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The Role of Physical Activity in the Management of Treatment-Resistant Depression: Evidence and Future Directions

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ABSTRACT

Treatment-resistant depression (TRD) is a clinical condition characterized by failure to achieve remission after at least two trials of different antidepressants given at adequate doses and duration. It affects about 30% of patients who suffer from major depressive disorder (MDD), which makes it a big public health challenge by its association with increased morbidity, impaired functioning and reduced quality of life. Novel treatment methods like ketamine, esketamine, psychostimulants, and neuromodulation, have improved management of MDD but many patients continue to experience persistent symptoms. Physical activity has demonstrated therapeutic benefits in depression treatment with its influence on biological pathways by means of neuroplasticity, neurotransmitter modulation, and immune regulation. It is a low-cost, accessible intervention with additional physical and psychosocial advantages. Evidence from clinical trials and meta-analyses suggests that various exercise types including aerobic, resistance, and mind-body training significantly reduce depressive symptoms and improve quality of life in patients struggling with depression. However, specific studies on physical activity in TRD are limited, with promising ongoing trials (e.g., TRACE-RMD) investigating

its efficacy as an adjunctive treatment. Incorporating exercise into standard treatment algorithms for TRD might yield positive outcomes and be valuable compliment to pharmacotherapy and psychotherapy but we still lack scientific data. Taking into consideration high prevalence and significant burden of TRD further research is needed. Creating and standardizing exercise protocols, improving adherence, and understanding long-term outcomes should be the goal of future studies.

KEYWORDS: major depressive disorder, exercise, depression, ketamine, psychotherapy, Brain-Derived Neurotrophic Factor,

INTRODUCTION

Treatment-resistant depression (TRD) is a clinical condition characterized by the failure to achieve remission after at least two trials of different antidepressants given at adequate doses and duration. FDA and EMA define it as depressive disorder which is non-responsive to two or more antidepressant therapies. It affects about 30% of patients who suffer from major depressive disorder (MDD), which makes it a big public health challenge by its association with increased morbidity, impaired functioning and reduced quality of life[1,2].

Current treatment options for TRD go beyond conventional approach and include therapies such as use of ketamine or esketamine, psychostimulants, neuromodulation techniques, and psychotherapies like cognitive behavioral therapy. However, many patients continue to suffer persistent symptoms which highlights the need for effective adjunctive treatment strategies[3,4].

Physical activity has been proven to have therapeutic benefits in treating depression and could be a promising treatment option in TRD. Exercise affects multiple biological and psychological pathways which influence the pathophysiology of depression and may enhance conventional treatments through neuroplasticity, neurotransmitter modulation, and immune system interactions. Taking into account low costs and high accessibility, integrating physical activity to the treatment regimen could improve outcomes for patients with drug-resistant depression[5-7].

This review aims to study available evidence for the efficacy of including physical activity in the treatment of depression with special attention given to TRD, discussing its clinical effectiveness, fundamental mechanisms, variety of types of exercises to apply, and practical leads to implement.

EPIDEMIOLOGY AND IMPORTANCE OF TREATMENT RESISTANT DEPRESSION

Among patients with major depressive disorder (MDD), a large proportion suffers from treatment-resistant depression (TRD), with prevalence ranging from 30% to 40% among groups treated with antidepressants. Some studies have shown even higher prevalence up to 41,5%, depending on studied population and diagnostic criteria. Epidemiology also affects various age and ethnic groups and many geographic regions, which emphasizes how global the problem is[8-10].

TRD has a huge impact on patients' quality of life. Compared to treatment-responsive depression, in TRD rate of suicidality is elevated. These patients experience increased severity of symptoms, and their quality of life is significantly reduced. Long-term illness strongly affects the deterioration of social relationships and general well-being[9,11,12].

Depression ranks among the leading causes of global disability. Taking into account the societal aspect, TRD is related to increased direct and indirect costs, which makes it a serious economic challenge for the healthcare system. The difficulty in achieving remission for patients with TRD highlights the importance of finding more effective treatment strategies[10,12].

PHYSICAL ACTIVITY AND DEPRESSION: GENERAL OVERVIEW

Physical activity is defined by any body movement created with skeletal muscles that results in energy expenditure. This includes not only structured exercises like strength or aerobic training and yoga, but also every day activities like walking or doing household chores. Exercise interventions encompass more planned, structured, and repetitive physical activities that are planned for the purpose of improving or maintaining health outcomes[13,14].

There are many studies that prove that both moderate and high intensity exercises significantly reduce depressive symptoms. These evidence applies to a various age groups, including adolescents, young adults, and older adults, emphasizing the versatility of physical activity as a therapeutic tool in depression. Recommendations suggest a frequency of 3–4 sessions per week 30-60 minutes each, maintained for at least six weeks to achieve significant improvements. These findings highlight that recreational physical activity has a greater impact on reducing depression than work-related activity[15-18].

EVIDENCE FOR PHYSICAL ACTIVITY IN TREATMENT RESISTANT DEPRESSION

There are many systematic reviews and clinical trials which study physical activity interventions in patients with MDD. Meta-analyses of randomized clinical trials made across different populations prove that resistance exercise training reduces depressive symptoms in adults, regardless of health status[19]. Unfortunately to date, there are not many scientific studies that have examined the effects of physical activity on patients with TRD as an adjunct to conventional therapies, so we need to be careful when extrapolating data from other works. A recent promising, randomized controlled trial, TRACE-RMD, is designed to assess the influence of a physical exercise on resistant major depression, including impact on quality of life and disease severity, however, we still must wait for complete and certain research results[20].

It has been proven that physical activity improves the quality of life and reduces symptoms in MDD[21]. Secondary data analyses from exercise programs reveal significant improvement measured in depression rating scales. Patients who followed structured exercise intervention have noticed improvement from moderate/severe to mild/minimal depression on a rating scale, suggesting additional benefits when combined with standard therapies[22,23]. Positive outcomes in these patients underline the need for studying this intervention in TRD.

MECHANISM OF ACTION OF PHYSICAL ACTIVITY IN DEPRESSION TREATMENT

Neurobiological mechanisms

Physical activity plays a role in depression treatment by influencing several pathways, especially by promoting neuroplasticity. A key molecule involved in neuronal growth, synaptic plasticity, and resilience of brain circuits implicated in mood regulation is brain-derived neurotrophic factor (BDNF). Research shows that physical activity enhances levels of BDNF. Increased levels of this important molecule have been linked to recovery of function in brain areas such as the hippocampus and prefrontal cortex, which are often malfunctioning in depression. Moreover, physical activity affects the function of neurotransmitters which play important role in mood regulation like serotonin, dopamine, and norepinephrine. These molecules are also crucial to the mechanism of action of many antidepressants. Exercise also activates specific brain circuits associated with motor control and emotional regulation, improving synaptic plasticity and supporting antidepressant effects[24-26].

Neuroimmune Modulation and Anti-Inflammatory Effects

One of the most important pathophysiological mechanisms behind depression is neuroinflammation and dysregulation of the immune system. Physical activity has been shown to regulate immune function by modulating cytokine production. Exercises are proven to promote anti-inflammatory environment in the brain by reducing pro-inflammatory markers. The chronic low-grade inflammation that is often observed in TRD is reduced by immunomodulatory effect of physical activity. Exercise influences microglial activation and promotes release of anti-inflammatory molecules, leading to neuroprotection and mitigation of depressive symptoms[27,28].

Psychological and Cognitive Benefits

Psychological and cognitive advantages are very relevant to depression treatment. Physical activity provides improvements in these areas. Exercise upswings executive function, attention, and memory which are usually impaired in depression. These improvements contribute to better decision-making, problem-solving skills, and daily functioning[29].

Furthermore, regular physical activity has also been associated with enhanced sleep quality and reduced sleep disturbances, which is of utmost importance as lack of sleep usually exacerbates depressive symptoms[14,27].

Moreover, fatigue is frequently reported by patients with depression. It turns out that physical activity can also have a positive effect on vitality and self-efficacy. Not only does it have positive effect on self-image and a sense of accomplishment but also promotes social interaction which is important in building patients' resilience. Physical activity can counter negative thought patterns typical in depression. As patients notice improvements in mood and cognitive function, motivation to maintain physical activity grows, which supports a positive feedback loop[14].

TYPES OF PHYSICAL ACTIVITY INTERVENTIONS AND THEIR EFFICACY

Endurance/Aerobic Training

Endurance/aerobic training are types of physical activities that include walking, jogging, cycling, and swimming. From a general health point of view, aerobic exercises improve cardiovascular fitness and have been linked with beneficial neurobiological and psychological effects. Moreover, these exercises are very well studied in terms of their benefits for depression treatment. Studies such as systematic reviews and meta-analyses show that aerobic exercise help to significantly reduce depressive symptoms. This applies to various age groups. Regarding the time and frequency, it is highlighted that best result are seen when performed for 30 to 60 minutes per session, 3–4 times weekly, over at least 6 weeks[16,30,31].

Resistance/Strength Training

Resistance or strength training which often includes weight lifting or body-weight exercises, has been proven to have equal or even superior efficiency compared to aerobic exercise in reducing symptoms of depression. Data shows this applies especially to younger populations. Key factor seems to be consistency, which means that resistance training should be performed multiple times per week in order to improve mood and physical function, likely mediated by physiological and psychosocial mechanisms[16,19,30].

Mind-Body Interventions

Mind-body exercises contain mindfulness or meditative components. These include yoga, tai chi and qigong. Research puts the main emphasis on the dual focus on physical activity and mental relaxation which may add some improvement in emotional regulation and importantly stress reduction. However, studies shows that these interventions have moderate influence in reducing depressive symptoms. Nevertheless, regular sessions over several weeks, consisting of 30–60 minutes practice have been proven to reduce anxiety, improve mood and quality of life[16,30].

High-Intensity Interval Training (HIIT)

High-intensity interval training (HIIT) is a type of activity characterized by short bursts of intense activities altered with recovery periods. There is growing interest in this type of activity among scientist, but we are still waiting for research results as studies specifically focused on HIIT in TRD remain limited. However, early evidence in some populations suggests that HIIT can effectively reduce depressive symptoms. This means potentially a time-efficient alternative to traditional aerobic training[21].

Taking this all into consideration, broad spectrum of physical activity interventions demonstrate efficiency in reducing depressive symptoms. Studies show particularly strong evidence for weight training and aerobic exercises. Mind-body practices may confer added benefits, while HIIT still require further well-designed trials to confirm its efficiency. The type of physical activity should be individually selected for a specific patient in order to notice significant improvements and therapeutic benefits.

COMPARISON WITH OTHER NOVEL TREATMENTS FOR TREATMENT RESISTANT DEPRESSION

Pharmacological Advances: Ketamine and Esketamine

Over a past decade the use of ketamine and its S-enantiomer, esketamine turned out to be a significant improvement in a treatment of a drug-resistant depression. Ketamine, administered intravenously, demonstrated rapid antidepressant effects within hours, offering relief for

patients nonresponsive to conventional monoaminergic antidepressants. Esketamine nasal spray, FDA-approved since 2019 for adjunctive treatment of TRD, is recognized as "breakthrough therapy" with its novel mechanism targeting NMDA receptors and modulating glutamate neurotransmission[32]. Esketamine similarly to ketamine provides rapid symptom alleviation. Because of potential side effects such as dissociation and sedation, both substances require use under medical supervision. Clinical trials consistently show that with the treatment applied, symptoms improve within days[33-35].

Psychostimulants and Other Therapies

Psychostimulants, like methylphenidate and modafinil, have been explored as beneficial strategies in TRD, particularly to address residual symptoms such as fatigue, cognitive dysfunction, and hypersomnia. Evidence of studies over psychostimulant efficiency are mixed. Some trials show modest improvements on mood and energy levels, but one of the greatest concerns is a long-term safety and abuse potential. Studies over neurostimulation techniques such as repetitive transcranial magnetic stimulation and psychedelic-assisted therapies remain limited and need well-designed trials to confirm efficacy and safety[3].

Physical Activity in the Broader Treatment Landscape

Physical activity has a broad health benefit including improved mood, physical health and cognitive function. Moreover, physical activity is a low-cost, accessible intervention without significant adverse effects and with additional psychosocial benefits. Even though exercise does not provide the rapid antidepressant effects of ketamine, it plays a notable role in improving depressive symptoms, betterment of quality of life, and potentially prolonging remission periods[5,6].

PRACTIAL CONSIDERATIONS FOR CLINICAL IMPLEMENTATIONS

Physical activity interventions are not without contraindications. These include acute cardiovascular events, uncontrolled hypertension, severe musculoskeletal disorders, and certain neurological impairments. Most clinical trials excluded patients with severe physical limitations or unstable medical conditions that contraindicate exercise. Additionally, patients with severe depressive symptoms followed by high suicide risk require stabilization before initiating physical activity programs. In order to ensure safety, prescribed physical activity must be preceded by careful, comprehensive clinical assessment. The most important condition for the effectiveness of this therapy is the appropriate selection of the patients for the treatment method[36,37].

Designing Physical Activity Programs Tailored for TRD Patients

An individual approach to the patient is important when prescribing an exercise program. The individual variables considered are physical fitness, preferences, symptoms, and comorbidities. Protocols often suggest moderate-intensity aerobic exercise, resistance training, or a combination of both, typically prescribed 3 to 4 times per week for 30 to 60 minutes per session. Most promising benefits are placed in multimodal exercise combining endurance, strength, and flexibility components. Exercise programs do not have to be supervised only, but can also be performed at home, with specialized programs which can potentially improve compliance and outcomes. In order to maintain adherence behavioral strategies, self-monitoring, and psychoeducation are recommended[22,36,38].

Adherence Challenges and Motivational Strategies

Compliance is a significant challenge with patients struggling with depression. The difficulty is low motivation, fatigue, and cognitive impairments which affect sick patients. Strategies to improve adherence include personalized exercise plans that align with patient interests, goal setting, frequent follow-up, social support, and motivational interviewing techniques. Structured programs incorporating cognitive-behavioral elements have demonstrated increased motivation and maintenance levels in depressed patients. Nowadays there is a lot technology-based options such as web-based exercise platforms and activity trackers that may improve patients' engagement[22,38,39].

GAPS IN KNOWLEDGE AND FUTURE RESEARCH DIRECTIONS

Need for Standardized Exercise Protocols for Treatment-resistant depression

Despite growing evidence supporting physical activity as an effective intervention for treating depression, there remains a lack of standardized exercise protocols specifically designed for TRD. It is highly difficult to establish consensus guidelines, because current research focuses on exercise modality, intensity, frequency, and duration. Developing well-defined, evidence-based exercise prescriptions tailored for TRD patients is a critical gap identified in the literature. Standardization would possibly improve evaluation and facilitate practical use[20,31,40].

Long-Term Outcomes and Potential Biomarkers of Response

Long-term studies are needed to research the sustainability of exercise-induced antidepressant effects and their impact on overall prognosis. Most randomized controlled trials have focused on short-to-medium term effects of physical activity, typically ranging from 6 to 16 weeks. An important gap is caused by limited data on long-term maintenance of benefits and relapse

prevention in TRD. Another need is identifying biomarkers predictive of response. Biomarkers such as brain-derived neurotrophic factor (BDNF) levels, inflammatory markers, and neuroimaging correlates have been proposed, but we still need more clinical trials research[5,31,40].

Combination Therapies and Personalized Treatment Approaches

Research indicates that in order to increase the effectiveness of TRD therapy, it is necessary to combine different therapeutic modalities such as cognitive-behavioral therapy (CBT), pharmacotherapy and novel agents like ketamine but there is still little attention brought to including physical activity in this category. Research around exercise as a primer before CBT sessions suggest potential synergistic effects, however, it requires further investigation[41]. Personalized approaches considering patient preferences, comorbidities, and biological characteristics could improve compliance and health outcomes. High-quality randomized controlled trials are still needed to establish best management strategies incorporating physical activity in TRD.

CONCLUSIONS

Taking it all into consideration, scientific evidence confirms that physical activity is an effective component of intervention in depression. Clinical trials and meta-analyses show that various forms of exercise, including aerobic, resistance, and mind-body interventions, significantly reduce depressive symptoms and improve quality of life in multiple patient populations. The antidepressant effect of physical activity depends on many biological, psychological, and cognitive mechanisms, making it a multifaceted method of treatment. In addition, physical activity has advantages such as low cost, accessibility, and improvement of physical health, complementing pharmacological therapies including novel agents like ketamine or esketamine.

Current scientific literature based on randomized research and meta-analysis strongly supports the component of physical activity in the comprehensive management of MDD, opting for its incorporation into clinical practice to improve the patient's health outcomes. Unfortunately we still lack scientific research that would primarily focus on patients with TRD.

Taking into consideration high prevalence an significant burden of TRD further research is needed. Incorporating exercise into standard treatment algorithms might yield positive outcomes and be valuable compliment to pharmacotherapy and psychotherapy but we still lack scientific data.

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Author's contribution

Conceptualization: J.Klonowska; methodology: J.Klonowska; check: W.Wasiniewska; formal analysis: S.Kosek; investigation: M.I.Sroka; resources: T.Kandefer; data curation: S.Kosek; writing - rough preparation: R.J.Walkowski; writing - review and editing: M.Barański; visualization: M.I.Sroka; supervision: W. Wasiniewska; project administration: T.Kandefer; receiving funding- no specific funding.

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