

Impact of Aerobic Exercise on Depression

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Disclosures

- The Speakers have no Financial or Industry Disclosures
- No off-label medication use is discussed

Background

- Overview of Major Depressive Episodes
- Treatment of Depression in Athletes
- Running/aerobic exercise as treatment for depression

Major Depressive Episodes

- MEDICAL CONDITION ASSOCIATED WITH CORONARY HEART DISEASE, HYPERTENSION AND DIABETES
- FOUND TO BE AN INDEPENDENT RISK FACTOR FOR DM2 AND HTN
- ASSOCIATED WITH LOW PHYSICAL ACTIVITY BUT MULTIPLE STUDIES FIND THE HAVING DEPRESSION ALONE INCREASES RISK FOR CAD AND METABOLIC PROBLEMS
- STRONG ASSOCIATION WITH COMPLETED SUICIDE

MDE-Key Clinical Features

Prolonged Low Mood, Sadness and or Depressed Mood-often lasting weeks or longer, expression of mood varies with culture and other demographics.

Loss of the capacity to feel pleasure-other people often notice this first-not smiling or laughing, lack of interest in work or hobbies

Associated with:

- change in appetite or unexplained weight loss or gain
- inattention
- disrupted sleep
- excessive guilt
- delusions
- hallucinations
- suicidal thoughts

Depression Screening

The **Patient Health Questionnaire=9 (PHQ9)** is validated for screening, aid in diagnosis and treatment response

A short version of the PHQ9 (the PHQ2) is 85% sensitive for major depression

- **0=none, 1=less than 1 / 2 the days, 2=half the days, 3 everyday or almost every day**
- **Little interest or pleasure in doing things the past 2 weeks: 0 1 2 3**
- **Feeling down depressed or hopeless the past 2 weeks: 0 1 2 3**

Rates of Mood Disorders in Runners

- Lifetime rate of MDE for adults is 15-20% in general population
- Studies are limited in athletes but the rate of MDE is similar to general population with some difference in risk factors:
 - Overtraining, injury, aging and retirement from sport
 - Rates are very high in NFL (American Football) players
- *ULTRA Study Data on Prevalence of Depression Anxiety and Drug Abuse*
- Reported Medical Conditions:
 - Depression and bipolar disease: **11.8%**
 - Anxiety **7.8%**
 - Alcohol and drug abuse **3.4%**
- **There is an overlap of Overtraining Syndrome and Major Depression**

Treating Depression in Athletes

- There are a small number of studies looking at the impact of treating athletes with antidepressants on performance.
- **SSRI's (Lexapro Prozac), SNRI's (Effexor) and Bupropion (Welbutrin)** do not have significant effect on performance. Combining antidepressants with exercise may have a synergistic effect on reducing depression severity
- WADA has investigated Bupropion as a possible PED but multiple studies have a small n and mixed results
- **Tricyclic Antidepressants (Amitriptyline, Nortriptyline)** have significant cardiac side effects and anticholinergic activity that can have a negative impact on training and athletes treated with these medications should be closely monitored by experienced healthcare professionals

Aerobic Exercise as Treatment for Depression

Evidence/Research

- Clinical Trials
- Comparison to other treatments
- Basic science/physiologic mechanisms

Clinical Studies

- Moderate aerobic exercise for at 30-40 minutes a day, 4 days a week for 2-3 months has significant effect in reducing the symptoms of depression
- For clinical depression that is *mild to moderate* in severity, 2-3 months of regular aerobic exercise may be as effective as antidepressant medications and Talk Therapy. Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, et al. Exercise for depression. Cochrane Database Syst Rev. 2013;9:CD004366.
 - Stanton R, Reaburn P. Exercise and the treatment of depression: a review of the exercise program variables. *J Sci Med Sport* (2014) 17:117-82. doi: 10.1016/j.jsams.2013.03.010
 - B Stubbs, D Vancampfort, Challenges Establishing the Efficacy of Exercise as an Antidepressant Treatment: A Systematic Review and Meta-Analysis of Control Group Responses in Exercise Randomised Controlled Trials. *Sports Med Springer International Publishing Switzerland* 2015

Clinical Evidence

- Over 32 Clinical Trials and several open trials examining effect of exercise on depression
- Overall there is a moderate positive effect on MDE
- 2 RCT trials found no difference in remission rates compared to medications in moderate depression
- Larger impact on elderly
- Reduces the symptoms of depression in patients with co-morbid CAD

Meta-Analysis



- *Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. F.B. Schuch et al. / Journal of Psychiatric Research 77 (2016) 42-51*
- *Data from 25 RCT*
- *Found larger effect than previous studies and Cochrane reviews*
- *Pooled data found difference in intensity and structure*
- *Moderate to Intense Aerobic Exercise had largest affect on reducing depression*
- *Supervised exercise interventions were more effective*
- *Indicates previous studies may have underestimated the efficacy of aerobic exercise in treatment of Major Depressive Episodes*

How does exercise
cause and
antidepressant effect?

Adiponectin

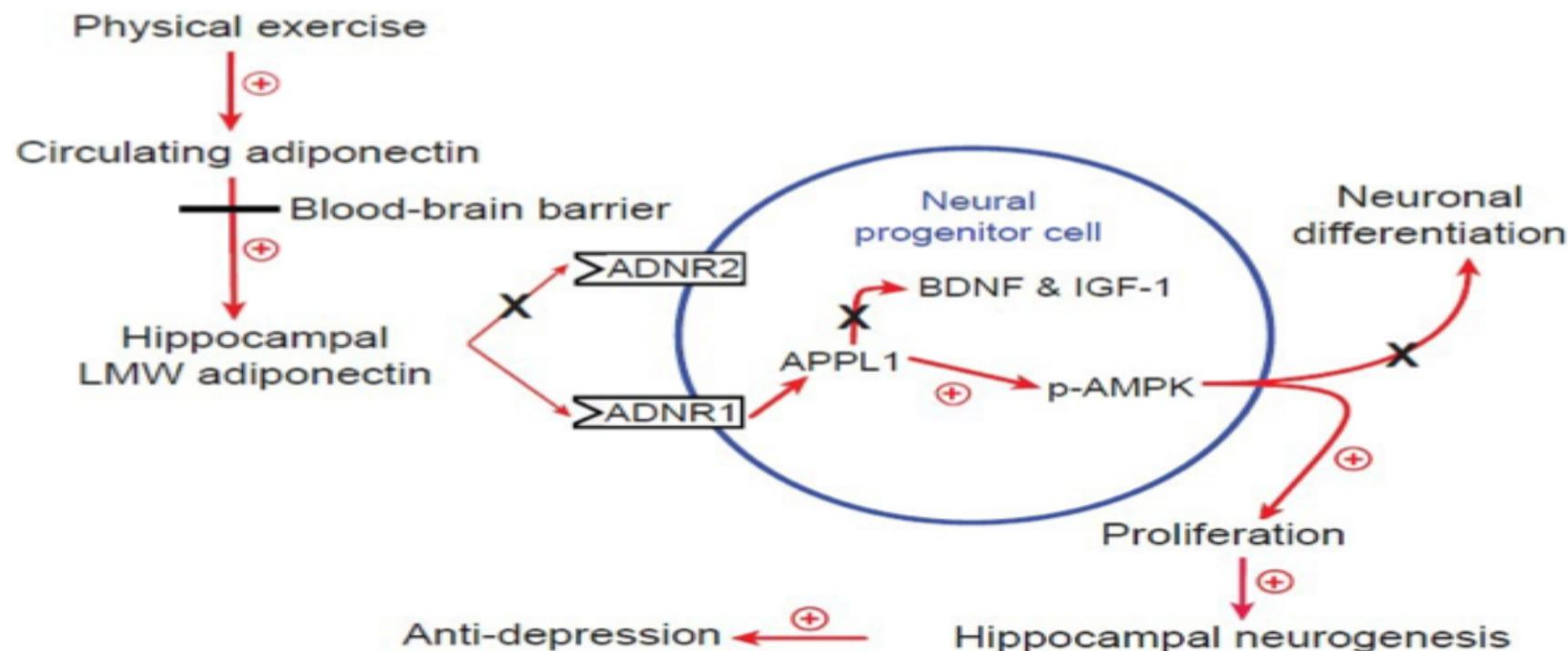
Adiponectin, is secreted by peripheral mature adipocytes *during physical exercise*-the hormone stimulates hippocampal neurogenesis and is found reduce depression in animal models

- Suk Yu Yau, Ang Li, Aimin Xu, Ph.D. and Kwok-fai So, Ph.D. *Fat cell-secreted adiponectin mediates physical exercise-induced hippocampal neurogenesis: an alternative anti- depressive treatment?* Neural Regen Res. 2015 Jan; 10(1): 7-9.

PMC full text: [Neural Regen Res. 2015 Jan; 10\(1\): 7-9.](#)
 doi: [10.4103/1673-5374.150637](#)
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Figure 1



Schematic diagram illustrating the potential mechanism mediating the anti-depressive action of physical exercise.

As shown in this cartoon, physical exercise initially raises circulating adiponectin levels. The low-molecular-weight (LMW) form of adiponectin passes through the blood-brain barrier, and accumulates in the hippocampus to activate adiponectin receptor (ADNR) 1 expressed by neural progenitor cells. Following the relay of adapter protein containing PH domain, PTB domain and leucine zipper motif 1 (APPL1), the phosphorylated AMP-activated protein kinase (p-AMPK) is increased, subsequently initiating the downstream proneurogenic cascade that enhances hippocampal cell proliferation without affecting neuronal differentiation. The enlarged population of adult-born neurons changes the activity of neural circuits and enables the antidepressant effects elicited by physical exercise. Brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1) do not seem to directly crosstalk with this adiponectin-stimulated proneurogenic pathway.

5-HT_{2C} Receptors in the Basolateral Amygdala and Dorsal Striatum

- Activation of these serotonin receptors found to have an antidepressant and anxiety reducing activity in animal models
- Exercise found to both increase up regulation of 5HT_{2c} in the Amygdala and Dorsal Striatum
- Exercise also increased sensitivity of those receptors

Hypocretin/Orexin Suppression

Antidepressant effects of exercise are produced via suppression of

hypocretin/orexin and melanin-concentrating hormone in the basolateral amygdala. T.-K. Kim et al. / Neurobiology of Disease 79 (2015) 59-69

- In mice model of depression, mice with vigorous exercise had significantly shorter duration of illness
- Immunohistochemistry found significant suppression of hypocretin/Orexin and MCH

Brain Derived Neurotrophic Factor

- Aerobic Exercise found in several well designed studies to increase both serum and CSF BDNF
- No association with increased heart disease with the elevated BDNF
- One RTC found in depressed patients randomized to structured exercise and usual care had both increased BDNF over control and improved Depressive symptoms
 - *Exercise increases serum brain-derived neurotrophic factor in patients with major depressive disorder. A. Kerling et al. Journal of Affective Disorders 215 (2017) 152-155*

Integrating Exercise Into Practice

- Motivating patients
- Creating an integrated training plan
- Risk assessment of patients

Motivation

- *Motivating factors and barriers towards exercise in severe mental illness: a systematic review and meta-analysis.* Psychological Medicine, 1-13. ©Cambridge University Press 2016
- 12 studies met inclusion criteria with an n=6431
- Study questioned motivations and barriers to exercise in those with mental illness

Motivations:

- Fitness
- Weight loss
- Improve mood
- Reduce stress

Barriers:

- Lack of supervision during exercise
- Mood symptoms

Summary

- Depression is a serious medical condition that is often not recognized and treated
- There are evidence based and effective treatment options including pharmacologic and non-pharmacologic interventions
- Aerobic Exercise can be an effective treatment for Major Depressive Episodes if they are supervised and motivations and barriers to exercise are addressed

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QUESTIONS