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Tese de Doutorado

Exercício físico e depressão: Efeitos em desfechos clínicos e em biomarcadores

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Orientador: Prof. Dr. Marcelo Pio de Almeida Fleck

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Tese apresentada ao curso de Pós-graduação em ciências médicas: Psiquiatria da Universidade Federal do Rio Grande do Sul como requisito para a obtenção do título de Doutor em Psiquiatria.

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Para Adriana,

minha companheira em todos os momentos

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ABREVIATURAS E SIGLAS

BDNF – Do inglês, *Brain-derived neurotrophic factor*

ECT – Eletroconvulsoterapia

g – Tamanho de efeito de *Hedges*

ISRS – Inibidor Seletivo da Recaptação de Serotonina

kcal/kg/semana – Quilocaloria por quilograma de peso por semana.

NNT – Número Necessário para tratar.

TBARS – Do inglês, *Thiobarbituric acid reactive substances*

TCC – Terapia Cognitivo Comportamental

TDM – Transtorno Depressivo Maior

THB – Transtorno do Humor Bipolar

QV – Qualidade de Vida

YLDs – Do inglês*, Years lived with disabilites*

SUMÁRIO

PREFÁCIO

As relações entre depressão e exercício físico são objetos de estudo bastante antigas e já foram exploradas em diversos contextos e culturas. Apesar da riqueza e da quantidade de informações existentes, ainda existem muitas incertezas, tanto no que dizem respeito à própria entidade nosológica e a fisiopatologia da depressão, quanto nas formas e mecanismos com os quais o exercício pode interagir com ela. Grandes também são as incertas no que diz respeito à generalização para as populações em diferentes apresentações do fenômeno, incluindo os casos com maior gravidade.

Tentando trazer algumas respostas para tantas dessas perguntas, foi desenhado o ensaio clinico randomizado que foi o ponto de partida da presente tese. Estudo esse que ganhou uma importância maior após possibilidade de avaliar biomarcadores, que poderiam clarificar a ainda bastante obscura área das alterações biológicas do exercício na depressão.

É importante ressaltar que o ensaio clínico foi o ponto de partida da tese e que durante a execução e a escrita dos resultados é que as revisões sistemáticas foram realizadas. De um modo geral, no desenvolvimento de um curso de doutorado, se sugere que primeiro sejam feitas as revisões sistemáticas para o aluno já conhecer as lacunas e aprofundar as suas hipóteses. No entanto, na presente tese, as revisões foram feitas no final. Esse fato ocorreu, pois ao iniciar o doutorado, já existiam dezenas de revisões sistemáticas com meta-analise, algumas bastante recentes, avaliando os efeitos do exercício físico nos sintomas depressivos em pacientes clinicamente

deprimidos. Neste contexto, surgiram as ideias das duas ultimas revisões, que abrangem pontos específicos, relevantes, porém pouco explorados.

Os leitores perceberão que os artigos não estão em sua ordem cronológica, visto que os estudos 1 e 2 ainda não foram submetidos enquanto o 3 e o 4 já foram publicados, sendo o artigo 4 o primeiro a ser publicado. Todavia, optou-se por colocar a tese nessa ordem por ser mais didática e fluente para o leitor com os artigos 1 e 2 aparecendo antes na tese.

Dessa forma, a tese ficou assim organizada: a) *Introdução*, destacando os assuntos a serem explorados; b) *Revisão de literatura*, abordando tópicos que as revisões não exploraram, como o uso do exercício físico no tratamento da depressão em geral e em diferentes gravidades de episódios depressivos, comparações e relações com outros tratamentos e a forma de prescrever exercício físico; c) *Artigo 1,* que explora os potenciais preditores ou moderadores do efeito antidepressivo do exercício na depressão clinica; d) *Artigo 2*, que explora os efeitos do exercício em alguns marcadores biológicos em pacientes clinicamente deprimidos; e) *Artigos 3 e 4* que consistem num ensaio-clínico que avalia o efeito "*add-on"* do exercício físico ao esquema antidepressivo medicamentos nos sintomas depressivos e na qualidade de vida (QV) (artigo 3) e nos marcadores biológicos (artigo 4). A tese é finalizada com as considerações finais e conclusões, em que é discutido no que a presente tese pode ter contribuído para o avanço do conhecimento na área.

RESUMO

O exercício físico vem sendo cada vez mais utilizado como uma intervenção terapêutica para a depressão. Diversos estudos mostram a sua eficácia em episódios depressivos mais leves. Sua eficácia em episódios mais graves como em indivíduos hospitalizados ainda não foi suficientemente estudada. Faltam informações também sobre a existência de fatores que possam predizer ou moderar o efeito antidepressivo do exercício como também informações sobre os potenciais mecanismos ou correlatos biológicos que possam estar associados aos efeitos antidepressivos do exercício em indivíduos deprimidos. A presente tese consiste de quatro artigos, sendo o primeiro uma revisão sistemática sobre os potenciais fatores preditores ou moderadores do efeito antidepressivo do exercício, o segundo, uma revisão sistemática sobre os potenciais mecanismos ou correlatos biológicos do exercício, o terceiro, um ensaio clínico randomizado avaliando os efeitos do exercício físico em pacientes internados com depressão grave, e o ultimo, uma análise dos efeitos do exercício em marcadores de neurogênese e estresse oxidativo. Os resultados encontrados na primeira revisão sugerem que existem vários potenciais candidatos a preditor ou moderador do efeito antidepressivo do exercício físico; entretanto, a literatura não é suficientemente robusta para sugerir de forma consistente sua existência. De acordo com a segunda revisão, o exercício pode potencialmente promover respostas agudas em diversos biomarcadores. No entanto, as respostas crônicas em adaptação ao treinamento parecem ser menos consistentes. Cabe ressaltar que a literatura apresenta diversas limitações importantes, impedindo conclusões mais sólidas, tanto para as respostas agudas quanto para as crônicas. Com o ensaio clinico,

evidenciamos que o exercício físico pode ser uma intervenção terapêutica eficaz na redução dos sintomas depressivos e na melhora de alguns domínios da qualidade de vida de participantes hospitalizados com depressão grave. Enquanto no ultimo artigo, utilizando uma amostra do ensaio clinico, foram encontradas diminuições nos níveis séricos de marcadores de stress oxidativo, porem, não houve alterações nos níveis de marcadores de neurogênese. A presente tese avança no entendimento do fenômeno do efeito antidepressivo do exercício, achando pontos a serem explorados em futuras investigações. Demonstra, também, a eficácia do exercício em pacientes hospitalizados com depressão grave. Por ultimo, mostra que existem diversos potenciais mecanismos e correlatos biológicos que possam vir a explicar ou estar associados a este efeito antidepressivo.

Palavras chave: Depressão; Exercício; Mecanismos; Mediadores; Moderadores; Neurogenese; Preditores; Stress Oxidativo.

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ABSTRACT

Physical exercise has been increasingly exploited as a therapeutic intervention for depression. Several studies have shown its effectiveness in milder severity of depression, however, their effectiveness in severe episodes in hospitalized individuals still needs further investigation. There is also a lack of information about factors that can predict or moderate the antidepressant effect of exercise and the potential mechanisms or biological correlates that are associated with antidepressant effects of exercise in depressed individuals.

This thesis consists of four articles. The first is a systematic review of potential predictors or antidepressant effect of exercise moderators. The second is a systematic review of the potential biological mechanisms or correlates of exercise. The third is a randomized clinical trial evaluating the effects of physical exercise in patients hospitalized with severe depression. The last one, is an analysis of the effects of exercise on neurogenesis markers and oxidative stress. The findings of the first review suggest that there are several potential candidates predictors and moderators. However, the literature is not robust enough to suggest any predictor or moderator with greater consistency. According to the second review, exercise can potentially promote acute responses in several biomarkers. On the other hand, the chronic adaptations to exercise training appear to be less consistent. The literature contains several important limitations, preventing more solid conclusions regards the acute and chronic responses. According to the clinical trial, we observed that exercise can be an effective therapeutic intervention in reducing depressive symptoms and improving some domains of quality of life of participants hospitalized with severe depression. Finally, in the fourth article, using a sample of the clinical

trial, serum levels of oxidative stress markers decreases were found., However, no changes in the levels of neurogenesis markers were found. This thesis advances in the understanding of the antidepressant effect of exercise phenomenon, finding points to be further explored regarding the predictors and moderators. It also demonstrates the antidepressant effectiveness of physical exercise in hospitalized patients with severe depression. Finally, shows that there are several potential mechanisms and biological correlates that may explain or be associated with this antidepressant effect.

Key-words: Depression; Exercise; Mechanisms; Mediators; Moderators; Neurogenese; Oxidative Stress; Predictor.

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1 INTRODUÇÃO

O Transtorno Depressivo Maior (TDM) é uma condição crônica que, conforme dados do Global Burden of Disease 2010 (1), foi responsável por 40.5% dos anos perdidos por incapacidade entre os transtornos mentais em um período de trinta anos (1980-2010). Além do curso crônico, a alta prevalência contribuiu de forma significativa para este alto impacto causado na sociedade. A prevalência da depressão pode variar bastante entre diferentes países e culturas. Dados brasileiros sugerem que a prevalência ao longo da vida seja alta aqui também no Brasil, estimada em aproximadamente 13% (2).

Episódios graves apresentam pior funcionamento social, pior prognóstico, maior risco de suicido, mais complicações clinicas e um maior impacto na qualidade de vida (QV) (3). Em muitos casos, a internação hospitalar pode ser de grande utilidade, fornecendo um tratamento e um cuidado intensivo, apesar de não ser necessariamente um critério de gravidade (3).

O exercício, por sua vez, é um tratamento eficaz para o TDM (4-9). Contudo, poucos estudos avaliaram os efeitos do exercício físico em pacientes hospitalizados com depressão grave. Martinsen et al. (10) investigou os efeitos do exercício físico como uma estratégia complementar em pacientes hospitalizados e potencialmente graves; entretanto, o estudo não utilizou nenhum instrumento para avaliação diagnóstica. Em outro estudo, Knuben (11) avaliou os efeitos de uma intervenção breve (10 sessões) em pacientes internados com depressão grave. A amostra do estudo, no entanto, foi composta também por pacientes com Transtorno do Humor Bipolar (THB) e

distimia e não uma amostra composta exclusivamente por pacientes gravemente deprimidos, fator que pode enviesar a análise e limitar estimativas acerca do real efeito antidepressivo do exercício nessa população.

Atualmente, existem diversos candidatos a potencias mediadores ou mecanismos biológicos envolvidos no efeito antidepressivo do exercício. Estudos em seres humanos não deprimidos ou em modelos animais levantaram hipóteses como as neuroendócrinas, neurotróficas, inflamatórias, oxidativas ou em relação a mudanças no volume e na ativação cerebral (12-22). Entretanto, poucas dessas hipóteses foram testadas em amostras de pacientes clinicamente deprimidos.

A presente tese teve como objetivo contribuir na compreensão das relações entre exercício e depressão, avaliando os potenciais fatores mediadores ou moderadores da resposta ao exercício, os efeitos de uma intervenção com exercício em desfechos clínicos e biológicos em pacientes internados com depressão grave e revisando a literatura acerca dos mecanismos ou correlatos biológicos do efeito antidepressivo do exercício em pacientes clinicamente deprimidos.

2 DESCRIÇÃO DA JUSTIFICATIVA E DOS OBJETIVOS

2.1 JUSTIFICATIVA

O exercício físico é eficaz na redução dos sintomas depressivos em populações não clínicas, sem o diagnóstico de depressão, e em amostras com episódios depressivos com gravidade leve a moderada. Entretanto, existem ainda diversas lacunas a serem preenchidas. Não estão claros os fatores que podem predizer sucesso no tratamento baseado em exercício, a efetividade do exercício físico em pacientes internados com depressão grave, bem como, os mecanismos neurobiológicos pelos quais o exercício tem um efeito antidepressivo em amostras clinicas. Dessa forma, a presente tese justifica-se por revisar a literatura, buscando compreender e avaliar a existência de potenciais preditores de sucesso no tratamento da depressão através do exercício, revisar a literatura a respeito dos potenciais mecanismos neurobiológicos do efeito antidepressivo do exercício em amostras clinicas, e avaliar a efetividade do exercício físico como um tratamento complementar ao tratamento usual em pacientes internados com depressão grave, bem como, avaliar as potenciais alterações de correlatos biológicos, em marcadores, de neurogênese e de stress oxidativo, em pacientes internados com depressão grave.

2.2 OBJETIVOS

2.2.1 Geral

O objetivo geral do presente estudo foi de avaliar os efeitos antidepressivos do exercício físico, bem como, avaliar as alterações biológicas correlatas em pacientes internados com depressão grave utilizando duas estratégias metodológicas: a) busca na literatura de achados de outros autores (revisões sistemáticas); b) experimento (ensaio clínico randomizado).

2.2.2 Específicos

- Revisar os potenciais preditores e moderadores;

- Revisar os candidatos neurobiológicos para explicar o efeito antidepressivo do exercício;

- Avaliar, utilizando um ECR, os efeitos do exercício físico em desfechos clínicos de pacientes hospitalizados com depressão grave;

- Avaliar, utilizando um ECR, os efeitos do exercício físico em dois marcadores biológicos (TBARS E BDNF) em pacientes internados com depressão grave.

3 REVISÃO DE LITERATURA

3.1 EXERCÍCIO FÍSICO E DEPRESSÃO

Diversos estudos analisaram os efeitos do exercício em diferentes contextos (ex: Pacientes hospitalizados x ambulatoriais; exercício supervisionado x não supervisionado; sozinho x acompanhado ou em grupos; complementar a outros tratamentos x monoterapia), gravidades de doença (leve x moderado x grave) e intervenções de exercício (ex: aeróbico x anaeróbico x combinado) (4, 8, 9). De um modo geral, o exercício se mostra eficaz para tratar o TDM, apresentando um tamanho de efeito que varia de leve a forte para a redução dos sintomas depressivos (4, 8, 9, 23). Dessa forma, algumas entidades já incorporaram a recomendação de exercício físico nos seus guidelines para o tratamento da depressão (24, 25)

Alguns dos primeiros estudos a utilizar o método cientifico para avaliar os efeitos do exercício físico em pacientes deprimidos foram os estudos de Robert Brown (26), John Greist (27) e alguns anos depois o de Egil Martinsen (10). Naturalmente, estudos pioneiros em qualquer área estão sujeitos a incorrer em um maior número de vieses, devido a algumas falhas metodológicas importantes, como o pequeno numero de participantes envolvidos, ausência de controle de outros tratamentos e outros fatores de confusão. Tendo estes estudos como base, dezenas de novos estudos foram realizados no intuito de aperfeiçoar as intervenções, totalizando-se 39 ensaios clínicos randomizados, de acordo com a ultima meta-análise da colaboração Cochrane (4). Os estudos mais recentes trouxeram diversos avanços na compreensão dos efeitos antidepressivos do exercício em pacientes com TDM.

Contudo, muitos deles continuaram a apresentar limitações importantes como heterogeneidade da amostra, falta de randomização ou randomização inadequada, ausência de instrumentos padronizados de diagnósticos, entre outras limitações, deixando diversas lacunas na literatura a serem exploradas. Algumas destas limitações - como os efeitos do exercício em subgrupos específicos (ex: pacientes graves), o uso em adjuntivo com outros tratamentos, a prescrição, os potenciais moderadores e medidores - serão revisados a seguir.

3.2 EXERCÍCIO FÍSICO EM DIFERENTES GRAVIDADES DE EPISÓDIOS DEPRESSIVOS

Martinsen (10) avaliou os efeitos de nove semanas de exercício físico aeróbico nos sintomas depressivos de pacientes internados com episodio depressivo grave. No fim das nove semanas, os participantes tiveram reduções significativamente maiores quando comparados aos pacientes que estavam no grupo controle, sem exercício. Cabe ressaltar que, neste estudo, não houve nenhum controle e não foi apresentado nenhum dado acerca dos outros tratamentos que os pacientes estavam recebendo. Outra limitação importante do estudo é que não foi utilizado nenhum instrumento diagnóstico, o que não deixa claro se os participantes incluídos tinham exclusivamente o diagnostico de TDM ou se foram incluídos pacientes com Transtorno do Humor Bipolar (THB) em episodio depressivo grave.

Outro estudo, conduzido na Alemanha (11), corroborou os resultados do estudo norueguês de Martinsen (1985). De acordo com os autores, uma intervenção breve, de 10 sessões consecutivas de exercício, é eficaz para reduzir os sintomas depressivos e melhorar a Qualidade de Vida (QV) de pacientes internados com depressão grave. No entanto, a amostra foi também composta por pacientes com THB e distimia.

Interessantemente, algumas meta-análises compararam os efeitos antidepressivos do exercício em diferentes gravidades de episódios depressivos. Craf e Landers (5) mostraram um tamanho de efeito maior em depressões com gravidade de moderada a grave (g = -0.88) quando comparadas a depressões de gravidade leve a moderada (g = -0.34), sendo estes tamanhos de efeito forte e moderado, respectivamente.

Chad Rethorst et al (8), compararam o tamanho de efeito do exercício na redução dos sintomas depressivos em estudos que utilizaram amostras com o diagnóstico clinico de depressão e sem o diagnóstico. Os resultados mostram um tamanho de efeito maior em amostras clínicas (g = -1.03) quando comparado a amostras não clinicas (g = -0.58).

Contrariamente a esses achados, existe uma crença comum de que pacientes deprimidos não participam de exercícios extenuantes (28). Entretanto, segundo Martinsen (29), não existem evidencias empíricas que suportem essa crença. E ainda, os estudos de Martinsen (30) e Martinsen e Medhus (31) avaliaram a importância dada pelos pacientes à prática de exercício físico. Segundo a avaliação dos próprios pacientes, o exercício foi

reconhecido como sendo tão importante quanto outros tratamentos (ex: psicoterapias e fármacos).

3.3 COMPARAÇÕES E RELAÇÕES COM OUTROS TRATAMENTOS

James Blumenthal conduziu dois estudos comparando exercício e antidepressivos. Em seu estudo realizado em (32) o autor comparou três grupos de intervenção: um que utilizou o exercício como monoterapia, um que utilizou Sertralina como monoterapia e outro grupo que combinou Sertralina + exercício. Nesse estudo, não houve diferença na redução dos sintomas entre o grupo exercício e o grupo Sertralina. Entretanto, ambos foram menos efetivos que o grupo que combinou exercício + Sertralina. De forma semelhante, Blumenthal (33) comparou quatro grupos: dois que faziam exercício (um grupo supervisionado e outro que fazia individualmente em casa), um que utilizou Sertralina como monoterapia e um grupo controle (pílulas placebo). Ao final do estudo, não houve diferenças nas taxas de remissão e resposta entre os grupos exercício e o grupo Sertralina, sendo ambos superiores ao placebo.

Estudos comparando o exercício com psicoterapias são mais escassos e apresentam limitações bastante importantes. Klein (34) comparou exercício, relaxamento e terapia de grupo, mostrando que ambas as intervenções foram eficazes na redução dos sintomas, sem diferenças entre os grupos. Entretanto, o estudo apresentou uma perda de aproximadamente 50% dos participantes. Freemont e Craighead (35), no estudo mais recente localizado pela ultima revisão da Cochrane (2013) que comparou exercício a psicoterapia comparou

três grupos, um grupo exercício, um grupo de Terapia Cognitivo Comportamental (TCC) e outro grupo combinado (exercício + TCC), também não encontrou diferenças entre as intervenções.

Quando os estudos são meta-analisados (4), não são encontradas diferenças entre farmacoterapias e exercício ou psicoterapias e exercício. Naturalmente, existem muitas dificuldades metodológicas entre comparar intervenções diferentes. Por exemplo, é muito difícil controlar os efeitos inespecíficos da interação entre o paciente e os profissionais envolvidos, ou ainda, do diferente numero de sessões nos estudos.

Uma das vantagens do exercício é que ele pode ser utilizado como intervenção complementar, ou adjuntiva, simultaneamente com outras intervenções, promovendo um efeito aditivo na redução dos sintomas depressivos (36, 37). Diferentemente de alguns tratamentos como a eletroconvulsoterapia (ECT), o exercício físico não requer um período de *washout* medicamentoso.

3.4 PRESCRIÇÃO DO EXERCÍCIO

Exercício físico é um conceito muito heterogêneo, composto por diversas atividades, métodos, intensidades e volumes. Cabe ressaltar que atividade física e exercício físico são conceitos diferentes, sendo a atividade física: “qualquer movimento corporal produzido pelos músculos que resultem em um aumento do gasto calórico” e o exercício físico: “movimentos corporais

planejados, estruturados e repetitivos realizados, para manter ou melhorar um ou mais componentes da aptidão física” (38).

Ainda não estão estabelecidas quais são as doses mínimas ou ideais, das variáveis da prescrição do exercício prevenir ou tratar a depressão. Não está claro a contribuição das seguintes variáveis: modalidade, tempo de sessão, frequência, intensidade e gasto enérgico total de trabalho.

Alguns estudos compararam diferentes modalidades de treinamento: Martinsen (1989) comparou um grupo que se exercitou a 70% da capacidade aeróbica máxima com um grupo que realizou exercícios anaeróbicos de “baixa intensidade”, sendo estes exercícios de força, flexibilidade e equilíbrio e não encontrou diferenças entre os grupos nos sintomas depressivos. Uma redução significativa nos sintomas depressivos foi encontrada nos dois grupos. Doyne et al (39) realizaram um estudo em mulheres comparando um grupo de atividades aeróbicas (corrida) na intensidade de 80% da frequência cardíaca máxima, com um grupo que realizou exercícios de força, trabalhando em 10 estações, mantendo a frequência cardíaca entre 50%-60% da frequência cardíaca máxima e um grupo controle que ficou em uma lista de espera. Segundo os autores, não houve diferença entre os dois grupos de exercício, tendo ambos os grupos diminuído os sintomas depressivos. Apesar da pouca quantidade de estudos comparando diretamente as duas modalidades, Cooney (2013), mostrou em uma meta-análise pela primeira vez, que os exercícios anaeróbicos parecem ter um tamanho de efeito maior quando comparado aos aeróbicos na redução dos sintomas depressivos de pacientes deprimidos. Dado contrário as de meta-análises prévias.

As relações entre o tempo de sessão, expresso em minutos, e o efeito antidepressivo do exercício não estão bem estabelecidas. Nenhum estudo, ao melhor de nosso conhecimento, comparou o efeito de sessões breves com sessões mais longas de exercício. Entretanto, Rethorst (8) mostrou, em uma meta-análise, que estudos que utilizaram sessões com duração entre 45-59 minutos apresentam um tamanho de efeito maior quando comparada com durações maiores que 60 minutos ou menores que 44 minutos.

Um único estudo, de Dunn et al. (40), comparou duas frequências diferentes, mostrando que não houve diferenças entre quem se exercitou 3 vezes quando comparados com aqueles que se exercitaram 5 vezes por semana na intensidade ou na taxa de remissão dos sintomas. A diferença ocorreu apenas entre aqueles que realizaram doses diferentes de exercício, independentemente da frequência.

De forma independente, as variáveis relacionadas ao exercício não descrevem adequadamente a real “dose” de exercício, ou o impacto metabólico total. Dessa forma, o gasto calórico total, gerado pela interação entre modalidade, duração e a intensidade de exercício pode ser uma estratégia interessante se avaliar o impacto da sessão no metabolismo. Segundo Dunn (2005), uma “dose” de exercício aeróbico de 17.5 kcal por kilograma de peso por semana (kcal/kg/semana) tem maior efeito antidepressivo comparado a uma dose de 16 kcal/kg/semana, sendo que não houve diferença entre os pacientes que realizaram uma dose de 7 kcal/kg/semana com aqueles que realizaram sessões de alongamento ou ficaram no grupo controle(lista de espera). Da mesma forma, Trivedi et al (41) encontrou maiores taxas de resposta e um menor Numero Necessário para Tratar (NNT) em pacientes que

realizaram a dose de 16 kcal/kg/semana comparado aqueles que realizaram a dose de 4 kcal/kg/semana, também utilizando exercícios aeróbicos. Este estudo sugere a existência de uma relação de dose-resposta entre impacto metabólico total e o efeito anti-depressivo do exercício. Estudos futuros, utilizando análises de meta-regressão, poderiam auxiliar na identificação das formas mais eficazes de prescrever o exercício.

Cabe ressaltar que não existe um padrão claro que possibilite uma sessão única ou um modelo "*one size fit for all*" para se obter os efeitos antidepressivos do exercício em pacientes clinicamente deprimidos. A prescrição do exercício deve ser individualizada, buscando atender as necessidades, possibilidades e preferências de cada indivíduo, que tenha um planejamento com uma progressão gradual e constante, de modo a tornar o exercício físico factível e ao mesmo tempo eficaz (42, 43).

3.5 PREDITORES/MODERADORES DO EFEITO ANTIDEPRESSIVO DO EXERCÍCIO (ARTIGO #1)

Evidences towards a personalized medicine in exercise treatment for depression

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Em processo de submissão

3.6 POTENCIAIS MECANISMOS (MEDIADORES) BIOLÓGICOS DE AÇÃO DO EFEITO ANTIDEPRESSIVO DO EXERCÍCIO EM PACIENTES CLINICAMENTE DEPRIMIDOS (ARTIGO #2)

Neurobiological effects of exercise on Major Depressive Disorder: A systematic review

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Key-words: Depression; Exercise; Inflammation; Hormones; Neurotrophines; Neuroplasticity; Neuronal Activity; Oxidative stress.

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5 RESULTADOS

5.1 ARTIGO #3

Publicado no Journal of Psychiatric Research (IF – 4.09)

Exercise and severe major depression: Effect on symptom severity and quality of life at discharge in an inpatient cohort

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Abstract:

Background: Exercise is a potential treatment for depression. However, few studies have evaluated the role of adjunct exercise in the treatment of severely major depressed inpatients. The goal of this study was to evaluate the effects of add-on exercise on the usual treatment of severely depressed inpatients.

Methods: Fifty participants were randomized to an exercise (exercise + usual treatment) or a control (usual treatment) group. Twenty-five patients were randomly allocated to each group. The participants in the exercise group performed three sessions per week throughout the hospitalization period, with a goal dose of 16.5 kcal/kg/week plus the usual pharmacological treatment. Depressive symptoms and the Quality of Life (QoL) of the participants were assessed at the baseline, the second week, and discharge.

Results: A significant group x time interaction was found for depressive symptoms and the physical and psychological domains of QoL. Differences between groups occurred at the second week and discharge with respect to depressive symptoms and the physical and psychological domains of QoL. There was no difference in the remission rate at discharge (48% and 32% for the exercise and control group, respectively). An NNT of 6.25 was found. No significant baseline characteristics predict remission at discharge.

Conclusion: Add-on exercise is an efficacious treatment for severely depressed inpatients, improving their depressive symptoms and QoL. Initial acceptance of exercise remains a challenge.

Key words: Exercise, Depression, Quality of Life.

Background

Depression is a highly prevalent condition with a life-long prevalence of approximately 12% in Brazil and 17% in the United States (Andrade et al., 2003). Moreover, depression is a leading cause of disability worldwide, accounting for 40.5% of the disability-adjusted life years (DALYs) caused by mental and substance-use disorders (Whiteford et al., 2013).

Currently, the first option for the treatment of depression is pharmacological antidepressants (Nemeroff, 2007). Despite the wide use of such antidepressants, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that only approximately 18% of patients remitted after 14 weeks of an adequate trial of a single agent (citalopram). In the second phase, after switching or augmentation of treatment, the remission rates ranged from 18% to 30% (Sinyor et al., 2010).

In severe depression, electroconvulsive therapy (ECT) is indicated as the most effective strategy; however, the side effects (memory impairment, nausea, headache, and temporary confusion) and the cardiovascular and neurological risks limit its broader use (Nemeroff, 2007). Also, despite approximately 50% of patients submitted to ECT were satisfied with the results, only 36% would only 36% would agree to perform an ECT again (Antunes et al., 2009).

Exercise, in contrast, is receiving much attention as a therapeutic option for depression (Daley, 2008, Deslandes et al., 2009, Mura et al., 2014, Schuch and de Almeida Fleck, 2013, Stanton and Happell, 2013, Stanton and Reaburn, 2013, Strohle, 2009). Indeed, several meta-analyses have revealed that exercise has at least a moderate effect on symptom reduction in major depression, serving as a useful strategy for depression of different severities and presenting few side effects (Cooney et al., 2013, Craft and Landers, 1998, Rethorst et al., 2009, Stathopoulou et al., 2006). Despite these encouraging results, most studies have evaluated the effects of exercise on moderately depressed outpatients (Cooney, Dwan, 2013, Craft and Landers, 1998, Rethorst, Wipfli, 2009, Stathopoulou, Powers, 2006) and only two evaluated in samples that were also composed by severely depressed inpatients. The studies, however, were

not exclusively composed by severely depressed inpatients (one had bipolar patients and the other did not used any criterion excluding bipolar depressed inpatients (Knubben et al., 2007, Martinsen et al., 1985).

Depression significantly affects Quality of Life (QoL) (Angermeyer et al., 2002, Berlim et al., 2004, Berlim et al., 2005, Caldieraro et al., 2013), and some evidence points to an inverse relationship between depression intensity and QoL (Caldieraro, Baeza, 2013). Furthermore, some studies have revealed that, even after achieving remission, some inpatients still experience impairments in QoL (Angermeyer, Holzinger, 2002, IsHak et al., 2011). In contrast, exercise has positive effects on some QoL domains in healthy individuals (Gill et al., 2011, Gillison et al., 2009) and in moderately depressed patients (Brenes et al., 2007, Carta et al., 2008, Mota-Pereira et al., 2011a, Schuch et al., 2011b).

To the best of our knowledge, no study has evaluated the effects of exercise on depressive symptoms and QoL on a sample composed exclusively of severely depressed (HAM-D > 25) inpatients.The primary aims of the present study were the following: 1) evaluate the effects of add-on exercise to the usual treatment on the depressive symptoms (reduction of symptoms, remission and response rates) of severely depressed inpatients. The secondary outcomes were QoL, adherence and the predictors of response to adjunct exercise on severely depressed inpatients.

Methods

Trial Design

The study was a randomized, controlled trial with two parallel arms. It was designed to evaluate the effects of add-on exercise in the treatment of severely depressed inpatients. The study was conducted in a single center in a university hospital (Hospital de Clinicas de Porto

Alegre, Brazil). The study was approved by the local ethics committee (07-438) and was registered as a clinical trial (www.clinicaltrials.gov) (Register: NCT01899716).

Participants

Eligible participants were major depressed inpatients evaluated trough the Mini International Neuropsychiatric Interview (MINI) according to the DSM-IV criteria (Association, 1994). The inclusion criteria were the following: score of 25 or higher on the Hamilton scale for depression (HAM-D), indicating very severe depression (Hamilton, 1967), not being involved in other physical activity programs during the hospitalization, aged between 18 and 60 years and possession of the capacity to read, understand and sign the informed consent statement. The exclusion criteria were as follows: current use of beta-blocking medications, psychiatric diagnosis of bipolar depression, schizophrenia, anorexia, dependence or abuse of alcohol or other drugs, three or more cardiovascular risk factors on the Physical Activity Readiness Questionnaire (PAR-Q) (Thomas et al., 1992) or any medical condition that limits or contraindicates the practice of exercise.

Interventions

The participants were randomized in two groups: exercise + treatment as usual (intervention) or treatment as usual (usual care). Randomization was conducted by individuals not directly involved in the study and assigned using opaque envelopes without contact with the outcome assessors.

Exercise + treatment as usual: The intervention group had to complete a weekly exercise dose of 16.5 kcal/kg of weight/week of aerobic exercise with a frequency of three times per week. For example, a participant weighing 70 kg had to perform exercise equivalent to 1120 kcal per week. This amount was divided by three to yield a goal of 373 kcal per session. The

exercise dose could be completed using three modalities, stationary bike (CICLE CL 204, CALOI, Brazil), treadmill (ADVANCED 3, ATHLETIC, Brazil) or a “transport” machine (CL 603, CALOI, Brazil). This method was planned to be flexible such that the participants could choose the preferred intensity, instead of a fixed intensity or time of exercise, to complete the daily requirement. This strategy was planned to be consistent with public health recommendations, and because it is flexible, the strategy is feasible for depressed individuals (Dunn et al., 2002, 2005, Trivedi et al., 2011, Trivedi et al., 2006a, Trivedi et al., 2006b).

The exercise sessions were performed individually and supervised by a research staff (FBS). The research staff instructed the patients beforehand on the proper use of the exercise machines and on how to complete the targeted exercise “dose”. The staff only assisted patients regarding exercise-related topics. No structured or components of motivational or cognitive strategies were used. The participants wore heart-rate monitors (Polar cs200, Finland) during the sessions to evaluate their energetic expenditure during the sessions. The exercise data, including the total time of exercise, average intensity, and energetic expenditure, were collected by the research staff. During the sessions, the participants had the option of listening to music according their preferred local radio station.

The sessions were composed of a warm-up, exercise bout, and cool-down. The warm-up consisted of stretching exercises for the lower limbs, 20 sec for each of the following muscular groups: hip extensors, hip flexors, hip adductors, and plantar flexors followed by 4 min of walking at 5 km/h on the treadmill. During the exercise bout, the participants could use different combinations of exercise between or within the sessions according to their preferences. The cool-down was similar to the warm-up. Throughout the study, the participants received other treatments such as antidepressants and/or electroconvulsive therapy (ECT).

Treatment as usual: The participants in the usual care group received their treatment as usual, which consisted of antidepressants and/or ECT. The pharmacological treatments and their respective doses were recorded.

All participants had access to occupational activities. The patients were not receiving psychotherapy. The pharmacological treatments and the date for discharge were decided by staff that were independent of the study.

Assessments, recruitment and outcomes

The aerobic capacity (VO_2), the clinical diagnosis and the resting heart rate were assessed at baseline. The caloric expenditure was calculated for each session. Patients were recruited during the first 24 hours of hospitalization, and outcome assessments were performed at three points: at the baseline (between 24-48 h of hospitalization), the second week of the study (after 14-15 days of the baseline assessment) and discharge (0-24 h before discharge).

Heart rate

The resting heart rate was determined after each participant sat for 5 min using a digital heart rate monitor (Polar cs200, Finland). The maximum heart rate was estimated using the formula proposed by Tanaka (Tanaka et al., 2001). Participants' reserve heart rates were calculated using the Karvonen formula (Karvonen and Vuorimaa, 1988).

Caloric expenditure

During the exercise sessions, a trained physiologist collected the mean heart rate every 5min of the polar devices and estimated the caloric expenditure. The caloric expenditure was estimated using the prediction model proposed by Keytel et al. (Keytel et al., 2005).

Aerobic capacity (VO_2)

To estimate the maximum VO_2, the single-stage sub-maximal test developed by Ebbeling et al. (Ebbeling et al., 1991) was conducted by a trained researcher. The test involved a 4-min warm-up and 4 min of testing on a treadmill (ADVANCED 3, ATHLETIC, Brazil).

During the warm-up, a comfortable speed between 2.0 and 4.5 mph was chosen by each participant with a grade of 0%. At this stage, the heart rate needed to remain between 50% and 70% of the age-predicted maximal heart rate. 'During the second, 4 minute phase of the test, treadmill speed was maintained and the grade increased to 5%. The steady-state heart rate was determined from the average heart rate during the final 30 sec of the last 2 min at the 5% grade. On completion of the test, an additional four minutes of walking at 0% grade was performed as a cooldown..

Diagnosis and pharmacological treatments

Diagnosis was evaluated with the Mini International Neuropsychiatric Interview (MINI) (Amorim, 2000, Association, 1994) by a psychiatrist. MINI evaluates current and past diagnoses using the DSM-IV criteria for mental disorders. MINI was translated to and validated in Brazilian Portuguese by (Amorim, 2000). The name and doses of pharmacological treatments were recorded at each assessment. The pharmacological treatments were converted to imipramine equivalents according to the strategy proposed by Bollini et al. (Bollini et al., 1999).

Depressive symptoms

The 17-item Hamilton scale for depression (HAM-D) (Hamilton, 1967) was the main outcome of the study. The HAM-D is the most widely used instrument for the assessment of the intensity of depressive symptoms. It is a clinician-rated scale composed of 17 items in which higher scores indicate greater depression intensity. In the present study, scores of 7 or less on the HAM-D were considered to indicate remission and a decrease of 50% of symptoms as response. The HAM-D assessments were performed by trained and blinded psychiatry residents.

Quality of Life

QoL was evaluated with the World Health Organization Quality of Life Assessment Instrument – Brief version. (WHOQOL-BREF) (1998). WHOQOL-BREF was translated and transculturally validated in Brazilian Portuguese (Fleck et al., 2000). The instrument is a self-rated scale composed of 26 items with scores ranging from 0 – 100. The scores were measured in four domains (physical, psychological, social relationships and environment), in which higher scores indicate better QoL.

Sample size test

The sample size estimate for the main outcome (HAM-D scores), which featured a two-sided type 1 error probability of 5% and a power of 90%, revealed the necessity to include 21 participants in each intervention group to detect a minimal relevant difference of 3 points on the HAM-D. The number of participants was inflated by 20% to ensure the statistical power of the analyses considering potential drop-outs, resulting in 25 individuals per group.

Analysis

Data are presented as means and standard deviation (SD) or means and standard error (SE). Categorical data are presented as frequencies. The participants' characteristics at baseline were compared between the exercise and usual care groups using one-way ANOVA or X^2 tests.

Data were analyzed using repeated-measure linear mixed models. An intent to treat analysis was conducted using the likelihood estimate of missing data present in the mixed-model analyses. The following covariance structures were tested: Diagonal Toeplitz, Huynh-Feldt, Akaike, Unstructured, and Auto-Regressive 1st order. The principle that best suited the subtests was used as a covariance matrix for each test. Age and gender were selected *a priori* and were included as possible covariates in the mixed models. The results of mixed models are expressed as model-based means adjusted to age, gender, and assessor. Potential baseline

predictors of response were tested using the Spearman correlation. Analyses were performed with the software SPSS 18.0.

Results

A total of 106 patients met the criteria and were invited to participate in the study. Of these patients, 56 (52.8%) refused to participate and 50 were randomized to the exercise + treatment as usual group (*n*=25) or the treatment as usual (usual care) group (*n*=25). See the detailed flowchart in Figure 1.

Insert Figure 1 here

Baseline data are shown in Table 1. The sample was predominately composed by women, had an average age of 40.30 years, weight of 66.85 kg, height of 1.63 m, body mass index (BMI) of 25.15, and resting heart rate of 85.84 beats per minute (BPM). Most of the participants had parents with a history of, current diagnosis of or treatment for major depression (66%) and were non-smokers before hospitalization (58%). No differences were found between the groups in gender distribution, age, weight, height, resting heart rate, previous tobacco use, or family history of depression. A trend characterized by a higher maximum VO_2 was observed for the exercise group. The difference, however, was not statically significant.

Insert Table 1 here

Depressive symptoms

Significant time, (F=310.94; p<0.001) group and group x time interactions were also found (F= 3.45; p=0.04). The differences between groups occurred in the second week, with a difference of 4.41 points (95% CI: -7.57 to 1.25; p=0.007), and at discharge, with a difference of 3.70 points (95% CI: 6.21 to 1.19; p=0.005) (Figure 2).

Insert Figure 2 here

There were no differences in the remission [n=12(48%) x n=8(32%); p=0.248] and response [n=21(84%) x n=15(60%); p=0.114] rates between the exercise and the usual care group. The Number Needed to Treat (NNT), calculated using the remission rate was 6.25.

Quality of Life

A significant time effect was found for the physical, psychological, social relationship and environment quality of life domains. A significant group x time interaction was found only for the physical and psychological domains. In the physical domain, the difference between the groups was 15.64 points (95% CI: 6.05 to 25.23; p=0.002) at the second week and 14.91 points (95% CI: 6.3 to -23.45; p=0.001) at discharge. For the psychological domain, the difference between groups was 12.99 points (95% CI: 1.68 to 24.29; p=0.025) at the second week and 19.10 points (95% CI: 9.58 to 28.62; p=0.01) at discharge. No significant group x time interaction was found for the social relationship or environment domains. The data are shown in Table 2.

Insert Table 2 here

Dropouts and hospitalization length

Three dropouts were reported (6%), two in the intervention group (8%) and one in the usual care group (4%). The reasons for dropout in the exercise group were lack of interest in/motivation to exercise (n=2). The participant in the usual care group had a “quick discharge”, and the corresponding data could not be collected. There were no adverse events in the exercise group. The mean (SD) hospitalization length was 23.36 (9.0) days for the exercise + treatment as usual group and 21.32 (8.2) days for the usual care group. There was no difference in the hospitalization length between groups (F=0.68; p=0.41).

Predictors of remission

Age, gender, weight, BMI, number of previous episodes and baseline HAM-D scores were tested. No significant predictors were identified for the whole sample or within either group.

Pharmacological and other treatments

The distribution of pharmacological treatments and ECT was not different between groups at any moment (Table 3). No significant group or time effect was found when comparing the doses using imipramine equivalents (data not shown). Using the same strategy, there was a non-significant trend (p = 0.09) for the group x time interaction. The average doses taken by the participants at discharge were 114.40 (25.1) mg and 195.32 (27.7) mg, respectively, for the exercise and usual care groups.

Insert Table 3 Here

Exercise intervention delivered

The mean (SD) length of each participant's session was 42.69 (15.3) min. The average intensity of each session was 58.91% of the heart rate reserve. Participants in the exercise group burned an average of 274.73 (44.3) kcal per session. Twenty two exercise sessions were not performed of a total of 237 (9.28%).

Discussion

The major finding of the present study was that add-on exercise to the conventional treatment of severely depressed inpatients was an effective strategy for reducing depressive symptoms and improving QoL. Despite the symptom reduction, there was no statistically significant difference in the remission or response rates between the groups at discharge or in the length of hospitalization.

The results support the previously published preliminary findings of this study (Schuch et al., 2011a) and are in accordance with the results other previous studies (Cooney, Dwan, 2013, Craft and Landers, 1998, Rethorst, Wipfli, 2009, Stathopoulou, Powers, 2006). For example, Knuben (Knubben, Reischies, 2007) showed significant effects of adjunct aerobic exercise after ten consecutive sessions based on clinician and self-rated assessments in 20 inpatients diagnosed with moderate to severe episodes (bipolar depression, major depression and dysthymia). The difference between the groups on the Bech-Rafaelsen Melancholy Scale (BRMS), a scale derived from the HAM-D, was approximately 4.3 points, and the results were very similar to those found in the present study (4.4 points at the second week and 3.7 points at discharge). However, Knuben et al. included inpatients diagnosed with bipolar disorder and dysthymia; therefore, the results may not be representative of a sample exclusively composed of majorly depressed inpatients. The results of the present study are also in accord with those of Martinsen et al. (Martinsen, Medhus, 1985), who found antidepressant effects of adjunct exercise on major depressed inpatients. However, it is not clear whether all included patients were severely depressed.

Improvements in the physical and psychological domains of QoL were found for exercise participants. These findings are in accord with those of previous studies with adjunct exercise in moderately depressed women (Carta, Hardoy, 2008) and are particularly important for the following two reasons: 1) exercise appears to promote an increase in some domains of QoL, whereas patients treated with medications and other treatments still present an impaired QoL (20, 21). For example, some studies have shown that exercise improves sexual function in depressed patients compared to antidepressants (Hoffman, Babyak, 2009, Lorenz and Meston, 2012). 2) QoL is inherently a Patient Reported Outcome (PRO) and reflects the perception of the participant concerning the results of a therapeutic approach (Johnston et al., 2013). Some evidence indicates that patients and clinicians may have different judgments concerning the results of an intervention (Dunlop et al., 2011), and it is possible that a PRO could evaluate other aspects beyond clinical symptoms as outcomes (IsHak, Greenberg, 2011). For this reason, the Food and Drug Administration (FDA) requires that clinical trials show significant improvements in PROs before the approval of a new treatment (2006).

There are several possible mechanisms to explain the antidepressant effects of exercise. Didactically, two broad categories of mechanisms can be discussed: biological/physiological and psychological mechanisms.

The biological mechanism involves changes in metabolism and the function of several biomarkers such as serotonin (Wipfli et al., 2011), beta-endorphins (Dishman and O'Connor, 2009, Heyman et al., 2012) endocannabinoids (Dietrich and McDaniel, 2004, Heyman, Gamelin, 2012), brain-derived neurotrophic factor (BDNF) (Gustafsson et al., 2009, Laske et al., 2010, Schuch et al., 2014, Toups et al., 2011) oxidative stress, and inflammation (Eyre and Baune, 2012, Eyre et al., 2013). Genetic pathways, such as pleiotropy or gene-by-exercise interactions, also appear to be possible explanations related to the antidepressant effects of exercise (de Geus and de Moor, 2008).

Several “psychological” mechanisms have been proposed to explain the antidepressant effects of exercise, for example, increased self-esteem (Craft, 2005, Foley et al., 2008), sexual function, (Hoffman et al., 2009) and sleep (Rethorst et al., 2013).

The dropout rates found in the present study were 8% for the exercise group and 4% for the usual care group. These rates are lower than the rates found in augmentation studies with supervised exercise in outpatients (28%) (Dunn, Trivedi, 2005) and similar to those found studies that used a mixed supervised/unsupervised, adjunct design in outpatients with resistant depression (6%) (Mota-Pereira et al., 2011b). Some possible explanations for the low dropout rate include the following: 1) participants who agreed to enter the study knew and agreed with the possibility of exercising. Thus, participants who did not accept this possibility did not enter the study. 2) The lack of need to move to a distant exercise site. In the present study, the sessions were performed inside a psychiatric unit in an exercise room. 3) The setting. The study was conducted in a hospital setting where there is constant supervision and a greater control on the treatments received. 4) The short duration of the intervention. In a short-term intervention, Knubben et al. (Knubben, Reischies, 2007) reported only one dropout and no side effects in a two-week intervention of depressed inpatients (including bipolar and unipolar depression). 5) The exercise protocol. This exercise protocol was designed to be effective, consistent with public health recommendations, and simultaneously flexible, allowing for the participants to exercise at their preferred intensity and modality (Dunn, Trivedi, 2002, Trivedi, Greer, 2006b). It is possible that the flexible design of the intervention was more suitable, enjoyable, and attractive than rigidly structured sessions (e.g., 30 min at 70% of the maximal heart rate). This hypothesis is supported by the study of Krogh et al. (Krogh et al., 2014), which showed that higher satisfaction with the exercise predicted higher adherence in exercise-based clinical trials. Importantly, the “dose” achieved not necessarily means more intense exercise. Some patients preferred performs longer sessions with lower intensities of exercise, whilst other preferred shorter sessions at higher intensity. This model of session does not explain the role of the volume x intensity of exercise, but a global caloric expenditure.. 6) Despite the previous experience with exercise and knowledge of exercise as an efficacious treatment may be a factor of adherence, the exercise practice in the last year may not explain the adherence in the study since 80% of patients in the exercise group have not exercised regularly in the last year. Further

studies evaluating the role of baseline physical activity and believe and expectancy in the efficacy of exercise are needed for a broader comprehension of the predictors of adherence.

Despite the low dropout rate, the acceptability was also low. In the present study, approximately half of the patients did not participate in the study. This refusal rate is greater than the refusal rate (until randomization) shown in studies of moderately depressed outpatients, with exercise as monotherapy (23%) (Krogh et al., 2012). These differences can be explained by the differences in the severity of depression at baseline (light to moderate and severe).

Studies have identified certain clinical factors as predictors of response to exercise treatment. For example, the TREAD US found that men presented higher remission rates at higher levels of exercise than women. In the TREAD US study, depression history also predicted response to exercise (Trivedi, Greer, 2011). Regarding the severity of symptoms at baseline, Blumenthal et al. (Blumenthal et al., 2007) demonstrated no predictive effects of the depressive symptoms at baseline on the remission rate. In the present study, age, BMI, weight, chronicity (number of previous episodes) and symptom severity at baseline did not predict remission at discharge. The main difference between the present study and the TREAD US study may be related to the different samples used. Despite the differences in samples between the present study and the Blumenthal study (Blumenthal, Babyak, 2007), both studies corroborate the finding that depressive symptoms may not be a significant predictor of response. However, the present study featured a small sample size (n=50), and more studies with larger sample sizes and including an analysis of other biological and clinical characteristics are needed to identify subgroups that might be more responsive to exercise.

Limitations and strengths

The study has the following strengths. 1) The present study is, to the best of our knowledge, the first randomized, controlled trial investigating the add-on effects of exercise to the usual treatment on depressive symptoms and the QoL for a sample composed exclusively by

inpatients with severe major depressive disorder. 2) The add-on design used allows for a "real-world" analysis, answering questions regarding effectiveness, tolerability and the safety of adding exercise to the treatment of inpatients with severe major depression. 3) The intervention was offered to all severely depressed inpatients that would be able to perform exercise, excluding those who were using beta-blocking medications and/or were pregnant, with ages ranging from 18 to 60. Thus, it is possible that the results of the present study reflect a scenario that is very similar to real-world cases in psychiatric hospitalizations and therefore have great external validity.

The study has the following limitations. 1) Due to the nature of the intervention, the participants were not blinded to the treatment. However, this is a common limitation of clinical trials involving exercise, especially when the control group does not receive an additional active intervention in a study. 2) There was a small sample size for remission outcome. There were no differences between groups in the remission rates at discharge. In the present study, the add-on design included a control group in which the participants received the usual treatment, composed of pharmacological treatment and in some cases ECT. Thus, a high remission rate (32%) was found. Despite the higher remission rate of the exercise group (48%), the difference was not statistically significant. The lack of significance in the remission rate might be explained by the lack of statistical power to detect significant differences between groups. Despite the lack of statistical significance, the observed NNT of 6.2 is clinically relevant. This NNT is even lower than the NNT found in previous studies in augmentation studies in treatment-resistant depressed patients (Trivedi, Greer, 2011). 3) The participants took different antidepressants and doses over time. The medications and doses were recorded, and the comparison of imipramine equivalents revealed that there was no difference between the groups. The analysis also revealed a group x time interaction, but it was not significant. The comparison of the antidepressants in imipramine equivalents does not eliminate but does decrease the risk of a systematic bias. Furthermore, the imipramine equivalents tended to be lower in the exercise group at discharge. 4) One could argue that additional effects might be related to non-specific factors, such as the support offered by the research team. However, the

research staff focused only on aspects related to exercise and did not provide any structured therapy for the participants. Moreover, the participants in the usual care group had the option to participate in other routine care activities, whereas the participants in the exercise group were performing the sessions. 5) Because 52% of the patients refused to participate in the study, the results cannot be extrapolated to all severely depressed inpatients but rather only to patients that are favorable to exercise. These result shows that only about half of patients accept participating in an exercise intervention during hospitalization. However, this participation rate is similar to the participation rates found in other studies involving depressed inpatients (Lapid et al., 2011). The predictors of acceptance/non-acceptance should be further investigated.

Even given the abovementioned limitations, the present study suggests that exercise is a safe and efficacious add-on alternative for severely depressed inpatients. However, initial acceptance is still a major challenge in the use of exercise in this population. The high external validity observed in this study supports the use of exercise as a viable treatment for inpatients with severe depressive disorder, decreasing their depressive symptoms and improving their QoL.

Further studies should elucidate the pathways related to the additive effects of exercise in conjunction with antidepressants. Moreover, further studies with larger sample sizes are needed to evaluate the predictors of adherence and response to exercise treatment.

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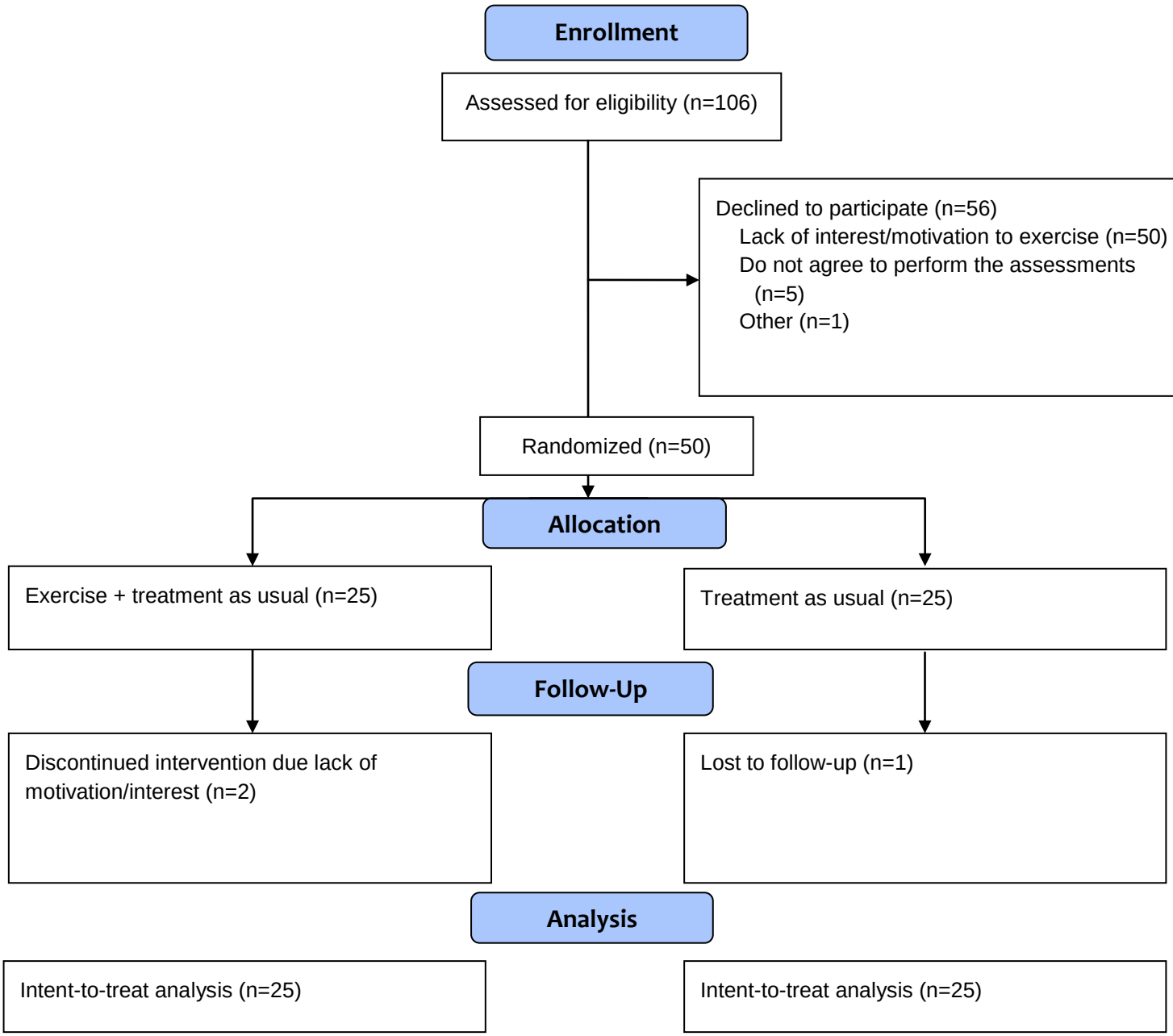

Figure 1. Participants flow diagram

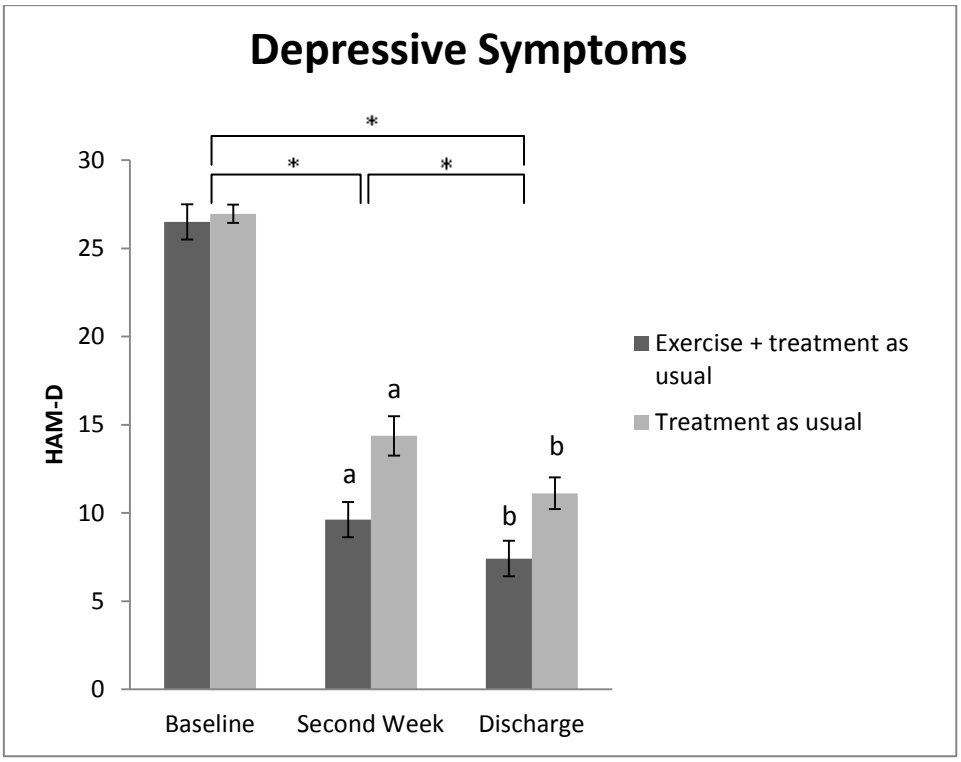

Figure 2. Effects of add-on exercise on depressive symptoms. Data expressed as model-based adjusted means and standard errors. Data adjusted by age, gender and assessor.
Post-hoc tests results, for time effect * and for group x time interaction[a,b]:
* $p < 0.001$
[a] $p = 0.007$
[b] $p = 0.005$

Table 1. Baseline characteristics

	Exercise Group (*N*=25)	Control Group (*N*=25)	*p* value
Age, years	38.84 (11.5)	41.76 (10.4)	0.35
Females, n (%)	18 (72%)	19 (76%)	0.74
Weight, kg	65.83 (11.5)	67.88 (12.8)	0.55
Height, m	1.63 (0.0)	1.62 (0.0)	0.84
Body mass index, kg/m^2	24.85 (5.2)	25.46 (3.5)	0.63
$VO_{2,}$ ml.kg.min-¹	29.12 (5.0)	26.40 (5.2)	0.06
Rest Heart Rate, BPM	84.72 (11.7)	86.56 (10.1)	0.55
Previous Tobacco use, n (%)	10 (40%)	11 (44%)	0.77
Previous episodes, n	2.40 (1.2)	2.04 (1.0)	0.27
HAM-D, score	26.52 (1.8)	26.96 (2.7)	0.51
History of depression in parents, n (%)	18 (75%)	15 (60%)	0.37
Regular exercise in the last year, n (%)	5 (20%)	3 (12%)	0.70

Data presented as mean (SD) or frequency (%). Differences analyzed trough ANOVA or X^2 tests. kg=kilograms, m=meters, VO_2 = maximal consume of oxygen, ml.kg.min-¹=milliliters.kilogram.minute-¹, BPM=beats per minute, HAM-D=Hamilton scale for depression.

Table 2. Effects of exercise on Quality of Life - WHOQOL

Domain	Time	Group		Time effect		Group x time interaction	
		Exercise (n = 25)	Control (n = 25)	F value	p value	F value	p value
Physical	Baseline[a]	35.36 (2.6)	33.28 (2.7)	32.96	< 0.001	4.08	0.023
	Second Week[b]	61.19 (3.4)*	45.55 (3.4)*				
	Discharge[b]	63.18 (3.1)#	46.83 (3.1)#				
Psychological	Baseline[a]	30.09 (3.5)	25.87 (3.5)	47.28	< 0.001	4.66	0.014
	Second Week[b]	55.75 (4.1)*	42.78 (4.1)*				
	Discharge[b]	60.16 (3.5)#	41.06 (3.5)#				
Social Relationships	Baseline[a]	49.20 (4.7)	40.35 (4.7)	5.59	0.007	1.89	0.162
	Second Week[b]	67.68 (4.4)	48.98 (4.4)				
	Discharge[b]	63.62 (4.1)	51.12 (4.1)				
Environment	Baseline[a]	45.34 (2.6)	42.07 (2.6)	11.16	< 0.001	0.53	0.588
	Second Week[b]	56.25 (3.0)	49.25 (3.0)				
	Discharge[b]	54.70 (3.1)	47.36 (3.1)				

Data analyzed using repeated measurement linear mixed models. Data presented with model-based means adjusted to age and gender and as Mean (Standard Error). The Post-hoc of bonferroni was used to detect where the differences occurred.
Post-hoc results:
Different letters indicates statistical differences in different times.
* indicates significant differences between groups at the second week
# indicates significant differences between groups at the discharge.

Table 3. Pharmacological treatments and ECT

	Exercise (n=25)	Control (n=25)	p value
	Baseline		0.292
Drug free	4	1	
SSRI	3	6	
Tryciclic	4	3	
Mood Stabilizer	1	0	
Tryciclic/SSRI + Tricyclic/SSRI	2	5	
Tryciclic/SSRI + Mood Stabilizer	4	4	
Antipsychotics	1	0	
Tryciclic/SSRI + ECT	1	1	
Tryciclic/SSRI + Antipsychotics	4	3	
ECT + Mood Stabilizer	0	1	
ECT only	1	1	
	Second Week		0.339
Drug free	3	0	
SSRI	5	6	
Tryciclic	2	1	
Mood Stabilizer	3	1	
Tryciclic/SSRI + Tricyclic/SSRI	2	3	
Tryciclic/SSRI + Mood Stabilizer	2	2	
Antipsychotics	2	2	
Tryciclic/SSRI + ECT	2	2	
Tryciclic/SSRI + Antipsychotics	3	4	
ECT + Mood Stabilizer	0	1	
ECT Only	1	3	
	Discharge		0.064
Drug free	4	1	
SSRI	5	4	
Tryciclic	1	1	
Mood Stabilizer	3	0	
Tryciclic/SSRI + Tricyclic/SSRI	2	5	
Tryciclic/ISRS + Mood Stabilizer	3	1	
Antipsychotics	2	0	
Tryciclic/SSRI + ECT	2	5	
Tryciclic/SSRI + Antipsychotics	2	5	
ECT + Mood Stabilizer	0	1	
ECT Only	1	2	

SSRI=Selective Serotonin Reuptake inhibitor, ECT=Electroconvulsive Therapy. The distribution between treatments was tested using chi-square tests. The dropouts were included in the analysis. In case of missing (n =1), the last used medication was carried forward.

5.2 ARTIGO #4

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The effects of exercise on oxidative stress (TBARS) and BDNF in severely depressed inpatients

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Abstract

Background: Exercise can be an effective treatment for depression. Although the efficacy of exercise is well established, little is known concerning the biological changes associated with the antidepressant effects of exercise. Methods: A randomized, controlled trial was conducted to evaluate the effects of adding exercise to to the usual treatment on the thiobarbituric acid reactive substances (TBARS) and brain-derived neurotrophic factor (BDNF) serum levels of severely depressed inpatients. Twenty-six participants were randomized to an exercise group (n=15, exercise + treatment as usual) or a control group (n=11, treatment as usual). The participants in the exercise group completed a targeted dose of 16.5 kcal/kg/week of aerobic exercise, three times per week, throughout their hospitalizations. The control group did not exercise during their hospitalizations. Results: The mean hospitalization length was of 21.63 (4.5) x 23.82 (5.7) days for exercise and control groups, respectively. The exercise group performed a median of 9 sessions. After adjusting for previous tobacco use, a significant group x time interaction was found for TBARS serum levels ($p=0.02$). A post hoc Bonferroni test revealed differences between the exercise and control groups at discharge. A significant time effect ($p<0.001$) but no group x time interaction was found ($p=0.13$) for BDNF serum levels. Conclusions: Adding exercise to the usual treatment of severely depressed inpatients decreases the TBARS serum levels of severely depressed inpatients after 3 weeks. Adding exercise had no additional effects on BDNF serum levels.

Keywords: Exercise; Physical Activity; Major Depression; Major Depressive Disorder; Brain-derived Neurotrophic Factor; Oxidative Stress; Lipid Peroxidation.

1. Introduction

Major depression is a chronic condition with high prevalence [1] and is associated with a heavy burden [2]. The pathophysiology of major depression is a complex and poorly understood phenomenon; however, there is an emerging body of evidence proposing some factors associated with this phenomenon, such as the oxidative stress system and neurogenesis.

Some evidence suggests that oxidative stress might play an important role in depression, being elevated in depressed patients [3-6]. Moreover, Stefanescu and Ciobica [7] provided evidence that different subtypes of depression, based on chronicity, can predict differences in the levels of some oxidative stress markers. Inversely, brain-derived neurotrophic factor (BDNF) levels, the most widely used marker of neurogenesis, are decreased in patients with major depression [8,9]; pharmacologic treatment can increase BDNF levels [9]. Interestingly, some evidence indicates that oxidative stress and neurogenesis may be associated. A study from Kapczinski et al. [10] suggests that the oxidative stress system, assessed through serum thiobarbituric acid reactive substances (TBARS), is inversely correlated with BDNF serum levels in mood disorders.

Notably, exercise has been considered a potential treatment for depression [11-15]. Although the mechanisms of the antidepressant effects are poorly understood, several studies have shown that exercise promotes changes in the oxidative stress system and in neurogenesis. For example, long-term exercise (3–20 weeks) promotes a redox imbalance, decreasing oxidative stress system activity and increasing the antioxidant system's defenses [16-20]. This mechanism is well established in animal subjects and healthy humans; however, to the best of our knowledge, no studies have evaluated the effects of exercise on oxidative stress markers in severely depressed inpatients. Along the same lines, recent studies of non-depressed individuals have shown that exercise can increase BDNF serum levels both acutely (in response to a single session) and in response to a training period [21-24]. In depressed patients, only two studies have investigated the acute response to exercise, and one study has investigated the response to long-term intervention. Gustafsson et al. [25] and Laske et al. [26] found increased BDNF

serum levels after a single bout of exercise. However, a recent study conducted by Toups et al. [27] showed no increases in the BDNF serum levels of mildly to moderately depressed patients after 12 weeks of aerobic physical exercise. To the best of our knowledge, no study has evaluated the effects of adding exercise to usual treatment on the BDNF serum levels of severely depressed inpatients.

The objective of this study is to determine the effects of adding exercise (independent variable) to the usual treatment of severely depressed inpatients on two biological markers (dependent variables): TBARS and BDNF serum levels. The study has two hypotheses:

First, adding exercise to the conventional treatment would decrease the TBARS serum levels of severely depressed inpatients. This hypothesis was proposed based upon previous studies that shown the anti-oxidant effects of exercise on healthy populations, as well as, in different clinical populations, and in the adaptative response to exercise proposed by Radak et al. [17-19].

The second hypothesis was that adding exercise to the conventional treatment would have an increase the BDNF serum levels of severely depressed inpatients. A recent study shows that exercise did not change the BDNF serum levels of light to moderate depressed patients [26]. On the other hand, depression severity is associated with greater decrease at BDNF serum levels. So it was possible that a greater impairment at BDNF serum levels related to higher severity episodes would be more sensible to changes.

2. Methods

The methodology involved a randomized, controlled trial to analyze the effects of adding exercise to the usual treatment for severely depressed inpatients on their TBARS and BDNF serum levels. Preliminary results of the depressive symptoms and quality of life of this sample were previously published [28]. This study was approved by the local ethics committee (07-438) and was registered at ClinicalTrials.org (NCT01899716).

2.1 Participants

The eligible participants were twenty-six (n=26) severely depressed inpatients, of whom fifteen (n=15) belonged to the exercise group and eleven (n=11) belonged to the control group, who were hospitalized in the Hospital de Clínicas de Porto Alegre between 2008 and 2011. Patients were selected according to the following inclusion criteria: (A) a diagnosis of Major Depressive Disorder according to the Mini-International Neuropsychiatric Interview (M.I.N.I), DSM-IV criteria (American Psychiatry Association, 1994), (B) a score of 25 or more on the Hamilton-17 [29], (C) not involved in other physical activity programs during hospitalization, (D) aged between 18 and 60 years old, and (E) able to understand and provide written informed consent.

Patients were excluded for the following reasons: (A) they had three or more cardiovascular risk factors according to the Physical Activity Readiness Questionnaire (PAR-Q) [30], (B) they were not able to exercise because of a medical condition, (C) they had a diagnosis of schizophrenia or bipolar disorder or they currently used alcohol or other drugs according to the M.I.N.I (DSM-IV criteria), and (D) they were taking beta blocker medications.

2.2 Interventions

Participants in the exercise (exercise + treatment as usual) group had the objective of completing a dose of 16.5 kcal/kg/week for the duration of their hospitalizations, three times per week, individually, supervised by a trained research staff person (S.F.B). These methods were adapted from previous studies [31,32]. Patients could choose the modality (stationary bike [CICLE CL 204, CALOI, Manaus, Brazil], treadmill [ADVANCED 3, ATHLETIC, Manaus, Brazil] or a transport [CL 603, CALOI, Manaus, Brazil]) and the intensity based on their preferences until they completed the targeted dose.

The exercise intensity was controlled and recorded by a digital heart rate monitor (Polar cs200). Patients could listen to music if they wished. Research staff instructed the patients beforehand on the proper use of the machines and on how to complete the targeted “dose” of exercise; however, the staff only assisted patients regarding the discussion of exercise-related

topics. The sessions were composed by a warm-up, main part, and cool-down. The warm-up was composed by 20 seconds of stretching exercises of the lower limbs (Hip Extensors, Hip Flexors, Hip Adductors, and Plantar Flexors) followed by four minutes of walking in a speed of five kilometers/hour in the treadmill. During the main part, each participant could use different combinations of exercise within the sessions or between the different sessions, according to their preferences, having the unique fixed criteria of complete the targeted dose. For example: A participant with 60 kg needs to complete 990 kilocalories per week. This 990 kilocalorie was divided by three sessions, resulting in 330 kilocalories per session. The cool-down was composed by 20 seconds of stretching exercises of the lower limbs (Hip Extensors, Hip Flexors, Hip Adductors, and Plantar Flexors) and four minutes, four minutes of walking in a speed of five kilometers/hour in the treadmill at the end of the session.

Patients in the control group (treatment as usual) could not perform exercises or other physical activity (e.g., stretching) during the hospitalization period. All patients received other depression treatments (e.g., pharmacological and/or electroconvulsive therapy [ECT]). All treatments were recorded.

2.3 Assessments

2.3.1 Heart rate assessments

The rest heart rate was collected after the participant sit during 5 minutes using a digital heart rate monitor (Polar cs200). The maximal heart rate was estimated using the Tanaka formula [33]. The energetic expenditure was calculated per session. At each 5 minutes of exercise, a trained physiologist assessed the mean heart rate, and calculate the energetic expenditure using the predicted model proposed by Keytel et al. [34] Participants' reserve heart rates were calculated using the Karvonen formula [35].

2.3.2 Vo2 assessment:

To estimate the vo2 max, the single-stage submaximal test developed by Ebbeling et al. [36] was conducted at baseline by a trained researcher. The test was composed by a warm-up of four minutes and four minutes of the test duration in a treadmill (ADVANCED 3, ATHLETIC, Manaus, Brazil). In the warm-up, a comfortable speed between 2.0 and 4.5 mph was chosen by the participant, with a grade of 0%. During the warm-up, the heart rate has needed to stay between 50% and 70% of the age-predicted maximal heart rate. Following the warm-up, the participant keeps at the same speed for an additional 4 minutes, with an increase of 5% in the grade. The steady-state HR was achieved from the average of the final 30 sec of the last two minutes at the 5% grade. After the test stage, the grade was decreased once again for more four minutes to cool-down.

2.3.3 Diagnostic and depressive symptoms:

M.I.N.I diagnostic interview was conducted by a trained psychiatrist at baseline to evaluate the psychiatric diagnosis following the American Psychiatric Association [37] criteria. Depressive symptoms were assessed using the Hamilton scale for depression [29] by a trained psychiatrist at baseline, in the second week and at discharge.

2.3.4 Lifestyle habits and presence of chronic conditions

Lifestyle habits such as previous tobacco use (the patients were prohibited from smoking during the hospitalization) and exercise before hospitalization were assessed at baseline. Presence of another chronic conditions (e.g: diabetes) was also collected at baseline. Data was considered as dichotomic variables (yes/no).

2.3.5 Medications and other treatments.

All of the patients' medications were recorded at baseline, in the second week and at discharge.

2.3.6 Blood samples:

Blood samples were obtained in the morning (10:30-11:30). Participants fasted a minimum of 2:30 hour's prior blood collections. The blood samples were collected at baseline, after two weeks and after completion of treatment. Venipuncture was used to obtain 5 ml of blood from each subject in an anticoagulant-free vacuum tube. The blood was immediately centrifuged at 4000×*g* for 10 min, and the serum was kept frozen at −80 °C until it was assayed. The samples were stored for a maximum period of 2 years.

2.3.7 Thiobarbituric Acid Reactive Substances (TBARS) assay

The levels of lipid peroxidation were measured using the TBARS (thiobarbituric acid reactive substances) assay kit (Cayman Chemical Company, Ann Arbor) according to the manufacturer's instructions. In this method, the quantification of lipid peroxidation products occurs through the plasma formation of substances reacting to thiobarbituric acid; after analysis, the final products of lipid peroxidation (lipid peroxides, malondialdehyde and other aldehydes of low molecular weight) react with 2-thiobarbituric acid (TBA) to form Schiff bases. These complexes exhibit colors whose concentrations can be determined spectrophotometrically at 535 mm. The results are expressed in µM of malondialdehyde (MDA).

2.3.8 Brain-derived neurotrophic factor (BDNF) assay

BDNF serum levels were measured with a commercial kit using the sandwich ELISA technique (Chemicon, USA). Microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1:2 in sample diluents, and the standard curve ranged from 7.8 to 500 ng/ml of BDNF. The plates were washed four times using a wash buffer; then a monoclonal anti-BDNF rabbit antibody was added (diluted 1:1000 with sample diluents), and the samples were incubated for 3 h at room temperature. Afterward, a second incubation using peroxidase-conjugated anti-rabbit antibody (diluted 1:1000) for 1 h at room temperature was performed. After the addition of the streptavidin-enzyme, substrate and stop solution, the amount of BDNF

(with the absorbance set at 450 nm) was determined. The standard curve demonstrates a direct relationship between optical density (OD) and BDNF concentration. All analyses were duplicated using a unique assay.

2.4 Statistics

Data are presented as the mean and standard deviation (SD) or standard error (SE) or as relative frequency. Differences between groups at baseline were tested using one-way ANOVAs. Categorical data were analyzed using chi-square tests. Shapiro-Welk and Levene tests were used to assess, respectively, the normality and the homogeneity of the data. The antidepressant doses used by the participants were converted to imipramine equivalents, as proposed by Bollini et al [38].

BDNF and TBARS serum levels were analyzed using generalized estimating equations (GEE). The models were fit for each covariate individually, and the predictors considered in these models included the covariate. The predictor variables considered in the multivariable models included all of the covariates and interactions. Each model tested contained terms for time, baseline serum levels, other covariates and interactions among covariates and time. Non-significant covariates were excluded from the model. The covariates to be tested were selected based on previous literature. For BDNF, the following covariates were tested: age, gender, baseline vo_2 max and weight [27]. For TBARS the following covariates were tested: age, gender, weight and previous tobacco use [39,40]. The results of the GEE are presented as model-based adjusted means.

A Bonferroni test was used to determine where the differences occurred in the models' approaches. The results were considered significant at $p \leq 0.05$. All analyses were performed in the statistical analysis package SPSS v.18.

3. Results

No differences between groups regarding age, gender, height, weight, body mass index, vo_2 max, previous tobacco use, depressive symptoms, number of previous episodes and practice

of regular exercise in the last year were found at baseline. The baseline characteristics are shown in table 1.

Insert table 1 here

3.1 TBARS serum levels

In the analysis of potential moderators, previous tobacco use had a significant covariance for TBARS serum level analysis and had to be included as a covariate in the model. Age, gender, baseline vo_2 max, height, and weight were also tested, with no significant covariates found.

The model, including previous tobacco use as a significant covariate, revealed a significant group x time interaction ($p=0.02$). Pairwise comparisons of estimated marginal means, using the Bonferroni test, showed differences between the control and exercise groups at discharge ($p=0.01$).

The mean TBARS serum level values and SEs for the exercise and control groups were presented in the table 2 and figure 1.

Insert figure 1 here

Insert Table 2 here

3.2 BDNF serum levels

The analysis of potential moderators revealed gender ($p=0.01$) to be a potential moderator for BDNF serum levels, and thus gender was included in the model. No other significant covariates were found.

A significant time effect (p=<0.001) for BDNF serum levels was found, indicating an increase in BDNF serum levels for both groups after the second week and after completion of treatment; however, there was no significant group effect or group x time interaction. The mean BDNF serum level values and SEs for the exercise and control groups were presented in the table 3 and figure 2.

Insert Figure 2 here.

Insert table 3 here

3.3 Exercise compliance and session characteristics

There were no dropouts. The mean (SD) hospitalization length was 21.63 (4.5) days for the exercise group versus 23.82 (5.7) days for the control group. The participants of the exercise group performed a median of 9 sessions (minimum 6, maximum 14). The average session length for each participant was 43.51 (19.4) minutes. The average intensity of each session was 59.13% (9.7) of the heart rate reserve. The average energetic expenditure was 270.64 (52.6) kilocalories per session. The most used equipment was the treadmill (64% of total time), the average time spent in the treadmill, per session, was of 29.6 (11.09) minutes.

3.4 Medication

The most frequently used antidepressant, expressed as the mean dose (SD) at baseline, was fluoxetine (n=8, 35 (17.7) mg), followed by amitriptiline (n=5, 95 (69.3) mg). Four patients did not use any medication at baseline. For the exercise group, the most frequently used antidepressant at baseline was fluoxetine (n=3, 26 (11.5) mg), and the one most frequently used by the control group was also fluoxetine (n=5, 40 (14.1) mg). In the second week, the most frequently used antidepressant by all groups was fluoxetine (total sample n=9, 40 (14.1) mg; exercise group n=4, 40 (14.1) mg; control group n=5, 40 (14.1) mg). After the completion of

treatment, the most frequently used antidepressant for the sample, exercise and control groups was fluoxetine (total sample n=9, 35 (13.3) mg; exercise group n=4, 35 (10) mg; control group n=5, 44 (16.7) mg). The number of patients receiving ECT did not differ between groups (exercise group, n=1 x control group, n=3; p=0.10). There was no difference in the medications used by the participants in the three moments. The class and types of the medications used by all participants were presented in the table 4. There were no differences in the doses of antidepressant used by the participants in the three moments, after conversion to imipramine equivalents (Table 5).

Insert table 4 here

Insert table 5 here

4. Discussion

The present study examined the effects of adding physical exercise on the TBARS and BDNF serum levels of severely depressed inpatients. The main findings of this study were that adding exercise decreased the TBARS serum levels of severely depressed inpatients in approximated 3 weeks; however, adding exercise to the usual treatment did not change BDNF serum levels in the same period. Since the study has an add-on design, the decreased in TBARS could be interpreted as both an independent effect of exercise or a synergic effect with the antidepressant strategy used.

The analysis revealed no differences in the second week between the TBARS serum levels of the exercise and control groups. However, a difference between groups was found in TBARS serum levels at discharge, revealing that add-on exercise to the usual treatment decrease the TBARS serum levels of severe depressed inpatients. This result corroborates with studies in animal subjects and in humans with other chronic conditions in which oxidative stress levels were elevated. For example, Xu et al. [41] showed that exercise decreased the TBARS serum levels of rats after myocardial infarct, and Mazzola et al. [42] showed that exercise prevented an increase in TBARS serum levels in hyperphenylalaninemic rats. In humans with other chronic

conditions, this study's findings corroborate those of Nemoto et al. [43]. In that study, eight weeks of aerobic exercise decreased the TBARS serum levels of patients with chronic obstructive pulmonary disease (COPD). In the present study, the differences between the groups occurred in a shorter period, revealing that three weeks of exercise is sufficient to begin promoting alterations in the oxidative stress system. One study of eight healthy and physically active men found an antioxidant reduction of 7% in TBARS serum levels after 3 weeks of high-intensity interval training (HIT) performed 3 times per week Bogdanis et al. [44]. The decrease was lesser than the decrease found in the present study (13%). The different magnitudes may be attributable to the different populations studied and exercises utilized. Furthermore, it is not clear if this decrease is due the exercise only or due the synergic effects of exercise + usual treatments.

One possible explanation for the exercise-induced decrease in TBARS serum levels is a possible systemic adaptation based upon the hormesis hypothesis proposed by Radak et al. [18]. According to this hypothesis, an acute bout of exercise promotes a transient increase in some reactive oxygen species (ROS), as well as some antioxidant enzymes, to prevent ROS damage and oxidative stress. After some time, an adaptive mechanism is initiated by some transcription factors, resulting in the increased activity of the antioxidant enzymes. This increased activity may result in a more effective repair system. In the present study, the antioxidant enzymes were not assessed; thus, it is difficult to determine the effects of exercise on the antioxidant system.

Previous tobacco use had a significant covariance in the analysis and was a potential factor of confusion. Patients who had used tobacco prior to hospitalization had higher TBARS serum levels compared with those who had never smoked and these data are in line with several studies that show that tobacco use increases oxidative stress [40,45]. This increase may be explained by the activation of some reactive molecules such as hydroxyl radicals, 4-hydroxynonenal and hypochlorous acid; as demonstrated by Luchese et al. [46], the presence of these substances increases the damage by oxidants, generating ROS. Interestingly, a recent study shows that exercise attenuates the oxidative stress increases related to tobacco use, revealing an interaction between exercise and smoking cessation on TBARS levels [45].

The present study failed to find significant effects of adding exercise on the BDNF serum levels of severely depressed inpatients. To the best of our knowledge, only one study has assessed the long-term effects of add-on exercise in the usual treatment of depressed patients. Toups et al. [27] compared two “doses” of exercise in 70 mildly to moderately depressed patients and found no changes in BDNF levels after 12 weeks of intervention. The results of the present study, with severely depressed inpatients, corroborate their findings and show no change after an add-on exercise on the BDNF serum levels of depressed inpatients.

There are many possible explanations for the lack of additive effects of exercise: (1) BDNF serum responses to exercise may be to be moderated by pharmacological treatments. Recent research has shown that Citalopram moderated the BDNF response to exercise [47]. In the present study, most participants used antidepressants, and it is possible that this medication limited any BDNF increases; (2) BDNF serum responses to exercise may be moderated by environmental factors, such as temperature and pollution [47,48]; (3) some genotypes may moderate the BDNF responses to exercise [49]; (4) finally, it is possible that the current treatments had already increased the BDNF serum levels to a “plateau” of normalization and that no additional intervention would promote any further increases. Despite the lack of differences between groups, both groups experienced an increase in their baseline BDNF levels. One possible explanation for the increased BDNF levels after the second week and the maintenance of these levels after completion is the usage of antidepressants throughout treatment [50].

The present study has some limitations: 1) the sample size used was small, even more considering the add-on model. However, a significant additive effect was found for TBARS serum level. On the other hand, the lack of additive effect at BDNF serum levels corroborates some recent findings with greater sample size [27]. 2) TBARS it is a technique which do not represent all oxidative stress changes, but a small fraction related to lipid peroxidation so this result cannot be generalized to others cellular components. Furthermore, the Malondialdehyde (MDA) an end-product of lipid peroxidation even though sensitive, has low specificity. Despite the low specificity, the assay for this evaluation is one of the most extensively studied indices of

lipid peroxidation [51]. 3) The antioxidant system was not assessed, so the present study cannot determine the role of exercise at antioxidant enzymes, as well as, the role of the antioxidant enzymes in the decrease of TBARS serum levels. 4) The add-on design, without one arm with exercise only, limits the comprehension of the effects of exercise only on TBARS or BDNF. For example, it is not clear if the decrease on TBARS serum levels was related to exercise solely or due the interaction between exercise and medications. In this line, further studies are needed to evaluate the effects of exercise only at oxidative stress system and BDNF. 5) Due the methodology of the training, it is not possible determine if the changes were related to the aerobic or the anaerobic component; however, the average intensity of exercise was of 59.13% (9.7) of the heart rate reserve. This intensity can be classified as being of moderate-to-vigorous difficulty in the aerobic zone [52]. 6) The exercise testing used was not validated in a sample of clinically depressed inpatients. However, the test was chosen to be quick and easy test, that not demand previous experience in treadmills. Lastly, 7) The years of disease were not evaluated. However, according to the DS-IV criteria, most of patients (57,7%, being 61,9% of the exercise group and 38,1% of the control group, with no difference between groups, p=0,346) could be considered as having a recurrent depression, or can be considered as chronic patients.

5. Conclusion

Adding exercise to the usual treatment decreased the TBARS serum levels but had no effect on the BDNF serum levels of severely depressed inpatients. Exercise may be considered a treatment option with positive effects on the oxidative stress system.

The lack of assessment of antioxidant enzymes limits a broader comprehension of the effects of exercise on the antioxidant system. The lack of an untreated group limits any generalization to unmedicated inpatients. Further studies using other oxidant and antioxidant markers are needed. Further studies comparing the effects of exercise on the BDNF serum levels of medicated and unmedicated inpatients are needed. Further studies evaluating the role

of aerobic and anaerobic exercise on BDNF and oxidative stress system, in depressed populations are needed.

Role of Founding source

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Table 1. Baseline characteristics

	Exercise Group (n=15)	Control Group (n=11)	P value
Age, years	42.81 (12.4)	42.52 (13.5)	0.96
Females, n (%)	11 (73%)	8 (72%)	0.65
Weigth, kg	64.72 (9.6)	70.22 (9.0)	0.15
Height, m	1.62 (0.0)	1.74 (0.3)	0.17
Body mass index, kg/m^2	24.78 (4.4)	25.52 (3.0)	0.61
Vo2 max, $ml.kg.min^{-1}$	29.11 (4.6)	26.92 (3.8)	0.36
Diagnosis of diabetes, n (%)	1 (6%)	1 (9%)	0.81
Previous Tobacco use, n (%)	8 (53%)	7 (63%)	0.70
Regular exercise in the last year, n (%)	2 (13%)	1 (9%)	0.73
Hamilton score	26.68 (2.6)	27.73 (4.1)	0.19
Previous episodes, n	2.6 (1.0)	1.9 (1.3)	0.12

Table 2. Effects of add on exercise at TBARS serum levels

Intervention	Baseline	Second Week	Discharge
	Mean (SE)	Mean (SE)	Mean (SE)
Exercise + Treatment as Usual	46.15 (4.2)	43.22 (4.5)	35.48 (3.7) *
Treatment as Usual	46.31 (6.0)	52.83 (5.8)	54.29 (5.2) *

Data expressed as µM of MDA.
GEE analysis revealed significant group x time interaction (p=0.02).
* = Bonferroni Post-hoc revealed a significant difference between groups at the discharge (p=0.01)

Table 3. Effects of add on exercise on BDNF serum levels

	Baseline	Second Week	Discharge
Group	Mean (SE)	Mean (SE)	Mean (SE)
Exercise	68.53 (8.9)	96.09 (8.6)	97.85 (8.1)
Control	82.89 (16.8)	111.83 (21.2)	97.13 (21.2)

Data expressed as ng/ml.

No significant group x time interaction was found in the GEE analysis.

Table 4. Pharmacological treatments and ECT

	Exercise (n=15)	Control (n=11)	p value
	Baseline		p=0.587
Drug free	3	1	
SSRI	3	3	
Tryciclic	4	2	
Mood Stabilizer	1	0	
Tryciclic/SSRI + Tricyclic/SSRI	0	2	
Tryciclic/SSRI + Mood Stabilizer	2	1	
Antipsychotics	0	0	
Tryciclic/SSRI + ECT	1	0	
Tryciclic/SSRI + Antipsychotics	1	1	
ECT + Mood Stabilizer	0	1	
	Second Week		p=0.415
Drug free	2	0	
SSRI	3	3	
Tryciclic	2	1	
Mood Stabilizer	3	0	
Tryciclic/SSRI + Tricyclic/SSRI	0	1	
Tryciclic/SSRI + Mood Stabilizer	2	1	
Antipsychotics	2	2	
Tryciclic/SSRI + ECT	1	0	
Tryciclic/SSRI + Antipsychotics	0	1	
ECT + Mood Stabilizer	0	1	
ECT Only	0	1	
	Discharge		p=0.137
Drug free	3	1	
SSRI	1	3	
Tryciclic	1	1	
Mood Stabilizer	3	0	
Tryciclic/SSRI + Tricyclic/SSRI	0	1	
Tryciclic/ISRS + Mood Stabilizer	3	0	
Antipsychotics	2	0	
Tryciclic/SSRI + ECT	1	1	
Tryciclic/SSRI + Antipsychotics	0	2	
ECT + Mood Stabilizer	0	1	
ECT Only	0	1	

SSRI=Selective Serotonin Reuptake inhibitor, ECT=Electroconvulsive Therapy. p value for chi-square tests.

Table 5. Medications used in imipramine equivalents

	Baseline	Second Week	Discharge
Group	Mean (SE)	Mean (SE)	Mean (SE)
Exercise	97.66 (19.2)	100.00 (26.6)	80.00 (25.2)
Control	142.18 (40.8)	148.18 (32.0)	145.45 (34.1)

Dose of medications converted to imipramine equivalents

GEE analysis did not reveal significant group (p=0.134), time (p=0.741) or group x time interaction (p=0.818).

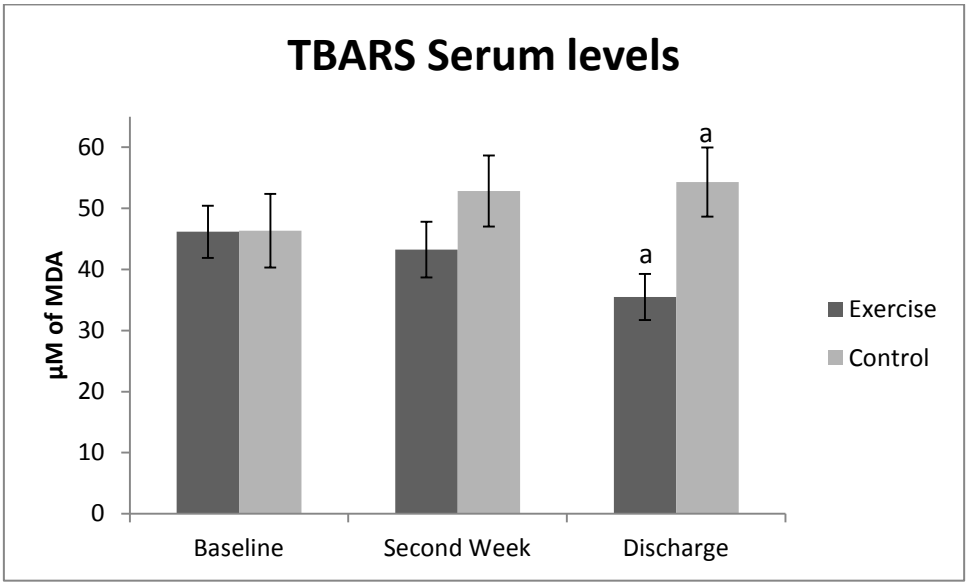

Figure 1. TBARS Serum Levels. Significant group x time interaction was found (p=0.02). a=significant differences between exercise and control group at the discharge (p=0.01). No significant time effect or group effect were found.

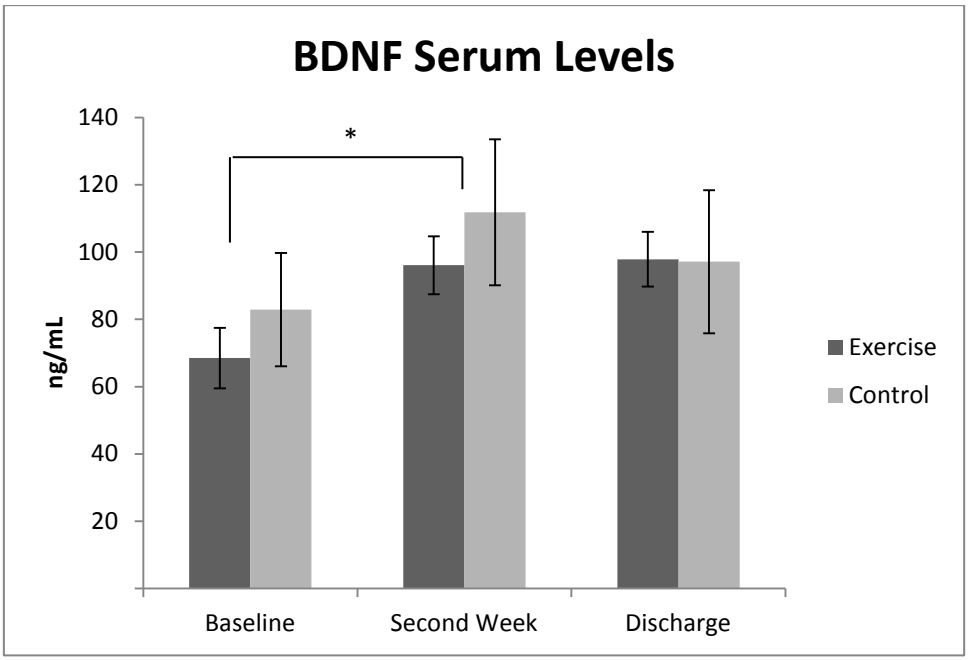

Figure 2. BDNF Serum Levels. Significant time effect (p<0.001) was found. *Bonferroni post-hoc revealed that the difference occurred between baseline and second week (p<0.001). No differences were found between second week and discharge. No differences were found between groups in any moment.

6 CONCLUSÕES E CONSIDERAÇÕES FINAIS

A presente tese teve como objetivo compreender de forma mais aprofundada os fatores moderadores e mediadores dos efeitos do exercício na depressão. Adicionalmente, utilizando-se de um ensaio clinico randomizado, a tese objetivou avaliar os efeitos do exercício físico em desfechos clínicos e biológicos em pacientes internados com depressão grave.

No primeiro estudo, foi feita uma revisão sistemática da literatura com os objetivos de conhecer alguns dos potenciais fatores que possuem efeito moderador ou preditor de sucesso ao tratamento na relação entre exercício físico e depressão. Os principais achados foram os seguintes a) existem diversos fatores que potencialmente possam predizer resposta ou remissão; b) não é possível até o momento obter conclusões mais consistentes a cerca de algum fator clínico, psicológico, social ou biológico que possa predizer sucesso no uso do exercício como tratamento para a depressão devido ao pequeno número de estudos, às inconsistências dos resultados e às limitações presentes; c) apenas um estudo avaliou potenciais moderadores entre diferentes tratamentos, sugerindo que, uma maior severidade dos sintomas físicos prediz uma melhor resposta ao exercício quando comparado com Inibidores Seletivos da Recaptação de Serotonina (ISRS), em idosos.

O segundo artigo, a segunda revisão sistemática, teve o objetivo de revisar estudos que avaliassem os efeitos agudos e crônicos do exercício físico em marcadores hormonais, neurotrofinas, de stress oxidativo, inflamatórios e de volume e atividade cortical em pacientes clinicamente deprimidos. O estudo mostrou que de forma aguda, o exercício parece promover diferentes respostas

hormonais, de neurotrofinas e inflamatórias. De forma crônica, o treinamento com exercícios potencialmente produz adaptações em alguns sistemas hormonais, em relação ao stress oxidativo sistêmico e na ativação cortical em pacientes clinicamente deprimidos. Os efeitos do treinamento em fatores neurotróficos e inflamatórios não são consistentes entre os estudos e não parece haver adaptações ao exercício em termos de volume em estruturas corticais. Novamente, os achados devem ser interpretados tendo em mente o pequeno número, as limitações e as inconsistências entre os estudos.

O terceiro artigo é o resultado final do ensaio clinico randomizado que buscou avaliar os efeitos do exercício, como uma terapia complementar em pacientes internados com depressão grave. Apesar da brevidade da intervenção, os participantes do grupo exercício apresentaram uma maior redução nos sintomas depressivos quando comparado aos participantes do grupo controle. Também, Houve uma melhora nos domínios físico e psicológicos da QV. Dessa forma, o estudo demonstrou que o exercício físico utilizado como um tratamento complementar pode ser uma ferramenta interessante para a redução dos sintomas depressivos e melhora da QV em pacientes internados com depressão grave.

O quarto artigo desta tese é derivado de uma análise de material biológico com parte da amostra do ensaio clinico. Este estudo mostrou as respostas de uma neurotrofina e de um marcador de stress oxidativo. Conforme os resultados encontrados, o exercício não foi capaz de alterar os níveis de BDNF, mas parece ter promovido uma redução nos níveis de TBARS, quando comparado ao grupo controle. Esse estudo lança a hipótese de que o stress oxidativo possa também estar de alguma forma correlacionado com os

efeitos antidepressivos do exercício físico em pacientes com depressão. Contudo, o pequeno número de participantes e as diversas limitações impedem conclusões mais definitivas.

As conclusões da presente tese são: 1) Ainda não é possível estabelecer com segurança os fatores que podem predizer sucesso ou auxiliar na escolha entre tratamentos em relação ao exercício, embora o presente artigo venha a trazer avanços identificando alguns potenciais alvos para estudos futuros e possa encorajar os pesquisadores a darem mais atenção a essa análise, até então pouco explorada nesta área; 2) O exercício físico parece produzir diversas respostas agudas em diferentes marcadores. As adaptações ao treinamento físico, no entanto, são menos consistentes apresentando resultados bastante contraditórios. Os estudos encontrados na revisão sistemática não dão suporte, com consistência, às hipóteses que associam o efeito antidepressivo do exercício às vias hormonais, neurotróficas, inflamatórias, oxidativas ou de alterações na ativação ou no volume de estruturas cerebrais em pacientes deprimidos; 3) O ensaio clinico randomizado permitiu concluir que o exercício pode ser uma intervenção interessante para pacientes internados com depressão grave hospitalizados, e não apenas para depressões de menor gravidade. Dessa forma, o estudo suporta o uso de intervenções com exercício em internações hospitalares para auxiliar na redução dos sintomas depressivos, bem como, melhorar a QV dos pacientes; 4) O exercício físico, em pacientes internados com depressão grave, não parece produzir efeitos a curto prazo nos níveis de fatores neurotróficos. Entretanto, parece haver uma redução nos níveis séricos de marcadores de

stress oxidativo. O estudo fornece evidências iniciais de que o estresse oxidativo possa ter algum papel com o efeito antidepressivo do exercício.

7 ANEXOS

7.1 ANEXO A – OUTRAS PRODUÇÕES INTELECTUAIS NA ÁREA DE EXERÍCIO FÍSICO E SAÚDE MENTAL FEITAS DURANTE O DOUTORADO

LIVROS PUBLICADOS

Schuch, F.B, Cadore, E.L, Rocha, N.S. Progress in Physical activity and Exercise and Affective and Anxiety Disorders: Translational Studies, Perspectives and Future Directions. Lausanne, Switzerland. Frontiers, 2015. http://journal.frontiersin.org/ResearchTopic/974 acessado em fevereiro de 2015

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