in anthropometric parameters, but other factors may be responsible for the favorable effect on depression. For instance, inclusion of supervised exercise sessions was probably favorable in increasing physical fitness and decreasing symptoms of depression. Accordingly, several studies support a direct relationship between increased PE and decreased depression (Fabricatore et al., 2011;

Greer and Trivedi, 2009). One prospective study (Brown et al., 2005) developed only with middle-aged women, showed a clear dose-response relationship between the increase of physical activity and decrease of depressive symptoms. Nonetheless, this study had a key limitation, as it relied on self-report measures of physical activity and depressive symptoms. Indeed, investigators examining antidepressant effects of PE have mainly used supervised, hospital exercise protocols, with fewer studies opting for home-based exercise (Craft et al., 2007). Furthermore, two trials found that supervised exercise leads to large improvements in functional fitness when compared to home-based exercise (Blumenthal et al., 2007; Kerse et al., 2010), and greater energy expenditure is related to larger reductions in depressive symptoms (Singh et al., 2005). Moreover, psychological factors have been amply demonstrated in literature so as to explain the effect that exercise has on depressive mood, including increased self-efficacy, sense of mastery, positive thoughts, and distraction from negative thoughts. However, the most recent and convincing approach, although less clear, involves possible neurobiological mechanisms that mediate the effects of exercise. This approach indicates that exercise reduces activity of the hypothalamic-pituitary axis (decreasing long-term basal levels of cortisol) (Sousa e Silva et al., 2010), improving the transmission rate of neurotransmission on the brain such as monoamines and beta-endorphins (Kubryak et al., 2012). It further reduces the levels of serum inflammatory markers such as the tumor necrosis factor (TNF), C reactive protein (CRP), IL-6 and IL-18 (Gleeson et al., 2011), and increases levels of other neurotrophic/growth factors, such as the brain-derived neurotrophic factor (BDNF) (Heyman et al., 2012).

Nevertheless, results of the present study must be carefully analyzed since the sample included a small number of patients. According to Faulkner et al. (2008), a wide interval expresses lack of precision and a narrower interval indicates relatively better precision. Conversely, these trials also have benefits. These patients obtain personalized attention and are closely supervised to ensure their evolution, and small exercise classes are suitable to develop task and social cohesion. It should be noted that many of these patients show discomfort about exercising in large groups, as they feel unfit, and assume others will be more competent to exercise. Therefore, exercising in small classes may facilitate self-perception in comparison with others.

The difficult compliance to exercise intervention in this clinical population has been widely acknowledged. According to several authors, adherence and patient displacement to PE programs is a critical aspect in long-term trials of patients with psychiatric disorders (Dunn et al., 2005; Rosenbaum et al., 2014). Adherence rates, especially for middle-aged depressed women, are not well documented and previous qualitative researches show low levels of attendance (Callaghan et al., 2011). In this study the percentage of adherence was

82%, similar to other RCT´s (Blumenthal et al., 2007; Brenes et al., 2007) with the same duration of PE intervention. It should be emphasized that patients enrolled in the PE intervention between January and April 2013, and throughout the four months attendance was 86%, 77%, 84% and 81% respectively. These levels of compliance are remarkable and showed treatment fidelity. Thus, it is important to bear in mind that initial acceptance is one of the major difficulties of the use of PE as a treatment (Schuch and Fleck, 2013). Moreover, the first two months of PE intervention coincided with decreased exposure to bright light that associated with key symptoms of MDD (such as tiredness, lack of motivation, loss of energy and generalized fatigue) and that can be a barrier to attendance (Leppamaki et al., 2002). According to Rimer and Dwan (2012), it is of utmost importance for researchers to define motivational strategies with the aim of reducing dropout rates. Hence, the exercise program was designed to optimize patients' adherence and several implemented strategies were determinants for the treatment fidelity observed (82%).

There were many strengths in this trial and they included: random allocation, inclusion of patients only recruited directly during routine external consultations by a psychiatrist, definition strategies before PE intervention promoting behavioral adherence that maximizes adhesion, and definition of specific goals for each patient that take into account their functional capacity. Additionally, for 16 weeks all patients were followed through routine psychiatric consultations with access to multidisciplinary teams of professionals from diverse areas (psychiatrists, physical training teachers, professor of exercise physiology). For post-intervention analyses, patients were assessed by their psychiatrists. In addition, we used a self-report rating scale. Their metabolic fitness and body composition parameters were evaluated before and after PE intervention. Nevertheless, some methodological weaknesses must be considered when interpreting results. For instance, we were not able to formally follow up the participants due to lack of funding and this is a potential limitation. Moreover, although this trial included a small number of patients**,** it focused specifically on women, and trials in depressed women are scarce (Callaghan et al., 2011). However, we should bear in mind that low statistical power negatively affects the likelihood that a statistically significant finding actually reflects a true effect due to the simple size (Button et al., 2013). Therefore, replication studies with larger samples are recommended.

7. Conclusion

This study demonstrated that PE is an effective treatment, adjuvant to pharmacological therapy for depressed women. Furthermore, we concluded that 16 weeks of aerobic PE resulted in decreasing the parameters of depression (BDI-II) and physical functioning.

Nonetheless, no differences in anthropometric (weight, body mass index and waist circumference) and self-esteem between groups were found. We also observed that a multi-disciplinary team and the defined strategies could effectively enhance treatment fidelity.

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Author contributions

Author Lara S. F. Carneiro designed the study, wrote the protocol, analyzed the data, undertook the statistical analysis and produced the first draft of the manuscript under the oversight of authors Professor José Vasconcelos-Raposo and Professor Maria Paula Mota. Author Professor Maria Augusta Vieira-Coelho identified potentially eligible patients for the clinical trial, and conducted the clinical evaluation of screened patients. Author Professor António Manuel Fonseca contributed to the manuscript. All authors made important contributions to the final manuscript and provided important intellectual content.

Conflict of interest

All authors report no conflict of interest.

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References

1. American Psychiatric Association, 2010. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, third ed.
2. Batterham, A.M., Hopkins, W.G., 2006. Making meaningful inferences about magnitudes. Int. J. Sports Physiol. Perform. 1, 50-57.
3. Blumenthal, J.A., Babyak, M.A., Doraiswamy, P.M., Watkins, L., Hoffman, B.M., Barbour, K.A., Herman, S., Craighead, W.E., Brosse, A.L., Waugh, R., Hinderliter, A.,

Sherwood, A., 2007. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom. Med. 69, 587-596.

4. Bolton, M.A., Lobben, I., Stern, T.A., 2010. The impact of body image on patient care. Prim. Care Companion J. Clin. Psychiatry 12, 2.

5. Brenes, G.A., Williamson, J.D., Messier, S.P., Rejeski, W.J., Pahor, M., Ip, E., Penninx, B. W. J., 2007. Treatment of minor depression in older adults: A pilot study comparing sertraline and exercise. Aging Ment. Health 11, 61-68.

6. Brown, W.J., Ford, J.H., Burton, N.W., Marshall, A.L., Dobson, A.J., 2005. Prospective study of physical activity and depressive symptoms in middle-aged women. Am. J. Prev. Med. 29, 265-272.

7. Button, K.S., Ioannidis, J.P., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S., Munafo, M.R., 2013. Power failure: Why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. 14, 365-376.

8. Callaghan, P., Khalil, E., Morres, I., Carter, T., 2011. Pragmatic randomised controlled trial of preferred intensity exercise in women living with depression. BMC Public Health 11, 465.

9. Campos, R.C., Gonçalves, B., 2011. The Portuguese version of the Beck Depression Inventory-II (BDI-II): Preliminary psychometric data with two nonclinical samples. Eur. J. Psychol. Assess. 27, 258-264.

10. Chu, I.H., Buckworth, J., Kirby, T.E., Emery, C.F., 2009. Effect of exercise intensity on depressive symptoms in women. Ment. Health Phys. Act. 2, 37-43.

11. Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Hillsdale, NJ: Lawrence Erlbaum Associates.

12. Cooney, G.M., Dwan, K., Greig, C.A., Lawlor, D.A., Rimer, J., Waugh, F.R., McMurdo, M., Mead, G.E., 2013. Exercise for depression. Cochrane Database Syst. Rev. 9, CD004366.

13. Craft, L.L., Freund, K.M., Culpepper, L., Perna, F.M., 2007. Intervention study of exercise for depressive symptoms in women. J. Womens Health 16, 1499-1509.

14. Craft, L.L., 2005. Exercise and clinical depression: Examining two psychological mechanisms. Psychol. Sport. Exerc. 6, 151-171.

15. Cumming, G., 2013a. The new statistics: Estimation for better research. [cited 2015 Jan 19]. Available from: http://www.thenewstatistics.com.

16. Cumming, G., 2013b. The new statistics: Why and how. Psychol. Sci. 25,1-21.

17. Daley, A., Jolly, K., 2012. Exercise to treat depression. BMJ 344, e3181.

18. Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446-457.

19. Dunn, A.L., Trivedi, M.H., Kampert, J.B., Clark, C.G., Chambliss, H.O., 2005. Exercise treatment for depression: Efficacy and dose response. Am. J. Prev. Med. 28,1-8.

20. Fabricatore, A.N., Wadden, T.A., Higginbotham, A.J., Faulconbridge, L.F., Nguyen, A.M., Heymsfield, S.B., Faith, M.S., 2011. Intentional weight loss and changes in

symptoms of depression: A systematic review and meta-analysis. Int. J. Obes. 35,1363-1376.

21. Faulkner, C., Fidler, F., Cumming, G., 2008. The value of RCT evidence depends on the quality of statistical analysis. Behav. Res. Ther. 46, 270-81.

22. Gleeson, M., Bishop, N.C., Stensel, D.J., Lindley, M.R., Mastana, S.S., Nimmo, M.A., 2011. The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. Nat. Rev. Immunol. 11, 607-615.

23. Greer, T.L., Trivedi, M.H., 2009. Exercise in the treatment of depression. Curr. Psychiatry Rep. 11, 466-472.

24. Heyman, E., Gamelin, F.X., Goekint, M., Piscitelli, F., Roelands, B., Leclair, E., Di Marzo, V., Meeusen, R., 2012. Intense exercise increases circulating endocannabinoid and bdnf levels in humans—possible implications for reward and depression. Psychoneuroendocrino. 37, 844-851.

25. Hopkins, W.G., 2010. Linear models and effect magnitudes for research, clinical and practical applications. Sport Science 14, 49-57.

26. Hopkins, W.G., Marshall, S.W., Batterham, A.M., Hanin, J., 2009. Progressive statistics for studies in sports medicine and exercise science. Med. Sci. Sports Exerc. 41, 3-12.

27. Kerse, N., Hayman, K.J., Moyes, S.A., Peri, K., Robinson, E., Dowell, A., Kolt, G.S., Elley, C.R., Hatcher, S., Kiata, L., Wiles, J., Keeling, S., Parsons, J., Arroll, B., 2010. Home-based activity program for older people with depressive symptoms: DeLLITE--A randomized controlled trial. Ann. Fam. Med. 8, 214-223.

28. Kessler, R.C., 2003. Epidemiology of women and depression. J. Affect. Disord. 74, 5-13.

29. Knapen, J., Vancampfort, D., Morien, Y., Marchal, Y., 2014. Exercise therapy improves both mental and physical health in patients with major depression. Disabil. Rehabil. 37, 1490–1495.

30. Kohut, M.L., McCann, D.A., Russell, D.W., Konopka, D.N., Cunnick, J.E., Franke, W.D., Castillo, M.C., Reighard, A.E., Vanderah, E., 2006. Aerobic exercise, but not flexibility/resistance exercise, reduces serum il-18, crp, and il-6 independent of beta-blockers, bmi, and psychosocial factors in older adults. Brain. Behav. Immun. 20, 201-209.

31. Krogh, J., Nordentoft, M., Sterne, J.A., Lawlor, D.A., 2011. The effect of exercise in clinically depressed adults: Systematic review and meta-analysis of randomized controlled trials. J. Clin. Psychiatry 72, 529-538.

32. Krogh, J., Videbech, P., Thomsen, C., Gluud, C., Nordentoft, M., 2012. DEMO-II trial. Aerobic exercise versus stretching exercise in patients with major depression-A randomised clinical trial. PLoS ONE 7, e48316.

33. Kubryak, O.V., Umriukhin, A.E., Emeljanova, I.N., Antipova, O.S., Guseva, A.L., Pertsov, S.S., Sudakov, S.K., 2012. Increased beta-endorphin level in blood plasma as an indicator of positive response to depression treatment. Bull. Exp. Biol. Med. 153, 758-760.

34. Lepine, J.P., Briley, M., 2011. The increasing burden of depression. Neuropsychiatr. Dis. Treat. New. 7, 3-7.

35. Leppamaki, S., Partonen, T., Lonnqvist, J., 2002. Bright-light exposure combined with physical exercise elevates mood. J. Affect. Disord. 72,139-144.

36. Mota-Pereira, J., Silverio, J., Carvalho, S., Ribeiro, J.C., Fonte, D., Ramos, J., 2011. Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. J. Psychiatr. Res. 45, 1005-1011.

37. National Institute for Health & Clinical Excellence, 2009. Depression: The NICE guideline on the treatment and management of depression in adults (updated edition).

38. Parker, G., 2005. Beyond major depression. Psychol. Med. 35, 467-474.

39. Rethorst, C.D., Wipfli, B.M., Landers, D.M., 2009. The antidepressive effects of exercise: A meta-analysis of randomized trials. Sports Med. 39, 491-511.

40. Rimer, J., Dwan, K., Lawlor, D.A., Greig, C.A., McMurdo, M., Morley, W., Mead, G.E., 2012. Exercise for depression. Cochrane Database Syst. Rev. 7, CD004366.

41. Rosenbaum, S., Tiedemann, A., Sherrington, C., Curtis, J., Ward, P.B., 2014. Physical activity interventions for people with mental illness: A systematic review and meta-analysis. J. Clin. Psychiatry 75, 964-974.

42. Salsali, M., Silverstone, P.H., 2003. Low self-esteem and psychiatric patients: Part II - the relationship between self-esteem and demographic factors and psychosocial stressors in psychiatric patients. Ann. Gen. Hosp. Psychiatry 2, 3.

43. Schuch FB, Fleck MPdA. Is exercise an efficacious treatment for depression? A comment upon recent negative findings. Frontiers in Psychiatry 2013; 4, 20.

44. Schuch, F.B., Vasconcelos-Moreno, M.P., Borowsky, C., Fleck, M.P., 2011. Exercise and severe depression: Preliminary results of an add-on study. J. Affect. Disord. 133, 615-618.

45. Shahidi, M., Mojtahed, A., Modabbernia, A., Mojtahed, M., Shafiabady, A., Delavar, A., Honari, H., 2011. Laughter yoga versus group exercise program in elderly depressed women: A randomized controlled trial. Int. J. Geriatr. Psychiatry 26, 322-327.

46. Silveira, H., Moraes, H., Oliveira, N., Coutinho, E.S., Laks, J., Deslandes, A., 2013. Physical exercise and clinically depressed patients: A systematic review and meta-analysis. Neuropsychobiology 67, 61-68.

47. Silverstone, P.H., Salsali, M., 2003. Low self-esteem and psychiatric patients: Part I - the relationship between low self-esteem and psychiatric diagnosis. Ann. Gen. Hosp. Psychiatry 2, 2.

48. Singh, N.A., Stravinos, T.M., Scarbek, Y., Galambos, G., Liber, C., Singh, M.A.F., 2005. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. J. Gerontol. A. Biol. Sci. Med. Sci. 60, 768-776.

49. Sousa e Silva, T., Longui, C.A., Rocha, M.N., Faria, C.D.C., Melo, M.R., Faria, T.G., de Souza, J.A., Rizzo, L.V., 2010. Prolonged physical training decreases mRNA levels of glucocorticoid receptor and inflammatory genes. Horm. Res. Paediatr. 74, 6-14.

50. Teychenne, M., York, R., 2013. Physical activity, sedentary behavior, and postnatal depressive symptoms: A review. Am. J. Prev. Med. 45, 217-227.

51. Trivedi, M.H., Greer, T.L., Church, T.S., Carmody, T.J., Grannemann, B.D., Galper, D.I., Dunn, A., Earnest, C.P., Sunderajan, P., Henley, S.S., Blair, S.N., 2011. Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. J. Clin. Psychiatry 72, 677-684.

52. Vasconcelos-Raposo, J., Fernandes, H.M., Teixeira, C.M., 2013. Factor structure and reliability of the depression, anxiety and stress scales in a large Portuguese community sample. Span. J. Psychol. 16, E10.

53. Vasconcelos-Raposo, J., Fernandes, M., Teixeira, C., Bertelli, R., 2012. Factorial validity and invariance of the rosenberg self-esteem scale among portuguese youngsters. Soc. Indic. Res. 105, 483-498.

STUDY 3

Impact of physical exercise on catechol-O-methyltransferase activity in depressive patients: A preliminary communication

Impact of physical exercise on catechol-O-methyltransferase activity in depressive patients: A preliminary communication

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Abstract

Background: Catechol-O-methyltransferase (COMT) is a catabolic enzyme involved in the degradation of bioactive molecules including the neurotransmitters epinephrine, norepinephrine, and dopamine. Higher COMT activity in depressive patients in comparison to non-depressed individuals has been reported. The effect of aerobic exercise on depressive patients has been studied and a number of researchers and clinicians believe it to be effective in the treatment of depression and to be involved in several molecular underlying mechanisms. However, the effect of physical exercise on this enzyme activity is unknown, and it remains to be elucidated if chronic exercise changes COMT activity. This randomized control trial evaluates the effects of chronic exercise on peripheral COMT (S-COMT) activity in women with depressive disorder.

Methods: Fourteen women (aged: 51.4±10.5 years) diagnosed with depression (according to International Classification of Diseases-10) were randomized to one of two groups: pharmacotherapy plus physical exercise (n=7) or only pharmacotherapy (n=7). The aerobic exercise program was supervised, lasting between 45-50 min/session, three times/week for 16 weeks. Erythrocyte soluble COMT were assessed prior to and after the exercise program.

Results: Exercise group when compared to a control group presented a significant decrease (p=0,02, r=-0,535) in S-COMT activity between baseline and post-intervention.

Limitations: These data are preliminary outcomes from a small sample and should be replicated.

Conclusions: Chronic exercise therapy combined with pharmacotherapy leads to significant decrease in S-COMT activity. Our results provide evidence that exercise interferes with S-COMT activity, a molecular mechanism involved in depression.

Keywords: Enzymes, Depression, Aerobic exercise, Catechols, Women.

1. Introduction

It is well known that unipolar depression is a debilitating disease that has a substantial negative impact on quality of life, morbidity/mortality, and cognitive function (Behr et al., 2012). Major depressive disorder (MDD) is not only characterized by intense dysregulation of affect and mood (Villanueva, 2013) but it is also linked with other abnormalities, namely in cognitive dysfunction (memory, executive function, processing speed and attention) (Carvalho et al., 2014). MDD has been consistently associated with catecholaminergic dysfunction (Opmeer et al., 2013), especially with a decrease in dopamine neurotransmission (Hasler et al., 2008). New studies have revived interest in the enzyme catechol-O-methyltransferase (COMT), one of the key modulators of the dopaminergic levels in the prefrontal cortex (PFC) of the human brain (Sengupta et al., 2008). COMT is an important enzyme for inactivation and metabolism of catechols, including dopamine, norepinephrine, estrogens and other catechol compounds (Chen et al., 2011). Two main COMT protein isoforms are known: a membrane bound form (MB-COMT), which is predominantly expressed in brain neurons and a soluble cytoplasmic (S-COMT), which is more abundant in peripheral tissues (Mannisto and Kaakkola, 1999). The COMT enzyme activity is encoded for the COMT gene (Antypa et al., 2013) and has a genetically polymorphic with a tri-modal distribution (Val/Val genotype, Val/Met genotype, and Met/Met genotype) (Hosak, 2007). Evidence from clinical investigations on the role of the COMT supports the finding that abnormal catecholamine transmission has been linked to the pathogenesis of disorders in mood, which include MDD (Massat et al., 2005).

An emerging multidisciplinary literature has documented the beneficial influence of physical activity on selective aspects of brain function (Hillman et al., 2008). Thus, physical exercise (PE) has been regarded as a useful non-pharmacological intervention strategy to improve cognitive function. In this context, physical activity engendered through aerobic exercise, in particular, benefits executive control processes of cognition in several domains such as in selective attention, planning, organizing, multitasking, inhibition, and working memory (Hotting and Roder, 2013; Kubesch et al., 2003) Despite knowing that aerobic exercise can enhance cognitive functioning by modulating particular aspects of brain functioning, there are a multitude of questions which remain to be answered, namely the mechanisms underlying this modulating effect (Stroth et al., 2010). It is possible that the effect of aerobic exercise on cognitive functions is partly mediated by dopaminergic modulation. One mechanism that accounts for up-regulation of dopamine in the brain has been associated to exercise inducing higher levels of serum calcium, which is transported to the brain (Lin and Kuo, 2013). Calcium ions in brain functions activate tyrosine hydroxylase through a calmodulin-dependent system (Sutoo et al., 1991). Calmodulin is a calcium-binding

protein, which is involved in many calcium-dependent enzyme activities, and in the synthesis and release of several neurotransmitters, including in dopamine synthesis (Sutoo et al., 2001). Subsequently, the increased dopamine levels lead to behavioral and physiologic changes. Nevertheless, assessing central dopamine levels in humans is problematic since dopamine cannot cross the blood–brain-barrier (Volkow et al., 1996). On the systemic level, an enzyme related to dopamine metabolism – the COMT could be used as an indicator of central dopamine availability. Animal studies have shown that the COMT enzyme, by catabolizing dopamine regulates its neurotransmission in brain areas, exerting influence on general levels of dopamine (Bilder et al., 2004). Indeed, COMT, one of the main modulators of the dopaminergic levels, has been documented as one of the potential moderators of the effect of PE on neurocognitive function (Leckie et al., 2012). Surprisingly, few studies have examined whether the COMT moderates the effect of chronic physical activity on neurocognitive function. Indeed, the majority of the studies have focused on COMT polymorphisms and no information on COMT activity has been described. Given the higher prevalence of depression in women, we set out to investigate the potential impact of exercise on S-COMT activity in depressive women.

2. Methods

The protocol was performed according to the Declaration of Helsinki, and the Ethics Committee of Centro Hospitalar de São João approved it (11th of March, 2013) with ethics reference number 112/13. All participants signed an informed consent prior to beginning the trial.

2.1 Participants

Fourteen women (mean age: 51.4±10.5) participated in this randomized control trial (RCT); seven patients engaged in moderate intensity exercise plus their usual pharmacological therapy (exercise group), and the other seven patients took their usual pharmacological therapy but were not assigned to any exercise (control group).

2.2 Inclusion Criteria

Eligible patients had to fulfill the following inclusion criteria: (1) women aged 18-65; (2) able and willing to provide informed consent and accept randomized group assignment; (3) with current diagnosis of: F33.1 (recurrent depressive disorder, moderate current episode), F34.1 (dysthymia) confirmed by a psychiatrist according to ICD-10 (International Classification of Diseases, 10th revision); (4) physically fit to do exercise confirmed in writing

by general practitioners; (5) normal ECG; (6) patients had to be sedentary (involved in sports activity for less than 1 hour per week).

2.3 Exclusion Criteria

The exclusion criteria were: (1) psychiatric co-morbidities; (2) current participation in other RCTs; (3) medical background indicating significant medical constraints; (4) current active alcohol/drug abuse or dependence; (5) pregnancy or planning to become pregnant in the next year; (6) taking beta-blocking medication; (7) change of pharmacological therapy during PE program; (8) change of drug therapy in the 6 weeks preceding the PE program; (9) exhibiting significant exacerbation of symptoms; (10) less than 60% of attendance of sessions; (11) undergoing complementary therapies.

2.4 Trial design

This trial was randomized and two-armed. The patients, physical training teacher, general practitioners, psychiatrists, or researchers performing the outcome assessment were not blinded in relation to treatment allocation. However, the laboratory technician who analyzed the blood samples was blinded in relation to patients.

These patients were randomized following a 1:2 scheme to one of two groups: aerobic exercise (n=7) and control (n=7). Randomization was implemented with sequentially numbered opaque, sealed envelopes.

3. Intervention

3.1 Exercise group

The aerobic group program consisted of 45-50 min per session, three times a week, for a total of 16 weeks. Sessions were supervised in the presence of a Physical Training Teacher. The patients carried pulse monitors (Polar FT1, Finland) during every session to ensure they exercised in the prescribed pulse interval. A rate of perceived exertion was used (Borg scale) in order to have a measure of the subjective intensity of exercise. This program was initiated with 10 minutes of general low-intensity warm-up, and then patients performed 30 minutes of aerobic, followed by 5 minutes of low-intensity period. The aerobic exercise involved aerobic traditional games, indoor and outdoor natural circuit workout with resistance bands, jump rotes, fitness balls, brisk walking and dancing. The intensity was gradually increased, being the average intensity of heart rate maximum (HRmax) for the four months 67%, 75%, 75% and 77% (RPE=12-13), respectively.

3.2 Control group

The control group comprised seven patients that continued their usual pharmacological therapy but were not assigned to any PE.

4. Outcome measures

All patients were evaluated for anthropometric parameters, functional assessment, depressive symptoms, and blood analysis at baseline and at the end of the PE intervention (16 weeks). Patients met with a psychiatrist throughout the study to assess symptomatology and medication tolerance. The dose of medication was kept constant in both groups. Patients were medicated with selective serotonin reuptake inhibitor (SSRIs); fluoxetine, escitalopram, sertraline and paroxetine. When convenient, benzodiazepines diazepam, lorazepam and estazolam were used as anxiolytic or hypnotics.

4.1 Psychiatric evaluation

Assessment procedures were performed in relation to psychiatric evaluation, where patients were considered eligible if referred to by a psychiatrist and fulfilled the ICD-10 criteria.

4.2 Physical functioning

To assess physical functioning, a performance battery was used: distance walked in six minutes, time to sit and stand from a chair in 30 seconds, and seated medicine ball throw.

4.3 Physical examination

Physical examination was carried out with the Tanita BC-418 Segmental Body Composition Analyzer, which was used to complete the body composition profile including weight and body mass index (BMI).

4.4 S-COMT assay

The analysis of the soluble COMT activity in erythrocytes was carried out as following: firstly, blood samples (5 mL) were collected in tubes containing ethylenediamine tetraacetic acid (EDTA) and plasma was separated by centrifugation (4°C, 1500 g); then, red blood cells were washed with three times the cell volume of cold 0.9% NaCl. The procedure was repeated in triplicate. The washed cells were immediately stored at -80°C until the enzymatic assay. After melting, the washed cell samples were haemolyzed with four times the cell volume of cold 1 mM sodium phosphate buffer (pH 7.4), vortex-mixed, and left to stand in an

ice bath for 10 min, before centrifugation (20 min, 4°C, 20000 g) to separate MB-COMT from S-COMT. The supernatant was used immediately for the measurement of soluble COMT enzyme activity. In addition, an aliquot of the supernatant was diluted (1:100) with 0.9% NaCl and stored at -20°C before measurement of the protein content.

The COMT assay was performed essentially according to the method of Schultz, Nissinen and Kaakkola (Schultz et al., 1989) with minor modifications (Souteiro et al., 2013). The incubation mixture contained 300 µL enzyme preparation, 375 µL incubation medium, and 75 µL 10 mM (final concentration 1 mM) adrenaline as the enzyme substrate. The final 750 µL reaction volume contained 100 mM sodium phosphate buffer (pH 7.8), 2 mM MgCl2, and 200 µM S-adenosyl-L-methionine. The samples were incubated in a water bath at 37°C for 60 min. The tubes were transferred to ice, and the reaction was stopped by adding 75 µL of ice-cold 2 M perchloric acid. After 10 min, the samples were centrifuged for 10 min at 4°C at 5400 g, and 500 µL aliquots of the supernatant filtered on 0.22-µm pore size Spin-X filter tubes (Costar) were used for the assay of metanephrine by means of high performance liquid chromatography with electrochemical detection.

S-COMT activity was expressed as the amount of metanephrine formed (in pmol) per mg of protein in the sample, per hour (pmol/mg prot/h), by the action of COMT on a single adrenaline concentration (1000 µM).

4.5 Statistical analysis

Descriptive statistics (means, standard deviation) were used to summarize socio-demographic, functional assessment and anthropometric variables. The kinetic parameters, maximum velocity (Vmax) and Michaelis-Menten constant (KM) values were calculated from non-linear regression analysis by using the Graphpad Prism Software package (version 6.0) for Mac OSX. All dependent variables were tested for normality according to the Shapiro-Wilks method. The measures showed significant deviations from a normal distribution. Consequently, our data do not meet the requirements of parametric tests. Thus, to allow for comparison in clinical characteristics at baseline and after 16 weeks, between two arms of the trial, non-parametric Mann-Whitney test was used. Furthermore, to determine changes from baseline to endpoint (16 weeks) in the exercise and control groups non-parametric Wilcoxon test was used. We analyzed data with IBM SPSS statistics software (version 21.0). A P-value of less than 0.05 was taken as significant. Likewise, effects were examined using magnitude-based inferences (Hopkins et al., 2009). According to Fritz et al. (2012), the z value can be used to calculate an effect size for Mann-Whitney and Wilcoxon nonparametric tests, through the following formula, $r=z/\sqrt{N}$. Thus, the effect size r was performed using the

software package effect size calculators PolyU. Cohen's guidelines for r are that a large effect is .5, a medium effect is .3, and a small effect is .1 (Cohen, 1988).

5. Results

5.1 Participants and baseline values

Fourteen patients were eligible for randomization, and seven patients were allocated to the exercise group and the other seven to the control group. Mean age of patients was 51,43 (SD=10,54). In relation to anthropometric parameters, average weight was 73,49 kg (SD=10,98) and a mean body mass index (BMI) of 30,51 kg/m2 (SD=5,06).

Furthermore, the majority of patients (78,60%) had the diagnosis of dysthymia (F34.1) whereas the others had recurrent depressive disorder (F33.1), (21,4%). Fluoxetine was the most commonly used SSRI (64,30%), followed by sertraline (21,4%). The analysis between the groups, using the Mann-Whitney test, showed no significant difference in the baseline characteristics in all analyzed variables (table 1).

Table 1 – Baseline data from patients allocated to exercise and control group.

	Exercise (N=7)	**Control (N=7)**	***p* value**
Demographic			
Age (years), mean (SD),	55,00±7,02	47,86±12,70	0,274
Anthropometric parameters, mean (SD),			
Weight, kg	74,29±12,63	72,69±10,00	0,871
Body mass index, kg/m^2	31,33±6,25	29,69±3,85	0,902
Functional assessment, mean (SD),			
Walk test, 6 minute	459,14±88,25	369,29±30,37	0,073
Medicine ball throw, seated	2,69±0,26	2,93±0,28	0,165
Chair stand test, 30 second	19,86±2,67	18,43±5,53	0,483
Depression characteristics, n (%)			
Recurrent depressive disorder	1 (14,3)	2 (28,6)	
Dysthymia	6 (85,7)	5 (71,4)	
Symptom severity, mean (SD),			
BDI-II	45,29±10,47	44,86±13,37	0,925
COMT activity			
Vmax (pmol/mg prot/h)	8,59±7,82	9,33±5,32	0,710

Abbreviation: **BDI**=Beck Depression Inventory.

5.2 Mean changes from baseline to last observation

After 16 weeks of exercise therapy, when both groups were compared, all physical functioning parameters had significant improvements in the exercise group in relation to the control group (table 2). Post intervention scores in distance walked in six minutes were 591,00±67,57 meters for the exercise group, and 375,57±49,83 meters for the control group, differing significantly (p=0,001, r=-0,802). Likewise, post intervention scores in seated medicine ball throw test were 3,42±0,29 for the exercise group, and 2,76±0,54 for the control group, showing a significant difference (p=0,026, r=-0,535). Similarly, post intervention scores in time to sit and stand from a chair in 30 seconds test were 26,29±3,50 seconds for the exercise group and 17,43±6,68 seconds for the control group, and differed significantly (p=0,014, r=-0,535).

At a single concentration of substrate (1000 μM of adrenaline) in the end of PE intervention, S-COMT activity was significantly higher (p=0,02, r=-0,535) in control patients (8,79±4,95 pmol/mg prot/h) than in exercise patients (2,71±1,68 pmol/mg prot/h).

There were no significant differences between the two groups, after 16 weeks in weight (p=1,000, r=0,000) and BMI (p=0,902, r=0,000) (table 2) variables.

Table 2 – Post intervention outcome from patients allocated to exercise and control groups, after 4 months of exercise intervention.

	Exercise (N=7)	**Control (N=7)**	***p* value**
Anthropometric parameters, mean (SD),			
Weight, kg	72,76±12,90	71,41±11,54	1,000
Body mass index, kg/m^2	30,72±6,52	29,11±4,23	0,902
Functional assessment, mean (SD),			
Walk test, 6 minute	591,00±67,57	375,57±49,83	**0,001**
Medicine ball throw, seated	3,42±0,29	2,76±0,54	**0,026**
Chair stand test, 30 second	26,29±3,50	17,43±6,68	**0,014**

6. Discussion

The aim of this RCT was to assess the effects of 16 weeks of PE (chronic exercise) on the S-COMT activity in a sample composed of depressive patients. The main finding of this study has provided evidence that chronic PE changes S-COMT activity. Indeed, after the intervention, patients in the experimental group (pharmacotherapy plus exercise) evidenced a significant decline in S-COMT activity whereas the control group (only pharmacotherapy) evidenced no changes in this enzyme (Figure 1). In this trial, the patients in the exercise

group significantly increased physical fitness, which confirms the efficacy of the exercise intervention.

Few studies have explored the role of the COMT gene in regulating the dopaminergic function on the cognitive functions through exercise. However, to our knowledge, no RCT has investigated the effect of chronic exercise in COMT enzyme activity in patients with depressive disorders, specifically in a sample composed of women. COMT activity is a particularly interesting mechanism involved in depressive disorders as it is higher in erythrocytes of depressive patients in comparison to healthy ones (Fahndrich et al., 1980; Puzynski et al., 1983). In addition, a decreased level of endogenous dopaminergic neurotransmission might make a significant contribution to depressive disorder (Pearson-Fuhrhop et al., 2014). So, if exercise decreases COMT activity, it is possible that it increases dopamine availability. Furthermore, the sample focused only on a female population, as several previous studies have well documented the fact that females have higher incidence rates of MDD than males (Kessler, 2003). Moreover, females have major lifetime prevalence of minor states such as dysthymia (Parker et al., 2014), which is a chronic, low-grade form of depression that increases the risk for MDD (Griffiths et al., 2000). In addition, the female patients with endogenous depression revealed a significantly higher COMT activity than males (Fahndrich et al., 1980). Additionally, estrogens fluctuation in females might be a biological risk factor which can lead to the occurrence of depression symptoms during critical periods, such as menopause, pre-menstrual period, postpartum (Lokuge et al., 2011). Indeed, this study highlights the evidence that there might be interactions between exercise and S-COMT, however, the true causes for the changes in enzyme activity responses to exercise require further clarification. One study (Stroth et al., 2010) that assessed whether variants of the COMT gene would be moderated by engaging in a running training for 17 weeks in a sample of healthy individuals showed that there are benefits associated with physical activity on cognitive flexibility and cognitive control, which are dependent on the COMT genotype. Moreover, Val/Val runners when compared to Met/Met runners had greater cognitive performance increment. Nevertheless, there are a limited number of studies on this matter and the pathways by which this effect occurs are controversial. Moreover, some of the limitations of this study included the absence of information with regard to the possible changes in COMT activity in human erythrocytes and lack of randomization of the study population.

As far as methodological strengths are concerned, our study followed a randomized design, compliance to the exercise program was high (83.3%), laboratory staff was blinded to patient allocation, and patients were referred to by psychiatrists, who provide a high level of external validity. Furthermore, all patients were medicated at the time of inclusion, which was

kept constant throughout the study, and thus increases the homogeneity of the sample. However, the small sample size should be considered a shortcoming of this study. Consequently, the results should be replicated in a large sample with the aim to validate the observed association between exercise and COMT activity. Hence, the results and the effect sizes observed in this study should be interpreted with caution. Additionally, little is known about the physiology of this relationship and it is important to note that the COMT enzyme is an indicator of relative central dopamine availability. Therefore, it should be stressed that it is difficult to make a definitive interpretation. At the same time, we need to bear in mind that in the present study, only the effect of exercise in S-COMT activity was investigated, i.e. MB-enzyme activity was not measured. Furthermore, no statement on the impact of exercise in cognitive function can be made on the basis of the present data. Nonetheless, there are several studies in humans reporting positive effects of exercise on cognitive function in both depressive patients (Kubesch et al., 2003) and healthy individuals (Hotting and Roder, 2013). However, this article provides a key contribution to better understand the role of exercise as an underlying modulation factor on the brain monoamine system. Indeed, the effects of COMT cannot be disregarded and must be taken into account when studying the effects of exercise on monoamine systems. Most importantly, future RCTs should analyze the effects of the dose-response of exercise in COMT activity as well as other potential moderators.

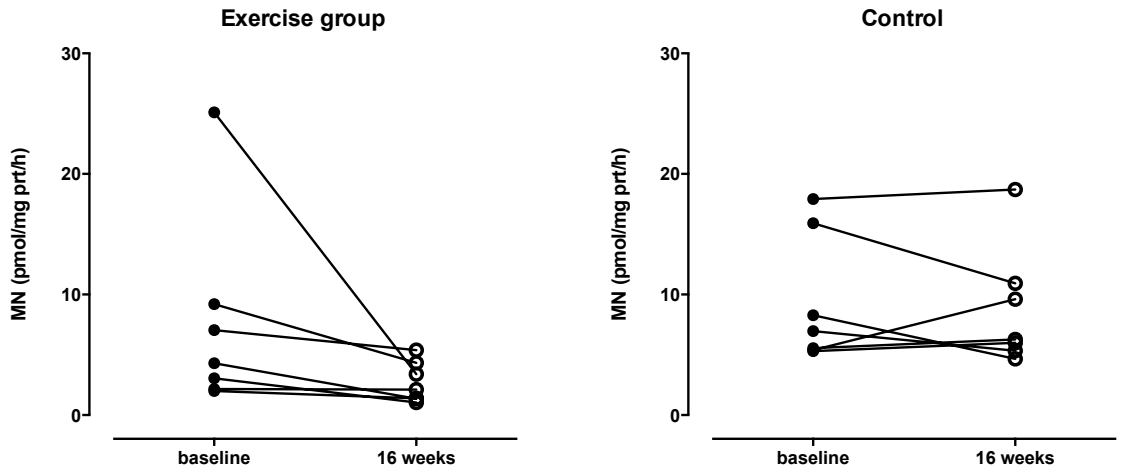

Figure 1 – Erythrocyte S-COMT activity (pmol/mg prot/h) in exercise group and controls at baseline and at the end of physical exercise program (W16).
Exercise group-p=0,0156 within group by Wilcoxon test.
Controls-p=0,8125 within group by Wilcoxon test.

7. Conclusion

To our knowledge, this is the first study that assessed the effects of chronic exercise in S-COMT activity in depressive females. In fact, combining a 16-week PE program with pharmacotherapy leads to a decrease in S-COMT activity. In this way, our findings support the hypothesis of a relation between S-COMT activity and exercise. Thus, this has opened up new paths to understand the potential of the exercise as a therapeutic complementary intervention in the treatment of depressive disorder.

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Author contributions

Author Lara S. F. Carneiro carried out the literature search and statistical analysis, wrote the first draft of the manuscript under the supervision of authors Professor José Vasconcelos-Raposo and Professor Maria Paula Mota, Author Professor Maria Augusta Vieira-Coelho identified potentially eligible patients for the clinical trial, conducted the clinical assessment of screened patients and coordinated sample, processed and prepared it for analysis. Author Engineer Paula Serrão performed experiments. Author Professor António Manuel Fonseca provided critical input to the manuscript. All authors contributed to and approved the final manuscript.

Conflict of interest

All authors report no conflict of interest.

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References

1. Antypa, N., Drago, A., Serretti, A., 2013. The role of COMT gene variants in depression: Bridging neuropsychological, behavioral and clinical phenotypes. Neurosci. Biobehav. Rev. 37, 1597-1610.

2. Behr, G.A., Moreira, J.C., Frey, B.N., 2012. Preclinical and clinical evidence of antioxidant effects of antidepressant agents: Implications for the pathophysiology of major depressive disorder. Oxid. Med. Cell. Longev. 2012, 609421.

3. Bilder, R.M., Volavka, J., Lachman, H.M., Grace, A.A., 2004. The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology 29, 1943-1961.

4. Carvalho, A.F., Miskowiak, K.K., Hyphantis, T.N., Kohler, C.A., Alves, G.S., Bortolato, B., PM, G.S., Machado-Vieira, R., Berk, M., McIntyre, R.S., 2014. Cognitive dysfunction in depression - pathophysiology and novel targets. CNS Neurol. Disord. Drug Targets 13, 1819-1835.

5. Chen, J., Song, J., Yuan, P., Tian, Q., Ji, Y., Ren-Patterson, R., Liu, G., Sei, Y., Weinberger, D.R., 2011. Orientation and cellular distribution of membrane-bound catechol-O-methyltransferase in cortical neurons: Implications for drug development. J. Biol. Chem. 286, 34752-34760.

6. Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Hillsdale, NJ: Lawrence Erlbaum Associates.

7. Fahndrich, E., Coper, H., Christ, W., Helmchen, H., Muller-Oerlinghausen, B., Pietzcker, A., 1980. Erythrocyte COMT-activity in patients with affective disorders. Acta Psychiatr. Scand. 61, 427-437.

8. Fritz, C.O., Morris, P.E., Richler, J.J., 2012. Effect size estimates: Current use, calculations, and interpretation. J. Exp. Psychol. Gen. 141, 2-18.

9. Griffiths, J., Ravindran, A.V., Merali, Z., Anisman, H., 2000. Dysthymia: A review of pharmacological and behavioral factors. Mol. Psychiatry 5, 242-261.

10. Hasler, G., Fromm, S., Carlson, P.J., Luckenbaugh, D.A., Waldeck, T., Geraci, M., Roiser, J.P., Neumeister, A., Meyers, N., Charney, D.S., Drevets, W.C., 2008. Neural response to catecholamine depletion in unmedicated subjects with major depressive disorder in remission and healthy subjects. Arch. Gen. Psychiatry 65, 521-531.

11. Hillman, C.H., Erickson, K.I., Kramer, A.F., 2008. Be smart, exercise your heart: Exercise effects on brain and cognition. Nat. Rev. Neurosci. 9, 58-65.

12. Hopkins, W.G., Marshall, S.W., Batterham, A.M., Hanin, J., 2009. Progressive statistics for studies in sports medicine and exercise science. Med. Sci. Sports Exerc. 41, 3-12.

13. Hosak, L., 2007. Role of the COMT gene Val158Met polymorphism in mental disorders: A review. Eur. Psychiatry 22, 276-281.

14. Hotting, K., Roder, B., 2013. Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci. Biobehav. Rev. 37, 2243-2257.

15. Kessler, R.C., 2003. Epidemiology of women and depression. J. Affect. Disord. 74, 5-13.

16. Kubesch, S., Bretschneider, V., Freudenmann, R., Weidenhammer, N., Lehmann, M., Spitzer, M., Grön, G., 2003. Aerobic endurance exercise improves executive functions in depressed patients. J. Clin. Psychiatry 9, 1005-1012.

17. Leckie, R.L., Weinstein, A.M., Hodzic, J.C., Erickson, K.I., 2012. Potential moderators of physical activity on brain health. J. Aging Res. 2012, 948981.

18. Lin, T.W., Kuo, Y.M., 2013. Exercise benefits brain function: The monoamine connection. Brain Sci. 3, 39-53.

19. Lokuge, S., Frey, B.N., Foster, J.A., Soares, C.N., Steiner, M., 2011. Depression in women: Windows of vulnerability and new insights into the link between estrogen and serotonin. J. Clin. Psychiatry 72, e1563-1569.

20. Mannisto, P.T., Kaakkola, S., 1999. Catechol-O-methyltransferase (COMT): Biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. Pharmacol. Rev. 51, 593-628.

21. Massat, I., Souery, D., Del-Favero, J., Nothen, M., Blackwood, D., Muir, W., Kaneva, R., Serretti, A., Lorenzi, C., Rietschel, M., Milanova, V., Papadimitriou, G.N., Dikeos, D., Van Broekhoven, C., Mendlewicz, J., 2005. Association between COMT (Val158Met) functional polymorphism and early onset in patients with major depressive disorder in a european multicenter genetic association study. Mol. Psychiatry 10, 598-605.

22. Opmeer, E.M., Kortekaas, R., van Tol, M.J., van der Wee, N.J., Woudstra, S., van Buchem, M.A., Penninx, B.W., Veltman, D.J., Aleman, A., 2013. Influence of COMT val158met genotype on the depressed brain during emotional processing and working memory. PLoS ONE 8, e73290.

23. Parker, G., Fletcher, K., Paterson, A., Anderson, J., Hong, M., 2014. Gender differences in depression severity and symptoms across depressive sub-types. J. Affect. Disord. 167, 351-357.

24. Pearson-Fuhrhop, K.M., Dunn, E.C., Mortero, S., Devan, W.J., Falcone, G.J., Lee, P., Holmes, A.J., Hollinshead, M.O., Roffman, J.L., Smoller, J.W., Rosand, J., Cramer, S.C., 2014. Dopamine genetic risk score predicts depressive symptoms in healthy adults and adults with depression. PLoS ONE 9, e93772.

25. Puzynski, S., Bidzinski, A., Mrozek, S., Zaluska, M., 1983. Studies on biogenic amine metabolizing enzymes (DBH, COMT, MAO) and pathogenesis of affective illness. II. Erythrocyte catechol-O-methyltransferase activity in endogenous depression. Acta Psychiatr. Scand. 67, 96-100.

26. Schultz, E., Nissinen, E., Kaakkola, S., 1989. Determination of catechol-O-methyltransferase activity in erythrocytes by high performance liquid chromatography with electrochemical detection. Biomed. Chromatogr. 3, 64-67.

27. Sengupta, S., Grizenko, N., Schmitz, N., Schwartz, G., Bellingham, J., Polotskaia, A., Stepanian, M.T., Goto, Y., Grace, A.A., Joober, R., 2008. COMT Val108/158Met polymorphism and the modulation of task-oriented behavior in children with ADHD. Neuropsychopharmacology 33, 3069-3077.

28. Souteiro, P., Vieira-Coelho, M.A., Serrao, M.P., Magina, S., 2013. Catechol-O-methyltransferase activity in psoriasis patients treated with psoralen plus ultraviolet A therapy. Photodermatol. Photoimmunol. Photomed. 29, 227-232.

29. Stroth, S., Reinhardt, R.K., Thone, J., Hille, K., Schneider, M., Hartel, S., Weidemann, W., Bos, K., Spitzer, M., 2010. Impact of aerobic exercise training on cognitive functions and affect associated to the COMT polymorphism in young adults. Neurobiol. Learn. Mem. 94, 364-372.

30. Sutoo, D., Akiyama, K., Yabe, K., 2001. Quantitative imaging of tyrosine hydroxylase and calmodulin in the human brain. J. Neurosci. Res. 63, 369-376.

31. Sutoo, D., Akiyama, K., Yabe, K., Kohno, K., 1991. Multiple analysis of tyrosine hydroxylase and calmodulin distributions in the forebrain of the rat using a microphotometry system. Brain Res. Bull. 26, 973-982.

32. Villanueva, R., 2013. Neurobiology of major depressive disorder. Neural Plast. 2013, 873278.

33. Volkow, N.D., Fowler, J.S., Gatley, S.J., Logan, J., Wang, G.J., Ding, Y.S., Dewey, S., 1996. PET evaluation of the dopamine system of the human brain. J. Nucl. Med. 37, 1242-1256.

STUDY 4

Monoamines and cortisol as potential mediators of the relationship between exercise and depressive symptoms

Monoamines and cortisol as potential mediators of the relationship between exercise and depressive symptoms

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Abstract

A randomized controlled trial was conducted to assess the effects of exercise plus pharmacotherapy on monoamine neurotransmitters (dopamine, noradrenaline, adrenaline, serotonin) and cortisol levels. A total of 26 women with clinical depression were randomly assigned to one of two groups: aerobic exercise plus pharmacotherapy or only pharmacotherapy. The exercise program consisted of aerobic exercise, 45-50 min/session, three times/week, for 16 weeks.

The biological parameters were measured before and after the exercise program. Adding exercise to pharmacotherapy had no additional effects on monoamines and cortisol plasma levels. These data are preliminary outcomes from a small sample and should be replicated.

Keywords: Depression, Women, Aerobic Exercise, Catecholamines, Cortisol.

1. Introduction

The contribution of exercise as an efficacious component of treatment for various mental disorders has been increasingly recognized (Rosenbaum et al., 2016). Indeed, a high number of intervention studies have been conducted, which analyzed several factors that might moderate the antidepressant effect of exercise on depression (Helmich et al., 2010). However, there are no consistent conclusions about the underlying neurobiological explanation to the antidepressant effect of exercise in subjects with major depressive disorder (Schuch et al., 2015). Accordingly, the efficacy of exercise in depressive disorder is attributed to physiological changes in monoamine metabolism (Stenman and Lija, 2013), hypothalamic–pituitary–adrenal (HPA) axis function (Sousa e Silva et al., 2010), neurotrophic factors (Szuhany et al., 2015), neuroinflammation (Kohut et al., 1957), and endocannabinoid system (Heyman et al., 2012). It is important to bear in mind that typical antidepressant medication for depression acutely blocks the reuptake or breakdown of the monoamines 5-hydroxytryptamine (5-HT or serotonin) and noradrenaline (NA), with 5-HT selective reuptake inhibitors (SSRIs) (Duman and Voleti, 2012) representing the highest prescribed medication for depression. Nonetheless, depressive disorder is a multifactorial disease with changes in several biomarkers, which does not involve only monoamines (Palhagen et al., 2010). Moreover, the cause of depression is far from being a simple deficiency of central monoamines (Krishnan and Nestler, 2008). This also explains why treatment with existing antidepressant drugs, most of which target monoamines, frequently does not show therapeutic response, or instead, shows only a partial response (Nemeroff, 2007). Several systematic reviews described the influence of exercise on the serotonergic system (Meeusen and De Meirleir, 1995; Meeusen et al., 2001) and in the HPA axis function (Schuch et al., 2015; Wegner et al., 2014), and had proposed that exercise might improve the efficiency of the monoamine system response and normalize HPA axis in depressive patients (Meeusen, 2005).

In order to identify possible biological mechanisms that might contribute to produce exercise effects on depressive disorder, we hypothesized that the exercise group (EG) would have a significant increase on monoamine levels (dopamine, DA; NA; adrenaline, AD; 5-HT) and a decrease in cortisol levels in comparison to the control group (CG). This is the first study developed in women with depressive disorder, which analyzed the influence of chronic exercise on monoamine responses and cortisol plasma levels.

2. Methods

2.1 Trial design

The **HAPPY BRAIN** trial was a two-armed randomized control trial (RCT) and a detailed description of the study has been previously published (Carneiro et al., 2015). Randomization was implemented with sequentially numbered opaque, sealed envelopes. Patients had clinical depression according to ICD-10 (International Classification of Diseases, 10th revision), diagnostic criteria (F32.1, F33.1, F34.1), and were diagnosed by psychiatrists. The sample was composed of 19 sedentary women, aged 18-65 years.

The patients, physical training teacher, general practitioners, psychiatrists or researchers were not blinded regarding treatment allocation, except for the laboratory, which analyzed the blood samples.

The protocol respected the Declaration of Helsinki, and was accepted by the Ethics Committee of Centro Hospitalar de São João with reference number 112/13 (March 11, 2013).

2.2 Exercise training protocol

Nine patients in the EG performed aerobic exercise, 45-50 min/session, three times/week, for 16 weeks. All sessions started with a ten-minute low-intensity warm-up, followed by 30 min of aerobics and 5 min of low-intensity cooling down. The aerobic exercise involved traditional games, indoor/outdoor natural circuit workouts with resistance bands, jump ropes, fitness balls, brisk walking, and dancing. The target heart rate zone was calculated according to Karvonen (1957). Exercise intensity was controlled with a heart rate monitor (Polar FT1, Finland). Average intensity for the 16 weeks was 72% of the maximum heart rate. The Rating of Perceived Exertion Scale (RPE) (Borg, 1974) was used to assess training intensity at a moderate level (RPE=12-13).

2.3 Control group

The CG involved ten patients who carried on with their usual pharmacological therapy but did not exercise.

3. Outcome measures

All patients were assessed to blood analysis at baseline and at the end of the exercise intervention.

Table 1 – Outcome measure scores at baseline and 16 weeks, with differences (p-value) and effect size (η^2p) for the differences.

	Exercise (N=9)	Control (N=10)	Time x Group	
Catecholamine´s			*p*-value	η^2p
Dopamine, ng/mL				
Baseline	15.82±5.75	20.29±5.55	0.028	0.254
16 weeks	15.03±6.14	13.29±2.28		
Noradrenaline, pg/mL				
Baseline	253.66±95.26	260.54±135.56	0.536	0.023
16 weeks	394.75±127.85	364.89±147.18		
Adrenaline, pg/dL				
Baseline	15.51±24.27	23.27±7.95	0.347	0.052
16 weeks	19.18±11.36	23.46±9.49		
Serotonin, ng/mL				
Baseline	17.04±13.52	38.83±37.90	0.252	0.076
16 weeks	12.32±8.86	51.32±31.53		
Cortisol, µg/dL				
Baseline	15.11±3.95	11.90±6.38	0.207	0.092
16 weeks	10.22±3.60	10.20±4.89		

3.1 Blood analyses

3.1.1 Blood Sampling and Preparation

Peripheral levels of monoamines were assessed at baseline and after the exercise intervention. The length of time between the last exercise session and the laboratory staff performing the blood analyses was approximately 18 hours post training. Blood samples were taken in tubes with a stabilization solution prepared exactly according to the Instruction Manual for the HPLC analysis of catecholamines in plasma from Chromsystems (Grafelfing, Germany).

3.1.2 Monoamines and cortisol quantification in plasma

Samples were prepared using the Reagent kit 5000 catecholamines in plasma, for HPLC analysis, from Chromsystems (Grafelfing, Germany).

Cortisol in plasma was measured using the chemiluminescent ADVIA Centaur Cortisol immunoassay. Measurements were performed in an ADVIA Centaur XP Immunoassay System (Siemens, Germany).

3.2 Statistical Analysis

Results were expressed by descriptive statistics (mean and standard deviation). All dependent variables were tested for normality according to the Shapiro-Wilks method before performing analyses. Potential group differences in baseline measures were evaluated by independent sample t-tests for all variables. Repeated measures ANOVA with assumed sphericity were used to analyze the time x treatment interactions for all outcome variables at baseline and 16 weeks. We analyzed data with IBM SPSS statistics software (version 21.0). A p-value of less than 0.05 was taken as significant. The effect size partial eta-squared (η^2p) was computed and reported for repeated measures ANOVA, which was provided with statistical software packages SPSS. Cohen (1988) provides benchmarks to define small (η^2=0.01), medium (η^2= 0.06), and large (η^2= 0.14) effects.

4. Results

4.1 Pre-exercise monoamines and cortisol blood plasma levels

The mean and standard deviation plasma levels of hormones measured at baseline in the EG and CG were 15.82±5.75 and 20.29±5.55 pg/mL for DA, 253.66±95.26 and 260.54±135.56 pg/mL for NA, 15.51±3.98 and 23.27±7.95 pg/dL for AD, 17.04±13.52 and 38.83±37.90 ng/mL for 5-HT, and 15.11±3.95 and 11.90±6.38 µg/dL for cortisol. Comparisons between groups, revealed no significant differences with respect to DA, NA, AD, 5-HT and cortisol.

4.2 Monoamines and cortisol blood plasma levels in response to exercise

Regarding DA, the response to exercise was statistically significant in the EG compared to the CG in the interaction between time X group. Observed F value was statistically significant in the DA variable in relation to the interaction ($F(1,17)=5.789$, $p=0.028$, $\eta^2p=0.254$). Likewise, the NA response to chronic exercise has not differed significantly ($F(1,17)=0.400$, $p=0.536$, $\eta^2p=0.023$) when considering the interaction between time X group. Furthermore, the AD response to exercise did not differ significantly in the interaction between time X group ($F(1,17)= 0.934$, $p=0.347$, $\eta^2p=0.052$). Moreover, the 5-HT response to exercise has not differed significantly in the interaction between time X group ($F(1,17)= 1.407$, $p=0.252$, $\eta^2p=0.076$) (Figure 1). The cortisol response to exercise did not differ when we observed the interaction between time X group ($F(1,17)=1.724$, $p=0.207$, $\eta^2p=0.092$) (Figure 2).

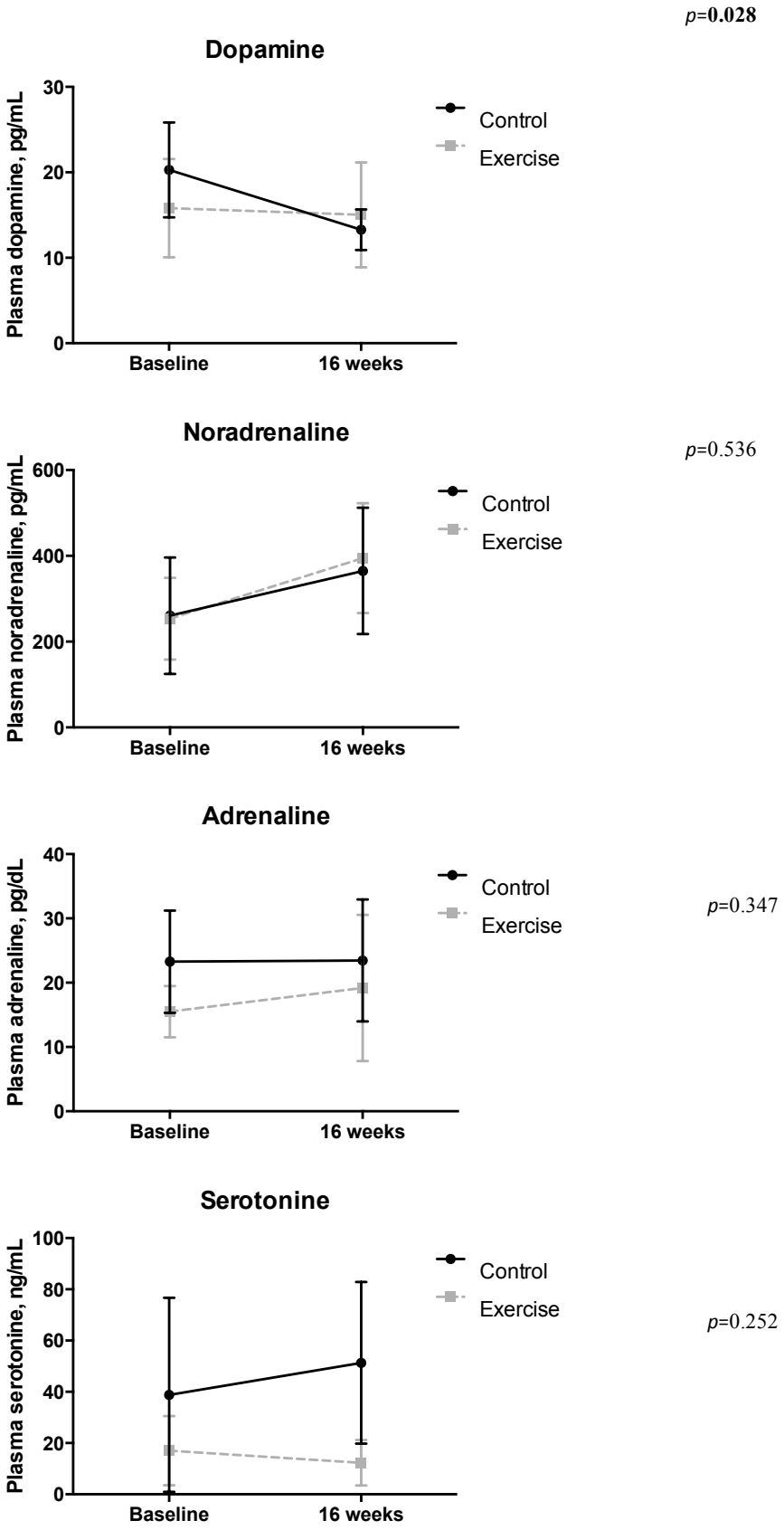

Figure 1 – Catecholamines response to aerobic exercise in depressed patients and controls. Baseline refers to mean basal value of plasma catecholamines assessed before exercise, 16 weeks refers to mean plasma catecholamines value assessed after 16 weeks of exercise.

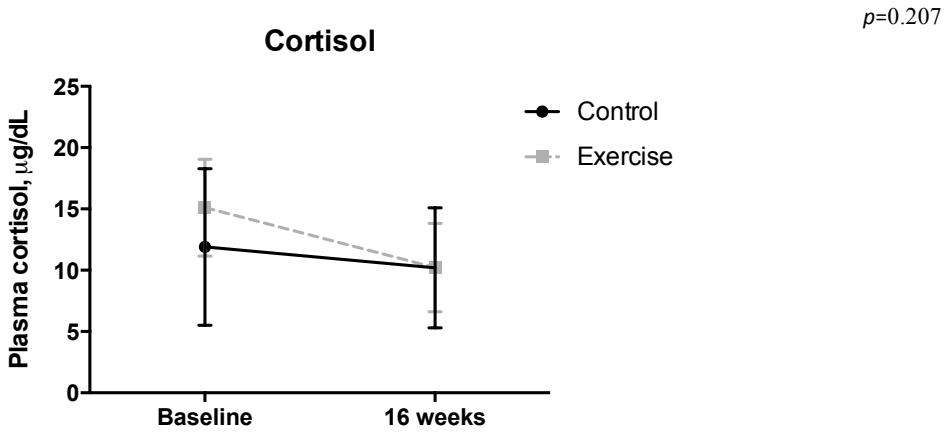

Figure 2 – Cortisol response to aerobic exercise in depressed patients and controls. Baseline refers to mean basal value of plasma cortisol assessed before exercise, 16 weeks refers to mean plasma catecholamines value assessed after 16 weeks of exercise.

5. Discussion

This RCT was conducted in conjunction with the **HAPPY BRAIN** study (Carneiro et al., 2015), which has shown that aerobic exercise training was an adjuvant therapy for treating women who suffered from depression, as it reduced the severity of depressive symptomatology and improved physical fitness.

However, in this study the comparison of plasma hormone concentration of monoamines (DA, NA, AD, and 5-HT) and cortisol at baseline and after 16 weeks between groups revealed statistically significant differences between groups over time with a large effect size in DA levels. Yet, changes were different from our expectations. Indeed, while the EG showed a weak decrease in DA levels, the CG showed a greater decrease. These results might be explained by changes in NA and AD synthesis. In fact, the synthesis of NA and AD depends directly on the activity of its rate-limiting enzyme, dopamine-b-hydroxylase (converts DA into NA) and phenylethanolamine-N methyltransferase (converts NA into AD). Regarding that DA is the precursor of NA, and that NA levels increased in both groups, it could be speculated that the weak decrease in plasma DA levels in the EG could be explained by an increase in NA and AD levels. Nonetheless, we do not have sufficient data to reach this conclusion.

In relation to 5-HT plasma levels, the results have shown a decrease in the EG, which seems contradictory to the hypothesis that exercise would be beneficial for depressive symptoms through an increase of 5-HT plasma levels. Researches involving animal and human beings suggested that the antidepressant effect of exercise is attributable to an

increase of 5-HT (Dey et al., 1992; Lee et al., 2013; Melancon et al., 2014). These results contradict our findings, and should be interpreted with caution. According to the literature, chronic exercise leads to a reduction in serum cortisol levels (Corazza et al., 2014), which is similar to the trend observed in our study.

The strength of this study is the sample randomization. Furthermore, all biomarkers were measured in plasma, which increased generalizability and comparability across studies.

The major limitations are the small sample size; patients´ large age range (18–65 years), which could contribute to a greater result variability; the inclusion of patients diagnosed with different subtypes of depressive pathology, and the presence of other sicknesses (arterial hypertension and hyperthyroidism) that can interfere with catecholamine responses.

6. Conclusion

This RCT does not provide evidence for a biologically mediated effect of exercise in women with depressive disorder. The lack of response to exercise could be related to the moderate intensity or training level. Indeed, it can be hypothesized that exercise may potentially have a differential effect depending on exercise characteristics, training status and gender.

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Conflict of interest

All authors report no conflict of interest.

Author contributions

Author Lara S. F. Carneiro carried out the literature search and statistical analysis, wrote the first draft of the manuscript under the supervision of authors Professor José Vasconcelos-Raposo and Professor Maria Paula Mota. Author Professor Maria Augusta

Vieira-Coelho conducted the clinical assessment of screened patients and coordinated sample, processed and prepared it for analysis. Author Professor Rita C. Alves wrote the performed experiments. Author Professor António Manuel Fonseca provided the manuscript critical input. All authors contributed and approved the final manuscript.

References

1. Borg, G.A., 1974. Perceived exertion. Exerc. Sport Sci. Rev. 2, 131-153.

2. Carneiro, L.S., Fonseca, A.M., Vieira-Coelho, M.A., Mota, M.P., Vasconcelos-Raposo, J., 2015. Effects of structured exercise and pharmacotherapy vs. pharmacotherapy for adults with depressive symptoms: A randomized clinical trial. J. Psychiatr. Res. 71, 48-55.

3. Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Hillsdale, NJ: Lawrence Erlbaum Associates.

4. Corazza, D.I., Sebastiao, E., Pedroso, R.V., Andreatto, C.A.A., Coelho, F.G.D., Gobbi, S., Teodorov, E., Santos-Galduroz, R.F., 2014. Influence of chronic exercise on serum cortisol levels in older adults. Eur. Rev. Aging Phys. A. 11, 25-34.

5. Dey, S., Singh, R.H., Dey, P.K., 1992. Exercise training: Significance of regional alterations in serotonin metabolism of rat brain in relation to antidepressant effect of exercise. Physiol. Behav. 52, 1095-1099.

6. Duman, R.S., Voleti, B., 2012. Signaling pathways underlying the pathophysiology and treatment of depression: Novel mechanisms for rapid-acting agents. Trends Neurosci. 35, 47-56.

7. Helmich, I., Latini, A., Sigwalt, A., Carta, M.G., Machado, S., Velasques, B., Ribeiro, P., Budde, H., 2010. Neurobiological alterations induced by exercise and their impact on depressive disorders. Clin. Pract. Epidemiol. Ment. Health 6,115-125.

8. Heyman, E., Gamelin, F.X., Goekint, M., Piscitelli, F., Roelands, B., Leclair, E., Di Marzo, V., Meeusen, R., 2012. Intense exercise increases circulating endocannabinoid and bdnf levels in humans—possible implications for reward and depression. Psychoneuroendocrino. 37, 844-851.

9. Karvonen, M.J., Kentala, E., Mustala, O., 1957. The effects of training on heart rate; a longitudinal study. Ann. Med. Exp. Biol. Fen. 35, 307-315.

10. Kohut, M.L., McCann, D.A., Russell, D.W., Konopka, D.N., Cunnick, J.E., Franke, W.D., Castillo, M.C., Reighard, A.E., Vanderah, E., 2006. Aerobic exercise, but not flexibility/resistance exercise, reduces serum il-18, crp, and il-6 independent of beta-blockers, bmi, and psychosocial factors in older adults. Brain. Behav. Immun. 20, 201-209.

11. Krishnan, V., Nestler, E.J., 2008. The molecular neurobiology of depression. Nature 455, 894-902.

12. Lee, H., Ohno, M., Ohta, S., Mikami, T., 2013. Regular moderate or intense exercise prevents depression-like behavior without change of hippocampal tryptophan content in chronically tryptophan-deficient and stressed mice. PLoS ONE 8,e66996.

13. Meeusen, R., 2005. Exercise and the brain: Insight in new therapeutic modalities. Ann. Transplant. 10, 49-51.

14. Meeusen, R., De Meirleir, K., 1995. Exercise and brain neurotransmission. Sports Med. 20, 160-188.

15. Meeusen, R., Piacentini, M.F., De Meirleir, K., 2001. Brain microdialysis in exercise research. Sports Med. 31, 965-983.

16. Melancon, M.O., Lorrain, D., Dionne, I.J., 2014. Changes in markers of brain serotonin activity in response to chronic exercise in senior men. Appl. Physiol. Nutr. Me. 39,1250-1256.

17. Nemeroff, C.B., 2007. Prevalence and management of treatment-resistant depression. J. Clin. Psychiatry 68 Suppl. 8,17-25.

18. Pålhagen, S., Qi, H., Mårtensson, B., Wålinder, J., Granérus, A.-K., Svenningsson, P., 2010. Monoamines, BDNF, IL-6 and corticosterone in CSF in patients with parkinson's disease and major depression. J. Neurol. 257, 524-532.

19. Rosenbaum, S., Tiedemann, A., Stanton, R., Parker, A., Waterreus, A., Curtis, J., Ward, P.B., 2016. Implementing evidence-based physical activity interventions for people with mental illness: An Australian perspective. Australas Psychiatry 24, 49-54.

20. Schuch, F.B., Deslandes, A.C., Stubbs, B., Gosmann, N.P., Silva, C.T., Fleck, M.P., 2015. Neurobiological effects of exercise on major depressive disorder: A systematic review. Neurosci. Biobehav. R. 61,1-11.

21. Sousa e Silva, T., Longui, C.A., Rocha, M.N., Faria, C.D.C., Melo, M.R., Faria, T.G., de Souza, J.A., Rizzo, L.V., 2010. Prolonged physical training decreases mRNA levels of glucocorticoid receptor and inflammatory genes. Horm. Res. Paediatr. 74, 6-14.

22. Stenman, E., Lilja, A., 2013. Increased monoaminergic neurotransmission improves compliance with physical activity recommendations in depressed patients with fatigue. Med. Hypotheses 80, 47-49.

23. Szuhany, K.L., Bugatti, M., Otto, M.W., 2015. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. J. Psychiatr. Res. 60, 56-64.

24. Wegner, M., Helmich, I., Machado, S., Nardi, A.E., Arias-Carrion, O., Budde, H., 2014. Effects of exercise on anxiety and depression disorders: Review of meta-analyses and neurobiological mechanisms. CNS Neurol. Disord. Drug Targets 13, 1002.

GENERAL DISCUSSION

The general purpose of this doctoral thesis was to analyze the efficacy of exercise, as a complementary therapy, on physiological and psychological parameters in patients with depressive disorder. Due to the fact that the research questions and respective results have already been extensively reported in different studies, only a brief summary is provided here. Furthermore, we provided suggestions for future research in this area of enquiry.

Patients with clinical depression, including those with MDD and sub-threshold depression, experience a markedly increased premature mortality in comparison to the general population (Cuijpers et al., 2014). It is not yet clear the precise causes of the increased mortality rates (Cuijpers et al., 2013), however, there is evidence that part of the mortality can be explained due to increased prevalence of metabolic diseases (Berge et al., 2013), and by unhealthy behaviors including physical inactivity (Becofsky et al., 2015). Considerable growing corpus of evidence supports the efficacy of exercise as an antidepressant treatment (Schuch et al., 2016b), and a recent meta-analysis demonstrated that exercise significantly improves physical and psychological domains and overall quality of life (Schuch et al., 2016c).

A critical review (Knapen et al., 2014) that analyzed four meta-analyses on effects of exercise as intervention for depression reported that exercise may be comparable to antidepressant medication and psychotherapy for patients with mild to moderate depression. Nevertheless, it seems to be a more realistic approach as an adjuvant treatment for severe depression.

Evidence from RCTs that assessed the efficacy of exercise has been accumulating for years and has led to published exercise guidelines from the National Institute for Health & Clinical Excellence (NICE, 2009) and APA (2010). Nonetheless, these guidelines remain general, and a more comprehensive set of exercise guidelines should be developed. In accordance with this, NICE (2009) define physical activity guidelines for depressive patients, and recommend aerobic exercise 3 times weekly, 45-60 min over 10-14 weeks (average 12 weeks). However, they do not include any considerations in relation to intensity guidelines. As well, the current guidelines of APA (2010) report that patients, suffering from depression of any severity and not having any medical contraindication in relation to exercise, should include physical activity as it is a reasonable addition to a treatment plan for MDD. Nevertheless, it does not specify a dose-response.

In recent years increasing publications have addressed new recommendations with the aim to specify guidelines in order to help clinical professionals (Nystrom et al., 2015; Perraton et al., 2010; Stanton and Reaburn, 2013).

Although the interest in physical activity for persons with depression is growing, and the methodological quality presented in RCTs has improved over the last 30 years (Schuch

et al., 2016b), there are still methodological flaws presented in RCTs and included in systematic reviews, which affect conclusions and limit practical recommendations (Nystrom et al., 2015).

Given this uncertainty, study 1 was designed to provide recommendations for clinical and daily practice in order to optimize outcome. Thus, a systematic review was carried out with an objective to clarify the optimal dose-response when prescribing exercise for patients with depression. Our secondary aim was to explore moderators of the antidepressant effects of exercise (physical fitness levels, aerobic capacity, and placebo effects) that could identify why and how treatments have effect (Kraemer et al., 2002).

The results presented in study 1, demonstrated that when we looked carefully at the information on physical activity prescribed, there is variability in protocols. The data confirm recent systematic reviews of RCTs (Perraton et al., 2010; Stanton and Reaburn, 2013) that suggest aerobic exercise, for at least a nine-week period with a minimum of three times weekly, 30-45 minutes/session, being beneficial. Interestingly, the intensity of exercise has been subjected to considerable research and debate, and identifying an optimal intensity is not yet possible according to the authors' viewpoint. Although previous research has documented that moderate intensity (60%–80% of maximum heart rate) or self-selected (preferred) intensity (Perraton et al., 2010; Stanton and Reaburn, 2013) result in beneficial outcomes on depressive symptoms, our results show lack of rigor and variety among RCTs in prescribed and monitored intensity. Therefore, a suitable intensity is missing as well as studies comparing different doses of exercise.

In this sense, our results corroborated the Cochrane Review (Rimer et al., 2012), which reported methodological differences between studies and lack of sufficient ones reporting exercise intensity parameters. Clearly, a priority should be to develop robust well-designed interventions that minimize heterogeneity among RCTs and complete reporting data, particularly in relation to intensity. This and other methodological weaknesses of RCTs included in systematic reviews limit conclusions and pose many challenges. Indeed, it remains still difficult to compare and analyze experimental studies due to several factors, including: the heterogeneity of exercise interventions and control groups; the absence of information in relation to the remission or clinical response; the variety in reported results (differences between groups or within groups) and; small sample size.

Thus, it is time to be pragmatic and move the field forward in quality research. Indeed, in spite of physical activity being recommended in clinical practice guidelines, the implementation as an option for the treatment of depression by physicians remains a challenge, and the argument is that the evidence supporting research is insufficient (Ekkekakis, 2015). One potential factor that could explain that the implementation of

recommendations into clinical practice is challenging, is related with the necessity to decide the best approach, based on psychiatric symptoms, previous physical activity history, the sub-types of depression and, the side effects of psychotropic medication (Stubbs et al., 2014). Thus, professionals with expertise in exercise prescription and knowledge of psychopathology are urgently required (Vancampfort et al., 2015b).

It should be noted that an extensive range of mediators could potentially interfere with the response or remission rates of patients, and the potential moderators of the antidepressant effects of exercise remain largely unknown (Schuch et al., 2016a). As reported previously, our secondary aim was to explore RCTs in relation to physical fitness levels, aerobic capacity, and placebo effects. However, given the differences in research design, it was difficult to generalize results. First of all, there are studies that only measure physical fitness levels and aerobic capacity at baseline, which makes the assessment of exercise efficacy unfeasible. Secondly, data analysis must be based preferably on differences between and within groups. Several times only one measure was included in the data-analysis. Thirdly, an important flaw was the physical fitness assessment with a self-report questionnaire, a method that is prone to systematic and random errors (Soundy et al., 2007). Lastly, to get a better understanding of the importance of physical activity it is cardinal to analyze if the improvements in physical fitness levels and aerobic capacity are correlated with changes in depressive symptoms. Studying these associations is one more step for developing efficient strategies, advancing our knowledge on the antidepressant impact of exercise, and avoiding misleading conclusions.

A common tendency in RCTs that investigate the effects of exercise as a therapeutic strategy for managing depressive symptoms is to compare an exercise intervention with control groups that engage in some type of physical activity (Schuch et al., 2016b). However, sometimes the exercise intervention group is compared with a placebo group, which comprises some form of physical activity (e.g. stretching). Indeed, this is not surprising and our results presented in study 1 showed that it is common practice to include placebo control groups including low frequency, stretching, flexibility, and exercise advice.

Recently one meta-analysis emphasized the necessity to quantify the magnitude of the placebo group effect in psychological outcomes and compare it with the effect of exercise intervention (Lindheimer et al., 2015). This study demonstrated that in the general population the placebo response for psychological outcomes in exercise RCTs exhibited a mean effect size of 0.20 (95 % CI 0.02–0.41). Our review findings indicated that frequently the results do not evidence differences between groups, albeit most often exhibit differences pre-post intervention. Additionally, a recent meta-analysis reported that control groups used in exercise RCTs provide large improvements in depressive symptoms (Stubbs et al., 2016b).

A number of limitations make any strong conclusions difficult. First of all, there were often missing data in the RCTs and the heterogeneity of methodologies make it difficult to draw firm conclusions (e.g. outcome measures, age ranges, sample sizes, statistical data analyses). Secondly, it is not possible to reach a conclusion in relation to the effectiveness of exercise in long-term. Moreover, participants, who were not limited to only individuals with clinical depression diagnosed by a trained health worker in a clinical setting, were included.

As reported previously, despite an exponential increase in the number of research papers in the last years, there is still a significant lack of well-designed intervention protocols. In order to analyze the effects of a 16-week planned supervised aerobic program on a clinical sample composed of women (n=19) with three subtypes of depression (F32.1, F33.1, F34.1), we performed an RCT (study 2).

We carried out an RCT to measure the efficacy of exercise as an adjunctive treatment to antidepressant drug therapy. Results demonstrated that exercise, as a complementary therapy, was effective in reducing depressive symptomatology (at the end of the trial, the treatment group displayed lower BDI rates compared to the control group). The results are in line with previous studies (Mota-Pereira et al., 2011; Pilu et al., 2007; Schuch et al., 2011) in which exercise as adjunctive with antidepressants was compared to pharmacotherapy alone. For example, the study of Mota-Pereira and colleagues demonstrated that while in the control group, none of the subjects exhibited clinical response or remission, in the intervention group there was a 21% rate of clinical response and 26% rate of remission.

Regarding the domains of anxiety and stress sub-scales (assessed by DASS-21), a significant reduction was found that indicated an anxiolytic effect of exercise. However, the depression sub-scale did not significantly differ between patients in the exercise and control groups. Nevertheless, despite the lack of statistical significance, the observed large effect size reported was clinically relevant.

Additionally, anthropometric parameters only presented significant difference between groups in fat mass percentage, with a significant decrease in the exercise group. Moreover, no differences were found in weight, body mass index, and waist circumference. The study of Becofsky et al. (2015) demonstrated that low fitness is more strongly linked with the onset of elevated depressive symptoms in comparison with body fatness. Our results corroborated one recent meta-analysis of exercise in individuals with schizophrenia, which demonstrated that improvements in symptoms occur in response to an exercise program, independent of changes in body weight and body mass index (Firth et al., 2015).

The **HAPPY BRAIN** study has attempted to provide a better understanding of the psychological implications of exercise for patients with depression.

The Rosenberg Self-Esteem Scale was used for evaluating the psychiatric patients' level of self-esteem. This scale has been used with adults too, even though it was developed as an instrument for adolescents (Babore et al., 2016).

According to one study (Rizwan and Ahmad, 2015) that compared self-esteem among psychiatric patients (including MDD) and normal controls, deficits in self-esteem in psychiatric subjects are determined by many factors. In this line, they do not trust themselves, and view themselves as awful people who are poor in all aspects of life when compared with normal controls. Secondly, they present dysfunctional social behavior, including more frequent negative social interactions. Another reason for the low level of self-esteem could be the role of stigmatization; they are frequently criticized by society, which exacerbates the feelings of inadequacy and inferiority. Among other factors, educational level, income and employment status have been reported as mediators of self-esteem on psychiatric patients (Salsali and Silverstone, 2003).

In the general population it has been reported in the literature enhancement in self-esteem through exercise. Unfortunately, research in this scope in patients with depression is scarce and has remained incapable of addressing how or why the change in depressive symptoms may occur mediated by changes in self-esteem. Past research suggested that physical self-esteem and increased physical self-perceptions may be mediating exercise-induced antidepressant effects (Legrand, 2014). The Exercise and Self-Esteem Model (EXSEM) is typically used to explain the relationships among physical activity, self-perceptions, and self-esteem (Sonstroem and Morgan, 1989). In this model, changes in physical condition, sports competence, physical strength and body attractiveness are proposed to have indirect effects on changes in global self-esteem.

In the **HAPPY BRAIN** trial we hypothesized that there would be a significant difference in the level of self-esteem among patients in exercise and control groups.

Considering self-esteem results, no differences were found between both groups. However, within groups, the analysis showed that the exercise group presented slight improvement in self-esteem. Taking into account the EXSEM model, it might therefore be expected improvement in depressive symptoms due to significant changes in physical condition on exercise group being verified. However, considering that body attractiveness is one factor that mediates this relationship, the absence of results in the anthropometric parameters could explain the lack of increase in self-esteem. The results could also be explained by the fact that the degree of low self-esteem in the psychiatric disorder varies according to the diagnostic (Silverstone and Salsali, 2003). Remarkably, the sample was composed mostly of patients with dysthymic disorder, and confirms the results of the study

by Silverstone and Salsali (2003), which demonstrated that patients with dysthymia have lower self-esteem.

One of the greatest challenges in this field has been overcoming barriers to engage in physical activity with the aim to optimize compliance and decrease dropouts from RCTs, which pose threat to the validity of the evidence (Stubbs et al., 2016a).

In the **HAPPY BRAIN study,** 82% of treatment fidelity during four months was observed. Motivational strategies with the aim to assure high levels of compliance to exercise were defined due to compliance being a predictor of the physical activity response. However, the implementation of motivational strategies can create a bias. The focusing on what is truly important helps to prioritize the goals. Physical activity programs designed for therapeutic purposes should go beyond mere exercise. Implicit or explicit symbolic elements are always present, particularly when the program is based on group sessions in order to achieve a common sense of group community.

Despite the fact that this trial has reached significant findings, some limitations should be addressed. First of all, the main limitation was the small sample size. Secondly, the sample included different sub-types of depression, which comprise heterogeneity and severity of symptoms, and the duration of illness. Therefore, for a better understanding of a causal relationship, it is important to differentiate between subtypes of depression. Thirdly, the clinical response and remission rate were not reported, and they are targets for successful management of depression (Riedel et al., 2010). Response is defined as 50% reduction in depressive symptoms between baseline and post-intervention assessed by severity rating scales (Möller, 2008). Remission is the goal of treatment that comprises complete resolution of depressive symptoms and restores mental and physical functioning (Trivedi, 2009). Remission is defined by a cut-off score on a rating scale for depressive symptoms in clinical studies.

Additionally, the lack of intention-to-treat analyses is known to often lead to overestimation of treatment effects. Lastly, this study had only a short-term period and did not comprise a follow-up period. Consequently, it is premature to draw conclusions on the long-term effectiveness of exercise.

One of the most important challenges in physical activity research in subjects with depression is to understand the physiological underpinning mechanisms that mediate this relationship. Despite the growing number of publications in this field in the last 10 years, the precise molecular and neurobiological mechanisms are not yet clear (Schuch et al., 2015). Study 3 provides a key contribution to understand the pathways to explain the antidepressant effects of exercise. Numerous theories have been advanced, with one original hypothesis being attributed to “chemical imbalance in the brain” (Schildkraut, 1965). The classical

monoamine deficiency hypothesis of depression theorized that levels of monoamines, including 5-HT, NA, and DA are generally low in the central nervous system (Hasler, 2010). Despite the classical theory mainly focusing on 5-HT and NA, there is growing interest in the role of DA (Nutt, 2006) due to the fact that it plays a role in anhedonia (the absolute or relative inability to experience pleasure) (Mitani et al., 2006), which is one symptom required for the diagnosis of MDD. Additionally, DA neurotransmission in the prefrontal cortex plays a crucial role in regulating motivation, psychomotor speed, concentration, which are disrupted in depressive patients (Dunlop and Nemeroff, 2007).

One of the key modulators of DA synaptic concentration in the prefrontal cortex is the enzyme COMT (Sengupta et al., 2008). However, evaluated central DA levels in humans are challenging since DA cannot cross the blood–brain-barrier (Volkow et al., 1996). Therefore COMT could be used as an indicator of central DA availability. Analyzing COMT activity would be interesting because depressed humans report higher COMT activity expression in the human brain in contrast to healthy control subjects (Puzynski et al., 1983).

Multidisciplinary literature has documented the beneficial influence of physical activity engendered through aerobic exercise on cognitive function, which might be partially mediated by its effects on DA (Leckie et al., 2012). However, the mechanisms underpinning cognitive improvement linked with increase in physical activity in humans are far from being clarified (Stroth et al., 2010). In fact, many of the recent discoveries have been in animal models, and translating them to humans poses many challenges. For example, researches done directly on brain are possible in animals, but it is unfeasible to do them in subjects without causing neurological damage (Toups and Trivedi, 2012), as well as symptoms like guilt and suicide are impossible to reproduce in animal models (Krishnan and Nestler, 2008).

Furthermore, the majority of studies include acute exercise responses that occur during or immediately after the exercise bout. Schuch et al. (2015) recommended that acute and chronic responses should be considered independently as they seem to result in opposite outcomes.

To the best of the authors' knowledge, the only study that assessed the effect of aerobic exercise (treadmill running) on human brain dopaminergic transmission indicated that there were no significant changes in synaptic DA concentration (Wang et al., 2000). Nonetheless, authors argued that it is likely that the failure to detect an effect could also be linked with the fact that the subjects were physically fit, influencing the activity of their striatal DA system. Additionally, the subjects ran vigorously on the treadmill for 30 min, suggesting that this level of exercise does not lead to changes in striatal DA release.

The identification of reliable mediators will open up new pathways and directions in understanding exercise as a therapeutic intervention. Thus, Sutoo and Akiyama (1996)

advanced one mechanism that leads to enhance brain DA synthesis. The up-regulation of DA has been connected to exercise, inducing higher levels of serum calcium that is transported to the brain via blood (Lin and Kuo, 2013). In the brain, calcium ions activate tyrosine hydroxylase (the rate-limiting enzyme for catecholamine synthesis) through a calmodulin-dependent system (Sutoo et al., 1991).

In this sense, the author's aim was to assess the effects of adding exercise to antidepressant medication on S-COMT activity of depressed patients in study 3. The sample included patients diagnosed with F33.1 (recurrent depressive disorder, moderate current episode), and F34.1 (dysthymia). Patients performed aerobic exercise lasting between 45-50 min/session, three times per week for 16 weeks, and erythrocyte soluble COMT were assessed pre-post intervention.

Our findings offer evidence that adding exercise to the pharmacological treatment significantly decreases the S-COMT activity, which is an enzyme that inactivates DA. Consequently, if exercise decreases the S-COMT activity, it is possible that it leads to an increase in DA availability levels, which are low in depressive patients. This is a preliminary study and recognizing the mechanisms of interaction that lead to these changes, requires clarification. Additionally, these data should be very carefully interpreted due to the fact that we only assessed the S-COMT activity and the membrane bound form (MB-COMT) enzyme activity was not evaluated. Another limitation is that the study featured a small sample size (n=14). Despite limitations, within this study these results offer a preliminary contribution to understand exercise as a potential mediator factor on the monoamine system.

Given the uncertainty with regard to the biological mechanisms underlying the antidepressant effects of exercise in depression in study 4, we analyzed whether monoamines (DA, AD, NA and 5-HT) and cortisol would be potential mediators of the relationship between exercise and depressive symptoms. Considering the origin of the noradrenergic, serotonergic, and dopaminergic neurons in the brain and their projections, it is clear that monoaminergic systems are responsible for several behavioral symptoms including mood, vigilance, motivation, fatigue, psychomotor agitation, retardation (Brigitta, 2002; Hasler, 2010). Additionally, depression is often described as a stress-related disorder (Helmich et al., 2010) and an extensive literature has documented that depressed patients consistently exhibit hyperactivity of the HPA axis, which results in increased levels of the glucocorticoid hormone cortisol in these patients (Anacker et al., 2011). Consequently, understanding the mode of action of chronic exercise on monoaminergic neurotransmitters can improve their utilization as adjuvant therapy in combination with other compounds.

Studies conducted on animals and humans showed that acute exercise results in a release of brain monoamines including NA, DA and 5-HT (Meeusen and De Meirleir, 1995).

Furthermore, studies have shown that acute exercise leads to the activation of the HPA axis resulting in increases in plasma cortisol (Gispen-de Wied et al., 2000; van der Pompe et al., 1999).

Nevertheless, it is unclear what impact exercise may have on these hormones in the long-term (lasting weeks or months) because it has received little attention. To the best of our knowledge, the effect of a long-term exercise plus pharmacotherapy on cortisol, and monoamines plasma levels have not yet been described in depressive disorder. The focus in this study was on discussing the results from studies employing a chronic exercise protocol, due to the fact that the acute and chronic exercises differ in the physiological changes they induce (Best, 2010).

In relation to monoamines, special attention was given to the biomarkers DA, NA and 5-HT because they are the three major monoamine neurotransmitters that are known to be modulated by exercise (Lin and Kuo, 2013).

This RCT was developed in conjunction with the **HAPPY BRAIN study**, which demonstrated that aerobic exercise as a complementary therapy for subjects with clinical depression reduced depressive symptomatology and improved physical fitness. Nevertheless, in this study, the authors focused attention in biological parameters that were measured before and after the exercise program (16 weeks).

The results showed no significant alteration in monoamines and cortisol plasma levels between the control and exercise intervention groups, which means that these biomarkers did not mediate the effect of exercise on improvements in depressive symptoms. However, cortisol plasma levels demonstrated trends to decrease. We suppose that lack of significance is due to the small number of patients. Indeed, there were no significant differences and it is important to note that the small sample size may reduce the chance of detecting a true effect (Button et al., 2013).

The results seem contradictory to the hypothesis that exercise leads to an improvement in depressive symptoms through an increase of monoamines and a decrease in cortisol levels. In fact, for example, one study developed with animal models demonstrated that after 4 weeks of chronic swimming exercise (30 min/day, 6 days per week) there was activation not only of the synthesis but also of the serotonin metabolism in the cerebral cortex (Dey et al., 1992).

Sarbadhikari and Saha (2006) demonstrated that chronic treadmill exercise elevated the levels of NA in brain regions that are linked to cognitive function, including hippocampus and central and medial amygdala.

Additionally, after eight weeks of physical activity (jogging), adolescent females with depressive symptoms revealed significant decreases in depression scores that were linked

with reduced stress hormone levels—24 h urinary cortisol (Nabkasorn et al., 2006). To the authors' view point, the decrease in depressive symptoms observed in the **HAPPY BRAIN study** may be mediated in part by improvement in physical fitness, decrease in anxiety and stress levels, and possibly other psychological mechanisms which were not assessed, including feelings of mastery, and greater self-efficacy. Moreover, dysfunctional social behavior has been associated to depression (Steger and Kashdan, 2009) and the supportive environment and opportunities for social interaction through exercise could be an opportunity to promote wellbeing. Indeed, it is important to note that a physical activity professional supervised all exercise sessions. However, these parameters were not assessed and therefore cannot be ruled out as potential mediators of this relationship.

Although the literature has recently shed light to the biological pathways, psychological mechanisms should not be discredited in order to consolidate knowledge in this scope. The best approach to understand exercise as a therapy is to combine biological, psychological and social factors. In this sense, it is highly important not only to develop treatment programs for depression so as to get a patient´s symptomatic remission and understand the biological mechanisms, but also to articulate with potential other factors including quality of life, cognitive impairment, psychological mechanisms (e.g. social support, improved perceptions of competence, enhanced self-efficacy, self-esteem) that could be behind the improvement.

Some limitations can be drawn from the available research. First of all, the absence of evidence in biological parameters might derive from confounding variables in the methodology (e.g. large age range, medication status, subtype of depressive pathology, length of treatment), which decrease the likelihood in detecting significant results. Moreover, only peripheral blood samples for plasma were collected and assessed. However, despite catecholamines not crossing the blood-brain barrier, Dienstbier et al. (1987) suggest that increasing peripheral catecholamine levels may have effects on central nervous system availability. Thus, these findings should be identified in future studies in order to minimize measurement bias.

CONCLUSION

After the findings found in the studies presented in this thesis, it is reasonable to highlight the following conclusions:

i. Based on systematic review results, there is evidence that aerobic exercise, performed for at least a nine-week period with a minimum of three times weekly, 30-45 minutes/session, is beneficial for depressive patients.
ii. Defining intensity dose, and analyzing physical fitness, aerobic capacity and placebo groups´ quality, continues to show flaws in the RCTs.
iii. Exercise is an efficacious treatment to the antidepressant medication for adults with depression, decreasing their symptoms and increasing physical fitness.
iv. Despite the reduction in depressive symptoms, no significant differences in weight, body mass index, waist circumference, and self-esteem were observed between exercise and control groups.
v. When comparing the S-COMT activity between two groups, substantial differences were observed. The S-COMT activity exhibited significant decline in the exercise group in relation to the control group.
vi. The exercise performed was not sufficient to promote significant changes in monoamines and cortisol plasma levels.
vii. It has not yet been possible to establish with certainty which mechanism explains the antidepressant effect of exercise.

FUTURE RESEARCH PERSPECTIVES

The greatest challenge is to ensure the integration of exercise professionals within the interdisciplinary mental health teams. To address the problem, firstly it is crucial not to underestimate the value of exercise as a therapeutic tool in wellness and specifically in mental health (Mueser and Cook, 2015). Specifically in Portugal, there is still a significant lack of awareness on the benefits of physical activity for patients with mental health disorders. There have been so many publications in the last years and so little changes in practice. In fact, integrating exercise as a therapeutic intervention requires a shift in culture and system reform (Vancampfort et al., 2015b). Consequently, for a successful implementation, changes in the health care are needed. In order to obtain that progress, mental health should have the same priority as physical health; it requires an alliance between those working within the health care system but also engaged across all of society.

Secondly, so as to provide safe interventions, qualified exercise professionals with expertise in exercise prescription, and also with knowledge of the psychopathology should be part of mental health teams, as they are able to identify and recognize depressive symptomatology, and secondary effects of psychotropic medication (Vancampfort et al., 2015b).

Thirdly, being aware and demystifying the idea that exercise is “not one for all” (Vancampfort et al., 2015a), neither is it a low cost treatment with only pros without cons, leading to immediate results, is a big step to achieve the progress and consequently better results and to increase the credibility of exercise as a therapy in mental health services.

The important task is now to move the field forward and to invest in the improvement of quality research. In this sense, future well-designed RCTs with large samples and long terms (above 12 weeks) are urgently required to achieve the optimum dose-response. Comparing different doses of exercise is an essential step to define quality guidelines, which are generally lacking.

Precise mechanisms underlying chronic effects of exercise on biomarkers (e.g. neurogenesis, inflammatory, endocannabinoids, epigenetic parameters) in depressive patients require future clarification. Lastly, to better understand exercise as an antidepressant in people with depression, effects on physical, social and psychological domains and overall quality of life must be addressed jointly.

REFERENCES

General Introduction

1. Akhtar-Danesh, N., Landeen, J., 2007. Relation between depression and sociodemographic factors. Int. J. Ment. Health Syst. 1, 4.

2. Alarcon, R.D., 2009. Culture, cultural factors and psychiatric diagnosis: Review and projections. World Psychiatry 8, 131-139.

3. Alloy, L.B., Abramson, L.Y., Whitehouse, W.G., Hogan, M.E., Panzarella, C., Rose, D.T., 2006. Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. J. Abnorm. Psychol. 115, 145-156.

4. Almeida, J.A., Xavier, M., Cardoso, G., Pereira, M.A., Gusmão, R., Corrêa, B., Gago, J., Talina, M., Silva, J., 2013. Estudo Epidemiológico Nacional de Saúde Mental. 1º Relatório.

5. Autry, A.E., Monteggia, L.M., 2012. Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol. Rev. 64, 238-258.

6. American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. Arlington, VA: American Psychiatric Publishing.

7. Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., Lombardo, C., Riemann, D., 2011. Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. J. Affect. Disord. 135, 10-19.

8. Barlow, D. H., Durand, V. M., (2009). Abnormal Psychology: An Integrative Approach, sixth ed. Toronto: Nelson Education.

9. Bauldry, S., 2015. Variation in the protective effect of higher education against depression. Soc. Ment. Health 5, 145–161.

10. Berk, M., Williams, L.J., Jacka, F.N., O'Neil, A., Pasco, J.A., Moylan, S., Allen, N.B., Stuart, A.L., Hayley, A.C., Byrne, M.L., Maes, M., 2013. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 11, 200.

11. Bilello, J.A., Thurmond, L.M., Smith, K.M., Pi, B., Rubin, R., Wright, S.M., Taub, F., Henry, M.E., Shelton, R.C., Papakostas, G.I., 2015. MDDScore: Confirmation of a blood test to aid in the diagnosis of major depressive disorder. J. Clin. Psychiatry 76, e199-206.

12. Bjelland, I., Krokstad, S., Mykletun, A., Dahl, A.A., Tell, G.S., Tambs, K., 2008. Does a higher educational level protect against anxiety and depression? The HUNT study. Soc. Sci. Med. 66, 1334-1345.

13. Brigitta, B., 2002. Pathophysiology of depression and mechanisms of treatment. Dialogues Clin. Neurosci. 4, 7-20.

14. Bulloch, A.G., Williams, J.V., Lavorato, D.H., Patten, S.B., 2009. The relationship between major depression and marital disruption is bidirectional. Depress. Anxiety 26, 1172-1177.

15. Callaghan, P., Khalil, E., Morres, I., Carter, T., 2011. Pragmatic randomised controlled trial of preferred intensity exercise in women living with depression. BMC Public Health 11, 465.

16. Campbell, S., Macqueen, G., 2004. The role of the hippocampus in the pathophysiology of major depression. J. Psychiatry Neurosci. 29, 417-426.

17. Carneiro, L.S., Fonseca, A.M., Vieira-Coelho, M.A., Mota, M.P., Vasconcelos-Raposo, J., 2015. Effects of structured exercise and pharmacotherapy vs. pharmacotherapy for adults with depressive symptoms: A randomized clinical trial. J. Psychiatr. Res. 71, 48-55.

18. Craft, L.L., 2005. Exercise and clinical depression: Examining two psychological mechanisms. Psychol. Sport. Exerc. 6, 151-171.

19. Cuijpers, P., Andersson, G., Donker, T., van Straten, A., 2011. Psychological treatment of depression: Results of a series of meta-analyses. Nord. J. Psychiatry 65, 354-364.

20. Dahl, J., Ormstad, H., Aass, H.C., Malt, U.F., Bendz, L.T., Sandvik, L., Brundin, L., Andreassen, O.A., 2014. The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. Psychoneuroendocrino. 45, 77-86.

21. Dale, E., Bang-Andersen, B., Sanchez, C., 2015. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. Biochem. Pharmacol. 95, 81-97.

22. Dantzer, R., O'Connor, J.C., Lawson, M.A., Kelley, K.W., 2011. Inflammation-associated depression: From serotonin to kynurenine. Psychoneuroendocrino. 36, 426-436.

23. de Souto Barreto, P., 2015. Global health agenda on non-communicable diseases: Has WHO set a smart goal for physical activity? BMJ 350, h23.

24. Dishman, R.K., Hales, D.P., Pfeiffer, K.A., Felton, G.A., Saunders, R., Ward, D.S., Dowda, M., Pate, R.R., 2006. Physical self-concept and self-esteem mediate cross-sectional relations of physical activity and sport participation with depression symptoms among adolescent girls. Health Psychol. 25, 396-407.

25. Doghramji, K., 2003. Treatment strategies for sleep disturbance in patients with depression. J. Clin. Psychiatry 64 Suppl 14, 24-29.

26. Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446-457.

27. Du, X., Pang, T.Y., 2015. Is dysregulation of the HPA-Axis a core pathophysiology mediating co-morbid depression in neurodegenerative diseases? Front. Psychiatry 6, 32.

28. Duman, R.S., Monteggia, L.M., 2006. A neurotrophic model for stress-related mood disorders. Biol. Psychiatry 59, 1116-1127.

29. Dwivedi, Y., 2010. Brain-derived neurotrophic factor and suicide pathogenesis. Ann. Med. 42, 87-96.

30. Essau, C.A., Lewinsohn, P.M., Seeley, J.R., Sasagawa, S., 2010. Gender differences in the developmental course of depression. J. Affect. Disord. 127, 185-190.

31. Eyre, H., Baune, B., 2012. Neuroimmunological effects of physical exercise in depression. Brain. Behav. Immun. 26, 251-266.

32. Fakhoury, M., 2015. New insights into the neurobiological mechanisms of major depressive disorders. Gen. Hosp. Psychiatry 37, 172-177.

33. Felger, J.C., Lotrich, F.E., 2013. Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications. Neuroscience 246, 199-229.

34. Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J., Vos, T., Whiteford, H.A., 2013. Burden of depressive disorders by country, sex, age, and year: Findings from the global burden of disease study 2010. PLoS Med. 10, e1001547.

35. Fiske, A., Wetherell, J.L., Gatz, M., 2009. Depression in older adults. Annu. Rev. Clin. Psychol. 5, 363-389.

36. Gaynes, B.N., Lloyd, S.W., Lux, L., Gartlehner, G., Hansen, R.A., Brode, S., Jonas, D.E., Swinson Evans, T., Viswanathan, M., Lohr, K.N., 2014. Repetitive transcranial magnetic stimulation for treatment-resistant depression: A systematic review and meta-analysis. J. Clin. Psychiatry 75, 477-489.

37. Hotting, K., Roder, B., 2013. Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci. Biobehav. Rev. 37, 2243-2257.

38. Hyde, J.S., Mezulis, A.H., Abramson, L.Y., 2008. The ABCs of depression: Integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression. Psychol. Rev. 115, 291-313.

39. Jeon, S.W., Kim, Y.K., 2016. Molecular neurobiology and promising new treatment in depression. Int. J. Mol. Sci. 17, 381.

40. Kallestad, H., Hansen, B., Langsrud, K., Ruud, T., Morken, G., Stiles, T.C., Grawe, R.W., 2012. Impact of sleep disturbance on patients in treatment for mental disorders. BMC Psychiatry 12, 179.

41. Karege, F., Vaudan, G., Schwald, M., Perroud, N., La Harpe, R., 2005. Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. Brain Res. Mol. Brain Res. 136, 29-37.

42. Kerling, A., Tegtbur, U., Gutzlaff, E., Kuck, M., Borchert, L., Ates, Z., von Bohlen, A., Frieling, H., Huper, K., Hartung, D., Schweiger, U., Kahl, K.G., 2015. Effects of adjunctive exercise on physiological and psychological parameters in depression: A randomized pilot trial. J. Affect. Disord. 177, 1-6.

43. Kerner, N., Prudic, J., 2014. Current electroconvulsive therapy practice and research in the geriatric population. Neuropsychiatry 4, 33-54.

44. Kessler, R.C., 1997. The effects of stressful life events on depression. Annu. Rev. Psychol. 48, 191-214.

45. Kessler, R.C., 2003. Epidemiology of women and depression. J. Affect. Disord. 74, 5-13.

46. Kessler, R.C., Bromet, E.J., 2013. The epidemiology of depression across cultures. Annu. Rev. Public Health 34, 119-138.

47. Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K.R., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication**.** Arch. Gen. Psychiatry 62, 617-627.

48. Knapen, J., Van de Vliet, P., Van Coppenolle, H., David, A., Peuskens, J., Pieters, G., Knapen, K., 2005. Comparison of changes in physical self-concept, global self-esteem, depression and anxiety following two different psychomotor therapy programs in nonpsychotic psychiatric inpatients. Psychother. Psychosom. 74, 353-361.

49. Knapen, J., Vancampfort, D., Morien, Y., Marchal, Y., 2014. Exercise therapy improves both mental and physical health in patients with major depression. Disabil. Rehabil. 37, 1490–1495.

50. Knöchel, C., Oertel-Knöchel, V., O'Dwyer, L., Prvulovic, D., Alves, G., Kollmann, B., Hampel, H., 2012. Cognitive and behavioural effects of physical exercise in psychiatric patients. Prog. Neurobiol. 96, 46-68.

51. Koenig, A.M., Thase, M.E., 2009. First-line pharmacotherapies for depression - what is the best choice? Pol. Arch. Med. Wewn. 119, 478-486.

52. Krishnan, V., Nestler, E.J., 2008. The molecular neurobiology of depression**.** Nature 455, 894-902.

53. Krogh, J., Nordentoft, M., Sterne, J.A., Lawlor, D.A., 2011. The effect of exercise in clinically depressed adults: Systematic review and meta-analysis of randomized controlled trials. J. Clin. Psychiatry 72, 529-538.

54. Krogh, J., Speyer, H., Gluud, C., Nordentoft, M., 2015. Exercise for patients with major depression: A protocol for a systematic review with meta-analysis and trial sequential analysis. Syst. Rev. 4, 40.

55. Kudielka, B.M., Kirschbaum, C., 2005. Sex differences in HPA axis responses to stress: A review. Biol. Psychol. 69, 113-132.

56. Kumar, P., Slavich, G.M., Berghorst, L.H., Treadway, M.T., Brooks, N.H., Dutra, S.J., Greve, D.N., O'Donovan, A., Bleil, M.E., Maninger, N., Pizzagalli, D.A., 2015. Perceived life stress exposure modulates reward-related medial prefrontal cortex responses to acute stress in depression. J. Affect. Disord. 180, 104-111.

57. Kurian, B.T., Greer, T.L., Trivedi, M.H., 2009. Strategies to enhance the therapeutic efficacy of antidepressants: Targeting residual symptoms. Expert Rev. Neurother. 9, 975-984.

58. Le Moal, M., 2007. Historical approach and evolution of the stress concept: A personal account. Psychoneuroendocrino. 32 Suppl 1, S3-9.

59. Legrand, F.D., Neff, E.M., 2016. Efficacy of exercise as an adjunct treatment for clinically depressed inpatients during the initial stages of antidepressant pharmacotherapy: An open randomized controlled trial. J. Affect. Disord. 191, 139-144.

60. Lepine, J.P., Briley, M., 2011. The increasing burden of depression. Neuropsychiatr. Dis. Treat. 7, 3-7.

61. Linde, K., Sigterman, K., Kriston, L., Rucker, G., Jamil, S., Meissner, K., Schneider, A., 2015. Effectiveness of psychological treatments for depressive disorders in primary care: Systematic review and meta-analysis. Ann. Fam. Med. 13, 56-68.

62. Liu, Y., Ho, R.C., Mak, A., 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. J. Affect. Disord. 139, 230-239.

63. Lorant, V., Deliege, D., Eaton, W., Robert, A., Philippot, P., Ansseau, M., 2003. Socioeconomic inequalities in depression: A meta-analysis. Am. J. Epidemiol. 157, 98-112.

64. Lotrich, F.E., 2015. Inflammatory cytokine-associated depression. Brain Res. 1617, 113-125.

65. Maes, M., 2011. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 664-675.

66. Maric, N.P., Adzic, M., 2013. Pharmacological modulation of HPA axis in depression - new avenues for potential therapeutic benefits. Psychiatr. Danub. 25, 299-305.

67. McMillan, K.A., Enns, M.W., Asmundson, G.J., Sareen, J., 2010. The association between income and distress, mental disorders, and suicidal ideation and attempts: Findings from the collaborative psychiatric epidemiology surveys. J. Clin. Psychiatry 71, 1168-1175.

68. Medina, J.L., Jacquart, J., Smits, J.A., 2015. Optimizing the exercise prescription for depression: The search for biomarkers of response. Curr Opin Psychol. 4, 43-47.

69. Meeusen, R., De Meirleir, K., 1995. Exercise and brain neurotransmission. Sports Med. 20, 160-188.

70. Melchior, M., Chastang, J.F., Head, J., Goldberg, M., Zins, M., Nabi, H., Younes, N., 2013. Socioeconomic position predicts long-term depression trajectory: A 13-year follow-up of the GAZEL cohort study. Mol. Psychiatry 18, 112-121.

71. Monroe, S.M., 2008. Modern approaches to conceptualizing and measuring human life stress. Annu. Rev. Clin. Psychol. 4, 33-52.

72. Monroe, S.M., Reid, M.W., 2009. Life stress and major depression. Curr. Dir. Psychol. Sci. 4, 18.

73. Morehouse, R., Macqueen, G., Kennedy, S.H., 2011. Barriers to achieving treatment goals: A focus on sleep disturbance and sexual dysfunction. J. Affect. Disord. 132 Suppl 1, S14-20.

74. Mouchet-Mages, S., Baylé, F.J., 2008. Sadness as an integral part of depression. Dialogues Clin. Neurosci. 10, 321-327.

75. Mura, G., Moro, M.F., Patten, S.B., Carta, M.G., 2014. Exercise as an add-on strategy for the treatment of major depressive disorder: A systematic review. CNS Spectr. 19, 496-508.

76. Muscatell, K.A., Slavich, G.M., Monroe, S.M., Gotlib, I.H., 2009. Stressful life events, chronic difficulties, and the symptoms of clinical depression. J. Nerv. Ment. Dis. 197, 154-160.

77. Nagayasu, K., Kitaichi, M., Nishitani, N., Asaoka, N., Shirakawa, H., Nakagawa, T., Kaneko, S., 2013. Chronic effects of antidepressants on serotonin release in rat raphe

slice cultures: High potency of milnacipran in the augmentation of serotonin release. Int. J. Neuropsychopharmacol. 16, 2295-2306.

78. Orth, U., Robins, R.W., 2013. Understanding the link between low self-esteem and depression. Curr. Dir. Psychol. Sci. 22, 455–460.

79. Pålhagen, S., Qi, H., Mårtensson, B., Wålinder, J., Granérus, A.-K., Svenningsson, P., 2010. Monoamines, BDNF, IL-6 and corticosterone in CSF in patients with Parkinson's disease and major depression. J. Neurol. 257, 524-532.

80. Papakostas, G.I., 2009. Diagnostic assessment of major depressive disorder. J. Clin. Psychiatry 70, e09.

81. Pariante, C.M., Lightman, S.L., 2008. The HPA axis in major depression: Classical theories and new developments. Trends Neurosci. 31, 464-468.

82. Parker, G., 2007. Is depression overdiagnosed? Yes. BMJ 335, 328.

83. Patten, S.B., Williams, J.V., Lavorato, D.H., Eliasziw, M., 2009. A longitudinal community study of major depression and physical activity. Gen. Hosp. Psychiatry 31, 571-575.

84. Paunio, T., Korhonen, T., Hublin, C., Partinen, M., Koskenvuo, K., Koskenvuo, M., Kaprio, J., 2015. Poor sleep predicts symptoms of depression and disability retirement due to depression. J. Affect. Disord. 172, 381-389.

85. Penzel, T., Kantelhardt, J.W., Lo, C.C., Voigt, K., Vogelmeier, C., 2003. Dynamics of heart rate and sleep stages in normals and patients with sleep apnea. Neuropsychopharmacology 28 Suppl 1, S48-53.

86. Philipp, M., Maier, W., Delmo, C.D., 1991. The concept of major depression. I. Descriptive comparison of six competing operational definitions including ICD-10 and DSM-III-R. Eur. Arch. Psychiatry Clin. Neurosci. 240, 258-265.

87. Piccinelli, M., Wilkinson, G., 2000. Gender differences in depression. Critical review. Br. J. Psychiatry 177, 486-492.

88. Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. JAMA Psychiatry 70, 31-41.

89. Renoir, T., 2013. Selective serotonin reuptake inhibitor antidepressant treatment discontinuation syndrome: A review of the clinical evidence and the possible mechanisms involved. Front. Pharmacol. 4,45.

90. Rimer, J., Dwan, K., Lawlor, D.A., Greig, C.A., McMurdo, M., Morley, W., Mead, G.E., 2012. Exercise for depression. Cochrane Database Syst. Rev. 7, CD004366.

91. Risch, A.K., Buba, A., Birk, U., Morina, N., Steffens, M.C., Stangier, U., 2010. Implicit self-esteem in recurrently depressed patients. J. Behav. Ther. Exp. Psychiatry 41,199-206.

92. Rizwan, M., Ahmad, R., 2015. Self-esteem deficits among psychiatric patients. Sage Open 5, 1-6.

93. Robinson, M.S., Alloy, L.B., 2003. Negative cognitive styles and stress-reactive rumination interact to predict depression: A prospective study. Cognit. Ther. Res. 27, 275–292.

94. Rosenberg, A.E., 1965. Society and the adolescent self-image - Rosenberg, M. Psychiatr. Q. 39, 751.

95. Salsali, M., Silverstone, P.H., 2003. Low self-esteem and psychiatric patients: Part II - the relationship between self-esteem and demographic factors and psychosocial stressors in psychiatric patients. Ann. Gen. Hosp. Psychiatry 2, 3.

96. Schildkraut, J.J., 1965. The catecholamine hypothesis of affective disorders: A review of supporting evidence. Am. J. Psychiatry 122, 509-522.

97. Schuch, F.B., Deslandes, A.C., Stubbs, B., Gosmann, N.P., Silva, C.T., Fleck, M.P., 2015a. Neurobiological effects of exercise on major depressive disorder: A systematic review. Neurosci. Biobehav. Rev. 61, 1-11.

98. Schuch, F.B., Vasconcelos-Moreno, M.P., Borowsky, C., Zimmermann, A.B., Rocha, N.S., Fleck, M.P., 2015b. Exercise and severe major depression: Effect on symptom severity and quality of life at discharge in an inpatient cohort. J. Psychiatr. Res. 61, 25-32.

99. Searle, A., Calnan, M., Lewis, G., Campbell, J., Taylor, A., Turner, K., 2011. Patients' views of physical activity as treatment for depression: A qualitative study. Br. J. Gen. Pract. 61, 149-156.

100. Semkovska, M., McLoughlin, D.M., 2010. Objective cognitive performance associated with electroconvulsive therapy for depression: A systematic review and meta-analysis. Biol. Psychiatry 68, 568-577.

101. Silverstein, B., Edwards, T., Gamma, A., Ajdacic-Gross, V., Rossler, W., Angst, J., 2013. The role played by depression associated with somatic symptomatology in accounting for the gender difference in the prevalence of depression. Soc. Psychiatry Psychiatr. Epidemiol. 48, 257-263.

102. Silverstone, P.H., Salsali, M., 2003. Low self-esteem and psychiatric patients: Part I - the relationship between low self-esteem and psychiatric diagnosis. Ann. Gen. Hosp. Psychiatry 2, 2.

103. Skapinakis, P., Weich, S., Lewis, G., Singleton, N., Araya, R., 2006. Socio-economic position and common mental disorders. Longitudinal study in the general population in the UK. Br. J. Psychiatry 189, 109-117.

104. Smith, K.M., Renshaw, P.F., Bilello, J., 2013. The diagnosis of depression: Current and emerging methods. Compr. Psychiatry 54, 1-6.

105. Sousa e Silva, T., Longui, C.A., Rocha, M.N., Faria, C.D.C., Melo, M.R., Faria, T.G., de Souza, J.A., Rizzo, L.V., 2010. Prolonged physical training decreases mRNA levels of glucocorticoid receptor and inflammatory genes. Horm. Res. Paediatr. 74, 6-14.

106. Stanton, S., Rosenbaum, S., Kalucy, M., Reaburn, P., Happell, B., 2015. A call to action: Exercise as treatment for patients with mental illness. Aust. J. Prim. Health 21, 120-125.

107. Stuart, M.J., Baune, B.T., 2012. Depression and type 2 diabetes: Inflammatory mechanisms of a psychoneuroendocrine co-morbidity. Neurosci. Biobehav. Rev. 36, 658-676.

108. Stubbs, B., Vancampfort, D., Rosenbaum, S., Ward, P.B., Richards, J., Soundy, A., Veronese, N., Solmi, M., Schuch, F.B., 2016. Dropout from exercise randomized controlled trials among people with depression: A meta-analysis and meta regression. J. Affect. Disord. 190, 457-466.

109. Toups, M., Trivedi, M.H., 2012. Biomarkers and the future of treatment for depression. Cerebrum 2012, 6.

110. Trivedi, M.H., 2009. Treating depression to full remission. J. Clin. Psychiatry 70, e01.

111. Tsuno, N., Besset, A., Ritchie, K., 2005. Sleep and depression. J. Clin. Psychiatry 66, 1254-1269.

112. Vavakova, M., Durackova, Z., Trebaticka, J., 2015. Markers of oxidative stress and neuroprogression in depression disorder. Oxid. Med. Cell. Longev. 2015, 898393.

113. Verduijn, J., Milaneschi, Y., Schoevers, R.A., van Hemert, A.M., Beekman, A.T., Penninx, B.W., 2015. Pathophysiology of major depressive disorder: Mechanisms involved in etiology are not associated with clinical progression. Transl. Psychiatry 5, e649.

114. Vracotas, N., Iyer, S.N., Joober, R., Malla, A., 2012. The role of self-esteem for outcome in first-episode psychosis. Int. J. Soc. Psychiatry 58, 41-46.

115. Wakefield, J.C., Baer, J.C., Schmitz, M.F., 2010. Differential diagnosis of depressive illness versus intense normal sadness: How significant is the 'clinical significance criterion' for major depression? Expert Rev. Neurother. 10, 1015-1018.

116. Walker, C., 2008. Depression and Globalization - The Politics of Mental Health in the 21st Century, New York, NY:Springer.

117. Watkins, E., 2015. Psychological treatment of depressive rumination. Curr. Opin. Psychology 4, 32–36.

118. Weber, C.C., Eckert, G.P., Muller, W.E., 2006. Effects of antidepressants on the brain/plasma distribution of corticosterone. Neuropsychopharmacology 31, 2443-2448.

119. Weibull, F., Cumming, J., Cooley, S.J., Williams, S.E., Burns, V.E., 2015. Walk this way: A brief exercise imagery intervention increases barrier self-efficacy in women. Curr. Psychol. 34, 477-490.

120. White, K., Kendrick, T., Yardley, L., 2009. Change in self-esteem, self-efficacy and the mood dimensions of depression as potential mediators of the physical activity and depression relationship: Exploring the temporal relation of change. Ment. Health Phys. Act. 2, 44-52.

121. Wohleb, E.S., Franklin, T., Iwata, M., Duman, R.S., 2016. Integrating neuroimmune systems in the neurobiology of depression. Nat. Rev. Neurosci. 17:497-511.

122. Wolpert, L., 2008. Depression in an evolutionary context. Philos. Ethics Humanit. Med. 3, 8.

123. World Health Organization. ICD-10. International Statistical Classification of Diseases and Related Health Problems 10th Revision, 2010. Available from: http://apps.who.int/classifications/icd10/browse/2010/en.

124. Young, J.J., Silber, T., Bruno, D., Galatzer-Levy, I.R., Pomara, N., Marmar, C.R., 2016. Is there progress? An overview of selecting biomarker candidates for major depressive disorder. Front. Psychiatry 7, 72.

125. Zbozinek, T.D., Rose, R.D., Wolitzky-Taylor, K.B., Sherbourne, C., Sullivan, G., Stein, M.B., Roy-Byrne, P.P., Craske, M.G., 2012. Diagnostic overlap of generalized anxiety disorder and major depressive disorder in a primary care sample. Depress. Anxiety 29, 1065-1071.

General Discussion

1. American Psychiatric Association, 2010. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, third ed.

2. Anacker, C., Zunszain, P.A., Carvalho, L.A., Pariante, C.M., 2011. The glucocorticoid receptor: Pivot of depression and of antidepressant treatment? Psychoneuroendocrino. 36, 415-425.

3. Babore, A., Trumello, C., Candelori, C., Paciello, M., Cerniglia, L., 2016. Depressive symptoms, self-esteem and perceived parent-child relationship in early adolescence. Front Psychol. 7, 982.

4. Becofsky, K.M., Sui, X., Lee, D.C., Wilcox, S., Zhang, J., Blair, S.N., 2015. A prospective study of fitness, fatness, and depressive symptoms. Am. J. Epidemiol. 181, 311-320.

5. Berge, L.I., Riise, T., Hundal, O., Odegaard, K.J., Dilsaver, S., Lund, A., 2013. Prevalence and characteristics of depressive disorders in type 1 diabetes. BMC Res. Notes 6, 543.

6. Best, J.R., 2010. Effects of physical activity on children's executive function: Contributions of experimental research on aerobic exercise. Dev. Rev. 30, 331-551.

7. Brigitta, B., 2002. Pathophysiology of depression and mechanisms of treatment. Dialogues Clin. Neurosci. 4, 7-20.

8. Button, K.S., Ioannidis, J.P., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S., Munafo, M.R., 2013. Power failure: Why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. 14, 365-376.

9. Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., Penninx, B.W., 2013. Differential mortality rates in major and subthreshold depression: Meta-analysis of studies that measured both. Br. J. Psychiatry 202, 22-27.

10. Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., Penninx, B.W., 2014. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. Am. J. Psychiatry 171, 453-462.

11. Dey, S., Singh, R.H., Dey, P.K., 1992. Exercise training: Significance of regional alterations in serotonin metabolism of rat brain in relation to antidepressant effect of exercise. Physiol. Behav. 52, 1095-1099.

12. Dienstbier, R.A., LaGuardia, R.L., Barnes, M., Tharp, G., Schmidt, R., 1987. Catecholamine training effects from exercise programs: A bridge to exercise-temperament relationships. Motiv. Emot. 11, 297-318.

13. Dunlop, B.W., Nemeroff, C.B., 2007. The role of dopamine in the pathophysiology of depression. Arch. Gen. Psychiatry 64, 327-337.

14. Ekkekakis, P., 2015. Honey, I shrunk the pooled SMD! Guide to critical appraisal of systematic reviews and meta-analyses using the Cochrane review on exercise for depression as example. Ment. Health Phys. Act. 8, 21-36.

15. Firth, J., Cotter, J., Elliott, R., French, P., Yung, A.R., 2015. A systematic review and meta-analysis of exercise interventions in schizophrenia patients. Psychol. Med. 45, 1343-1361.

16. Gispen-de Wied, C.C., Jansen, L.M., Duyx, J.H., Thijssen, J.H., van Engeland, H., 2000. Pituitary-adrenal function in adolescent psychiatric patients: Impact of depressive symptoms. J. Affect. Disord. 59, 71-76.

17. Hasler, G., 2010. Pathophysiology of depression: Do we have any solid evidence of interest to clinicians? World Psychiatry 9, 155-161.

18. Helmich, I., Latini, A., Sigwalt, A., Carta, M.G., Machado, S., Velasques, B., Ribeiro, P., Budde, H., 2010. Neurobiological alterations induced by exercise and their impact on depressive disorders. Clin. Pract. Epidemiol. Ment. Health 6, 115-125.

19. Knapen, J., Vancampfort, D., Morien, Y., Marchal, Y., 2014. Exercise therapy improves both mental and physical health in patients with major depression. Disabil. Rehabil. 37, 1490–1495.

20. Kraemer, H.C., Wilson, G.T., Fairburn, C.G., Agras, W.S., 2002. Mediators and moderators of treatment effects in randomized clinical trials. Arch. Gen. Psychiatry 59, 877-883.

21. Krishnan, V., Nestler, E.J., 2008. The molecular neurobiology of depression. Nature 455, 894-902.

22. Leckie, R.L., Weinstein, A.M., Hodzic, J.C., Erickson, K.I., 2012. Potential moderators of physical activity on brain health. J. Aging Res. 2012, 948981.

23. Legrand, F.D., 2014. Effects of exercise on physical self-concept, global self-esteem, and depression in women of low socioeconomic status with elevated depressive symptoms. J. Sport. Exerc. Psychol. 36, 357-365.

24. Lin, T.W., Kuo, Y.M., 2013. Exercise benefits brain function: The monoamine connection. Brain Sci. 3, 39-53.

25. Lindheimer, J.B., O'Connor, P.J., Dishman, R.K., 2015. Quantifying the placebo effect in psychological outcomes of exercise training: A meta-analysis of randomized trials. Sports Med. 45, 693-711.

26. Meeusen, R., De Meirleir, K., 1995. Exercise and brain neurotransmission. Sports Med. 20, 160-188.

27. Mitani, H., Shirayama, Y., Yamada, T., Kawahara, R., 2006. Plasma levels of homovanillic acid, 5-hydroxyindoleacetic acid and cortisol, and serotonin turnover in depressed patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 30, 531-534.

28. Möller, H.-J., 2008. Outcomes in major depressive disorder: The evolving concept of remission and its implications for treatment**.** World J. Biol. Psychiatry 9, 102-114.

29. Mota-Pereira, J., Silverio, J., Carvalho, S., Ribeiro, J.C., Fonte, D., Ramos, J., 2011. Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. J. Psychiatr. Res. 45, 1005-1011.

30. Mueser, K.T., Cook, J.A., 2015. Are we underestimating the value of exercise for wellness? Psychiatr. Rehabil. J. 38, 289-292.

31. Nabkasorn, C., Miyai, N., Sootmongkol, A., Junprasert, S., Yamamoto, H., Arita, M., Miyashita, K., 2006. Effects of physical exercise on depression, neuroendocrine stress hormones and physiological fitness in adolescent females with depressive symptoms. Eur. J. Public Health 179-184.

32. National Institute for Health & Clinical Excellence, 2009. Depression: The NICE guideline on the treatment and management of depression in adults (updated edition).

33. Nutt, D.J., 2006. The role of dopamine and norepinephrine in depression and antidepressant treatment. J. Clin. Psychiatry 67, 3-8.

34. Nystrom, M.B., Neely, G., Hassmen, P., Carlbring, P., 2015. Treating major depression with physical activity: A systematic overview with recommendations. Cogn. Behav. Ther. 44, 341-352.

35. Perraton, L.G., Kumar, S., Machotka, Z., 2010. Exercise parameters in the treatment of clinical depression: A systematic review of randomized controlled trials. J. Eval. Clin. Pract. 16, 597-604.

36. Pilu, A., Sorba, M., Hardoy, M.C., Floris, A.L., Mannu, F., Seruis, M.L., Velluti, C., Carpiniello, B., Salvi, M., Carta, M.G., 2007. Efficacy of physical activity in the adjunctive treatment of major depressive disorders: Preliminary results. Clin. Pract. Epidemiol. Ment. Health 3, 8.

37. Puzynski, S., Bidzinski, A., Mrozek, S., Zaluska, M., 1983. Studies on biogenic amine metabolizing enzymes (DBH, COMT, MAO) and pathogenesis of affective illness. II. Erythrocyte catechol-O-methyltransferase activity in endogenous depression. Acta Psychiatr. Scand. 67, 96-100.

38. Riedel, M., Moller, H.J., Obermeier, M., Schennach-Wolff, R., Bauer, M., Adli, M., Kronmuller, K., Nickel, T., Brieger, P., Laux, G., Bender, W., Heuser, I., Zeiler, J., Gaebel, W., Seemuller, F., 2010. Response and remission criteria in major depression--a validation of current practice. J. Psychiatr. Res. 44, 1063-1068.

39. Rimer, J., Dwan, K., Lawlor, D.A., Greig, C.A., McMurdo, M., Morley, W., Mead, G.E., 2012. Exercise for depression. Cochrane Database Syst. Rev. 7, CD004366.

40. Rizwan, M., Ahmad, R., 2015. Self-esteem deficits among psychiatric patients. Sage Open 5, 1-6.

41. Salsali, M., Silverstone, P.H., 2003. Low self-esteem and psychiatric patients: Part II - the relationship between self-esteem and demographic factors and psychosocial stressors in psychiatric patients. Ann. Gen. Hosp. Psychiatry 2, 3.

42. Sarbadhikari, S.N., Saha, A.K., 2006. Moderate exercise and chronic stress produce counteractive effects on different areas of the brain by acting through various neurotransmitter receptor subtypes: A hypothesis. Theor. Biol. Med. Model 23,33.

43. Schildkraut, J.J., 1965. The catecholamine hypothesis of affective disorders: A review of supporting evidence. Am. J. Psychiatry 122, 509-522.

44. Schuch, F.B., Deslandes, A.C., Stubbs, B., Gosmann, N.P., Silva, C.T., Fleck, M.P., 2015. Neurobiological effects of exercise on major depressive disorder: A systematic review. Neurosci. Biobehav. Rev. 61, 1-11.

45. Schuch, F.B., Dunn, A.L., Kanitz, A.C., Delevatti, R.S., Fleck, M.P., 2016a. Moderators of response in exercise treatment for depression: A systematic review. J. Affect. Disord. 195, 40-49.

46. Schuch, F.B., Morres, I.D., Ekkekakis, P., Rosenbaum, S., Stubbs, B., 2016b. A critical review of exercise as a treatment for clinically depressed adults: Time to get pragmatic. Acta Neuropsychiatr. 5, 1-7.

47. Schuch, F.B., Vancampfort, D., Rosenbaum, S., Richards, J., Ward, P.B., Stubbs, B., 2016c. Exercise improves physical and psychological quality of life in people with depression: A meta-analysis including the evaluation of control group response. Psychiatry Res. 241, 47-54.

48. Schuch, F.B., Vasconcelos-Moreno, M.P., Borowsky, C., Fleck, M.P., 2011. Exercise and severe depression: Preliminary results of an add-on study. J. Affect. Disord. 133, 615-618.

49. Sengupta, S., Grizenko, N., Schmitz, N., Schwartz, G., Bellingham, J., Polotskaia, A., Stepanian, M.T., Goto, Y., Grace, A.A., Joober, R., 2008. COMT Val108/158Met polymorphism and the modulation of task-oriented behavior in children with ADHD. Neuropsychopharmacology 33, 3069-3077.

50. Silverstone, P.H., Salsali, M., 2003. Low self-esteem and psychiatric patients: Part I - the relationship between low self-esteem and psychiatric diagnosis. Ann. Gen. Hosp. Psychiatry 2, 2.

51. Sonstroem, R.J., Morgan, W.P., 1989. Exercise and self-esteem: Rationale and model. Med. Sci. Sports Exerc. 21, 329-337.

52. Soundy, A., Taylor, A., Faulkner, G., Rowlands, A., 2007. Psychometric properties of the 7-day physical activity recall questionnaire in individuals with severe mental illness. Arch. Psychiatr. Nurs. 21, 309-316.

53. Stanton, R., Reaburn, P., 2013. Exercise and the treatment of depression: A review of the exercise program variables. J. Sci. Med. Sport. 17, 177-182.

54. Steger, M.F., Kashdan, T.B., 2009. Depression and everyday social activity, belonging, and well-being. J. Couns. Psychol. 56, 289-300.

55. Stroth, S., Reinhardt, R.K., Thone, J., Hille, K., Schneider, M., Hartel, S., Weidemann, W., Bos, K., Spitzer, M., 2010. Impact of aerobic exercise training on cognitive functions and affect associated to the COMT polymorphism in young adults. Neurobiol. Learn. Mem. 94, 364-372.

56. Stubbs, B., Probst, M., Soundy, A., Parker, A., De Herdt, A., De Hert, M., Mitchell, A.J., Vancampfort, D., 2014. Physiotherapists can help implement physical activity programmes in clinical practice. Br. J. Psychiatry 204:164.

57. Stubbs, B., Vancampfort, D., Rosenbaum, S., Ward, P.B., Richards, J., Soundy, A., Veronese, N., Solmi, M., Schuch, F.B., 2016a. Dropout from exercise randomized controlled trials among people with depression: A meta-analysis and meta regression. J. Affect. Disord. 190, 457-466.

58. Stubbs, B., Vancampfort, D., Rosenbaum, S., Ward, P.B., Richards, J., Ussher, M., Schuch, F.B., 2016b. Challenges establishing the efficacy of exercise as an antidepressant treatment: A systematic review and meta-analysis of control group responses in exercise randomised controlled trials. Sports Med. 46, 699-713.

59. Sutoo, D., Akiyama, K., 1996. The mechanism by which exercise modifies brain function. Physiol. Behav. 60, 177-181.

60. Sutoo, D., Akiyama, K., Yabe, K., Kohno, K., 1991. Multiple analysis of tyrosine hydroxylase and calmodulin distributions in the forebrain of the rat using a microphotometry system. Brain Res. Bull. 26, 973-982.

61. Toups, M., Trivedi, M.H., 2012. Biomarkers and the future of treatment for depression. Cerebrum 2012, 6.

62. Trivedi, M.H., 2009. Treating depression to full remission. J. Clin. Psychiatry 70, e01.

63. Van der Pompe, G., Bernards, N., Meijman, T.F., Heijnen, C., 1999. The effect of depressive symptomatology on plasma cortisol responses to acute bicycle exercise among post-menopausal women. Psychiatry Res. 85, 113-117.

64. Vancampfort, D., Stubbs, B., Ward, P.B., Teasdale, S., Rosenbaum, S., 2015a. Integrating physical activity as medicine in the care of people with severe mental illness. Aust. N. Z. J. Psychiatry 49, 681-682.

65. Vancampfort, D., Stubbs, B., Ward, P.B., Teasdale, S., Rosenbaum, S., 2015b. Why moving more should be promoted for severe mental illness. Lancet Psychiatry 2, 295.

66. Volkow, N.D., Fowler, J.S., Gatley, S.J., Logan, J., Wang, G.J., Ding, Y.S., Dewey, S., 1996. PET evaluation of the dopamine system of the human brain. J. Nucl. Med. 37, 1242-1256.

67. Wang, G.J., Volkow, N.D., Fowler, J.S., Franceschi, D., Logan, J., Pappas, N.R., Wong, C.T., Netusil, N., 2000. PET studies of the effects of aerobic exercise on human striatal dopamine release. J. Nucl. Med. 41, 1352-1356.