

Effectiveness of differentiated physical activity for the therapy of depression: a review

Efektywność zróżnicowanej aktywności fizycznej w terapii zaburzeń depresyjnych: praca przeglądowa

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Abstract

In various forms, depressive disorders may affect over 300 million people worldwide. Physical activity has been studied as a form of therapy for depression for many decades, with generally promising results as either a cost-effective therapy for mild to moderate depression or as an addition to conventional therapies for MDD (major depressive disorder). However, the mechanisms of how regular exercise may alleviate the symptoms of depression are poorly understood. Because structured and regular physical activity is already recommended to professionals as a useful tool of extending typical therapies, there is a growing need for data about what kinds of exercise would be of most benefit to individuals suffering from depression. The current state of knowledge remains inconclusive about many characteristics of the exercise therapy. Proposed therapies lack clear evidence that would suggest the effectiveness of a particular training regimen for remission of depressive symptoms. Among the main problems are differences among used therapies, diverse types of control groups, and variability of applied measures of the symptoms of depressive disorders. However, there is growing evidence suggesting that not the type nor the mode of exercise, but its caloric expenditure measured weekly in kcal and maintaining workout regularity may be the most important factors that should be taken into account when planning a structured antidepressant exercise therapy.

Key words: physical activity, depression, exercise, therapy.

Streszczenie

Według danych WHO zaburzenia depresyjne mogą dotyczyć ponad 300 milionów osób na całym świecie. Aktywność fizyczna jest badaną od wielu dekad formą terapii zaburzeń afektywnych. Uzyskano obiecujące wyniki jej stosowania jako relatywnie niedrogiej terapii łagodnej lub umiarkowanej depresji albo jako formy wsparcia konwencjonalnych terapii dużej depresji (major depressive disorder). Mechanizmy pozytywnego wpływu regularnych ćwiczeń fizycznych na zaburzenia depresyjne pozostają niedookreślone pomimo istnienia wielu prawdopodobnych hipotez. Tym niemniej usystematyzowana aktywność fizyczna jest współcześnie rekomendowana terapeutom i psychiatrom jako użyteczne narzędzie uzupełniające terapię. W związku z powyższym rośnie zapotrzebowanie na dane eksperymentalne opisujące korzyści z różnych rodzajów ćwiczeń fizycznych dla osób cierpiących na zaburzenia depresyjne. Obecnie dostępne dane naukowe niejednoznacznie określają efektywność poszczególnych cech terapii opartej na aktywności fizycznej. Proponowane modele ustrukturyzowanej terapii wciąż wymagają podstawy naukowej w postaci zreplikowanych danych doświadczalnych wykazujących wyższość jednych form terapii nad innymi. Głównymi przeszkodami utrudniającymi tworzenie spójnych hipotez są wielopłaszczyznowe różnice pomiędzy stosowanymi w badaniach rodzajami terapii, niepokrywające się kryteria doboru grup eksperymentalnych i kontrolnych oraz zmienność w zakresie metod pomiaru poziomu zaburzeń depresyjnych. Najnowsze dane naukowe wydają się wskazywać nie na rodzaj czy tryb ćwiczeń fizycznych, ale na łączny tygodniowy wydatek energetyczny oraz utrzymywanie regularnej aktywności fizycznej jako główne kryteria warunkujące wielkość efektu przeciwdepresyjnego, które należy uwzględnić przy planowaniu terapii.

Słowa kluczowe: aktywność fizyczna, depresja, ćwiczenia, terapia.

Introduction

Depression is an affective disorder affecting in varying degrees more than 300 million people worldwide, according to WHO (World Health Organisation) estimates (Depression Fact sheet 2017). Even in highly developed countries, the depression detectability rate is low and only half of those affected seem to receive any therapeutic support, with only slightly more than 40% of therapies fulfilling the minimal WHO criteria (Thornicroft 2017). Provided data suggest that exploration of alternative methods supporting conventional therapies or facilitating self-medication to lower the symptoms of depressive disorders may fulfil the needs of people afflicted by depression. Exercise therapy also seems to be more available and cost-effective in comparison to various kinds of psychotherapy and has fewer side effects than psychiatric treatment.

The author of this paper assumes the presence of a negative correlation between the frequency of physical activity and the intensity of depressive symptoms, as well as prolonged presence of this effect for some period after the intervention is finished. There is also evidence suggesting that variability of different characteristics of physical activity may also play a role in its effectiveness as a therapy for depression. Among them are: type of activity, duration and intensity of a single training session, and involvement of other individuals in performed activities in contrast to individual exercise.

The works described in this study included patients with clinically diagnosed depression, according to DSM or ICD-10 criteria, as well as those classified as depressed by questionnaire scales, of which the most popular seem to be the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HAMD).

Physical activity and depression

The psychological effects of physical activity have been described in professional English-language literature for at least 64 years (Tillman 1965). Therapy of depression with regular jogging, optimally combined with psychotherapy, was first suggested by Greist *et al.* in an article describing their study from 1979. Despite the low value of the experiment due to a low number of groups and methodological deficits, hypotheses about the psychological impact of regular aerobic training appear to be apt. Similar conclusions were proposed by Singh *et al.* in 1997, demonstrating a 50% reduction in depressive

symptoms, as well as an increased effect of pharmacotherapy and a positive effect of physical activity on overall quality of life in subjects aged 60 to 84 years. McCann and Holmes (1984), in a randomised study on young women exhibiting depressive symptoms on the BDI scale, demonstrated a significantly higher improvement in the BDI score in the group performing regular physical activity (dance) for 10 weeks compared with a placebo (stretch) and control (no activity) group. Contemporary results support this trend, as described by a meta-analysis by Cooney *et al.* (2014), which showed a statistically significant relationship between conducting physical activity and alleviation of depressive symptoms, as compared to lack of activity.

Types of physical activity

Statistically significant and persistent up to 12 months after study completion, a positive effect on depressive disorders was demonstrated by Doyno *et al.* (1987). The eight-week study consisted of 40 women divided into three groups: those performing aerobic activity (running), those performing anaerobic activity (strength training on 10 instruments), and a control group. There was no statistically significant difference between the training groups. Therefore, the authors suggest a lack of correlation between cardiorespiratory fitness (CRF) and intensity of depressive symptoms. These conclusions are supported by Martinsen *et al.* (1989), who concluded a study on depressed individuals by assigning them to two groups participating in an eight-week training program based either on aerobic or anaerobic physical activity. Despite the significant VO_2 max (maximum oxygen uptake measured in litres), a measure of CRF, no statistically significant differences were found between groups in the improvement of depressive symptoms.

In their meta-analysis, Cooney *et al.* (2013) combined 35 experiments differentiated by many characteristics. In the analysed studies the impact of physical activity intervention on severity of depressive disorders was studied. The compared studies divided depressed participants into groups receiving regular physical training for a specified number of weeks and control groups (placebo or no intervention). Statistical analysis was performed by distinguishing three subgroups according to the type of physical activity performed in the experimental group. In each of the subgroups, a statistically significant effect was observed in favour of physical activity groups:

moderate effect for groups performing aerobic exercises (SMD [Standardised Mean Difference] -0.55 , 95% CI [Confidence Interval] -0.77 to -0.34) and large effect for groups performing only resistance training (SMD -1.03 , 95% CI -1.52 to -0.53) or mixed training (SMD -0.85 , 95% CI -1.85 to 0.15), consisting of both types of activity. A wide confidence interval for the effect for mixed and strength training should be noted.

Exercise intensity

In the same meta-analysis, Cooney *et al.* differentiated studies also in terms of the intensity of activity performed in the experimental group. The largest effect was observed in studies using high-intensity activity (SMD -0.755 , 95% CI -1.30 to -0.24) and low- to moderate-intensity activity (SMD -0.83 , 95% CI -1.32 to -0.34) which does not allow for clear conclusions and generates demand for experiments that would directly compare groups differentiated in terms of intensity of exercise within the same type of activity.

Dunn *et al.*, in their 2005 randomised study on 80 adults with mild or moderate depressive disorders (HADS), applied a 12-week intervention in the form of aerobic exercise in an experimental group divided into four subgroups by: intensity (low or high energy expenditure, respectively, 7 and 17.5 kcal per kilogram of body weight) and activity frequency (three or five times a week). Individuals in the placebo group conducted stretching exercises three times a week. The study observed the largest statistically significant effect in the group performing the most intense physical activity, which may suggest an inverse correlation between energy expenditure during weekly training regimen and severity of depressive symptoms. The training routine suggested by the researchers which proved to be the most effective equalled about 30 minutes of daily physical activity of moderate intensity. No significant effect on depression symptoms was observed for the activity frequency variable.

Additional data on significance of activity intensity is provided by the study of Lampinen *et al.* (2000), which compared the change in severity of depressive symptoms in 663 older patients before and after the eight-year study period on a modified BDI scale. The authors demonstrated a correlation between intensity of regular activity decrease in time and severity of depressive symptoms. However, it should be

added that older people are a group for which intense exercise may not be optimal due to physical limitations. Such a proposition is made by Arent *et al.* (2000) in their meta-analysis studying the elderly. According to the results of the analyses, in the 65+ age group the most beneficial effect on depressive disorders is achieved by conducting low-intensity physical activity, which, in addition, guarantees a low risk of physical injury, which increases with age.

Another form of systematic approach to conducting physical activity intervention concentrates on exercise tests aimed at metabolic equivalent (MET) count. By definition, a single MET is "the amount of oxygen consumed while sitting at rest, and is equal to 3.5 ml O₂ per kg body weight × min" (Jette *et al.* 1990). The MET concept was created to provide a simple measure of energy expenditure during household chores and systematised exercise. In accordance to referring weekly exercise workload to depressive symptoms change, the MET measuring system has been used by De Moor *et al.* (2006) in their population study on 19,288 individuals. The authors state that participants who exercised for at least 60 minutes at 4 METs weekly reported significantly fewer depressive symptoms on the BDI scale than participants with a lower weekly exercise workload.

Intervention period

A meta-analysis by Cooney *et al.* also provides data on the subject of effectiveness of alleviating depression symptoms by conducting exercise interventions of different lengths. A short intervention lasting up to 12 training sessions shows a statistically significant moderate effect (SMD -0.42 , 95% CI -1.26 to 0.43), which seems to be even larger for interventions lasting 13-24 sessions (SMD -0.70 , 95% CI -1.09 to -0.31) and 25-36 sessions (SMD -0.80 , 95% CI -1.30 to -0.29). Correlation between depressive symptoms reduction and duration of training interventions was also demonstrated in a 1998 meta-analysis by Craft and Landers. The effect described in the study was significantly greater for the group performing physical activity for 9-12 weeks than for the exercise group training for eight weeks or less.

Individual vs. group exercise

Hypotheses about the causes of the effectiveness of group physical exercise on lowering depressive symptoms often mention the social factor, i.e. the effect of other individuals simul-

taneously exercising in the proximity of studied depressed individuals, which could further contribute to reducing the severity of depression. This issue was addressed by Legrand and Heuze (2007) in their study on a small group of people suffering from depression ($N = 23$). However, there were no significant differences between groups performing individually and in groups. Blumenthal *et al.* (2007) drew similar conclusions based on their findings in a group of 202 adults who had met criteria for severe depressive disorder before starting the study. There was a clear overall improvement among the patients but no significant differences between the supervised exercise group and the group exercising individually at home.

Physical activity as an aid to psychotherapy and psychiatric treatment

Interventions in the form of structured regular physical activity may be a valuable tool in the fight against depressive disorders, especially for individuals who do not undertake any conventional therapy. Cooney *et al.* included in their meta-analysis of four studies that directly compare groups of people with depression, those who received intervention in the form of regular physical activity, and those receiving pharmacological aid. They also compiled seven experiments that compared the effectiveness of physical activity therapy and cognitive-behavioural therapy. In both comparisons described in the meta-analysis, there was no statistically significant difference between physical activity and the second type of intervention, while the positive effect each of them had on depressive symptoms reduction was maintained. Sixteen weeks of psychiatric intervention with sertraline was compared by Blumenthal *et al.* (1999) to an exercise intervention consisting of regular aerobic activity of moderate intensity. Sertraline appeared to be more effective at first, although these differences ceased to be relevant at the end of the intervention period. There was no significant difference from the other groups in the group receiving combined therapy. More interesting data was provided by a follow-up of the previous study by Babyak *et al.* (2000). In a group of 156 individuals the authors showed statistically significant intergroup differences in the relapse ratio of depressive symptoms. The group receiving only physical training sessions during the four-month intervention period was found to be significantly less susceptible to

depression relapse than the pharmacological treatment group or the group receiving both interventions simultaneously. Continuation of regular physical activity after intervention was not relevant to the analysis. Before conducting the study, the authors assumed additive effects of both treatments on the treatment of depressive disorders during and after finishing intervention; however, no such effects were observed.

Comparably high effectiveness of group physical activity, ICBT (internet-based cognitive-behavioural therapy), and other therapies, chosen individually, was observed by Hallgren *et al.* in their 12-month study from 2016, which was completed by 797 individuals. The positive effect of a three-month intervention on remission of depressive symptoms strengthened among all groups during the subsequent nine months after intervention discontinuation.

Knapen *et al.* (2015), after analysing four meta-analyses, proposed a physical activity intervention as an effective addition to conventional therapies for individuals suffering from MDD. The wide range of benefits of regularly performing physical activity can be particularly beneficial in severe depressive disorders. Researchers, recognising the specificity of such conditions as MDD, stress the role of therapists in motivating and facilitating patients with regular physical activity, performing tasks that can be a serious challenge for them every day of the treatment. They proposed a number of methods that can be used in the supervision of physical activity therapy both in the initiation and maintenance phase of the intervention.

A meta-analysis by Schuch *et al.* (2016), taking into account the publication bias that could have afflicted data from the previous study by Cooney *et al.*, demonstrated an even greater efficacy of interventions in the form of physical activity alone for reducing the symptoms of depression. The authors of the second meta-analysis showed an inverse effect of publication bias among the researchers conducting the analysed studies, who seem to underestimate a therapeutic effect of physical activity on depressive symptoms. Schuch *et al.* in their conclusions went as far as describing systematic physical activity as an “evidence-based treatment for depression”.

The authors of the 2010 NICE (National Institute for Health and Clinical Excellence) guidelines, after basing their opinion on a series of meta-analyses, included regular physical activity as an effective form of therapy for mild to moderate depression among recommendations for professional therapists. They proposed con-

ducting the intervention in the form of three sessions per week, each 45-60 minutes in length, for an average period of 12 weeks.

A statistically significant impact of physical activity therapy on depression has not been demonstrated in four contemporary randomised clinical trials with the TREAD training protocol (Trivedi *et al.* 2011; Chalder *et al.* 2012) and two others (Krogh *et al.* 2009; Krogh *et al.* 2012), to which Schuch and Fleck refer in their 2013 scientific commentary. The commentators emphasise the importance of fully following the training protocols and the need to use a wide range of depressive symptoms evaluation tool criteria, which were only partly met in listed experiments.

In light of all the above data, intervention in the form of systematic physical activity seems to effectively reduce the symptoms of mild and moderate depression, and can also serve as an effective addition to conventional therapies for MDD. The provided studies seem to emphasise the low significance of the type of performed physical activity while underlining the high importance of maintaining regularity of exercise sessions. The complexity of the provided data highlights the variety of ways in which performing physical activity affects each individual suffering from a depressive disorder, reaching far beyond a single biological mechanism.

Hypotheses for the antidepressant effect of physical activity

In general, researchers point to a variety of explanations of the positive effect of physical activity on depressive disorders, resulting from the multi-faceted interactions of biological and psychological processes. For example, Rethorst *et al.* (2016) describe sleep disorders, psychosocial functioning, and cognitive functioning among the categories of depressive symptoms that are positively affected by physical activity, and Abt (2005) described different approaches to exercise as a treatment of depressive symptoms.

Physiological hypotheses

Craft and Perna (2004) proposed a number of physiological explanations of the benefits of physical activity for people suffering from depression. The endorphin hypothesis assumes that the increase in β -endorphins, the most studied endogenous opioids contributing to MDD aetiology, may cause mood improvement and elevated physical well-being resulting from physical exercise because they take part in

a number of complex behavioural and homeostatic processes (Hegadoren *et al.* 2009). In addition, β -endorphins are suspected to synergise with the endocannabinoid system and cortisol production (Heyman *et al.* 2012). Researchers, however, have no clarity as to the relationship of endorphin concentration in the peripheral nervous system with their actual concentration in particular areas of the brain. According to the lesser known thermogenic hypothesis, the increase in body temperature resulting in exercise may also favourably reduce the symptoms of depression and anxiety; however, this has been experimentally proven only for the latter group of disorders. In addition, according to the NICE recommendations, regular physical activity is considered to be a quality modulating factor for sleep, hygiene of which seems to be crucial in the therapy of depression.

Hypothalamic-pituitary-adrenal axis reactivity hypothesis

In reaction to stress, the hypothalamic-pituitary-adrenal (HPA) axis releases corticotropin-releasing hormone (CRH), which after being transported to pituitary gland stimulates production of the adrenocorticotrophic hormone (ACTH), thereby directly affecting the release of cortisol and other glucocorticoid hormones from the adrenal cortex (Hill *et al.* 2010). Among other effects, HPA axis glucocorticoid production modulates body metabolism and such brain functions as neurogenesis or neuronal growth (Pariante and Lightman 2008). Imbalances in functioning of the HPA axis have been linked to depression. Depressed patients often exhibit higher levels of basal cortisol than controls. Physical training tends to regulate the HPA axis response to stress by lowering its reactivity to stressful stimuli, which results in a higher *physiological toughness* by affecting both cortisol levels and biogenic amines levels, therefore lowering the symptoms of depression.

Monoamine hypothesis

The monoamine hypothesis coincides with the current state of scientific knowledge, which states that in individuals suffering from depressive symptoms, at least one of the following monoamines is deficient in the central nervous system: serotonin, dopamine, or noradrenaline (Nutt 2007). Previously cited Craft and Perna describe their studies on animal models in which physical exercise seems to increase the levels of noradrenaline and serotonin, which may be a premise for the monoamine hypothesis. Ho-

wever, it must be noted that while monoamine hypothesis may seem accurate, especially with proven effectiveness of tricyclic antidepressants and selective serotonin reuptake inhibitors on treating depressive symptoms, it has never been demonstrated to be true (Dantzer *et al.* 2011).

Brain-derived neurotrophic factor hypothesis

Carek *et al.* (2011) describe the BDNF (brain-derived neurotrophic factor) hypothesis, based on a protein closely associated with modulating brain plasticity, and deficits of which are related to deterioration of memory functions and atrophy of the hippocampus. It has been demonstrated that antidepressants reduce the risk of developing Alzheimer's disease (Claeyssen *et al.* 2015) and stimulate neuroplasticity. Researchers assume that similar effects could be associated with regular physical activity. Low BDNF levels in the central nervous system are also associated with an increased risk of depression (Erickson *et al.* 2012), which could be counteracted by performing intense physical activity. Elevation of BDNF levels, although in the peripheral nervous system, was observed after intensive exercise (cycling) by Heyman *et al.* (2012).

Endocannabinoid hypothesis

The very same study by Heyman *et al.* describes the role of the endocannabinoid system in the aetiology of depression. Two well-studied endocannabinoids, N-arachidonoylglycerol (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), by acting on the CB1 cannabinoid receptor, affect not only neurogenesis and BDNF production, but can also alter emotional and cognitive processes. Physical exercise is proven to positively affect plasma anandamide and 2-AG levels, a process that has been linked to a post-exercise intense feeling of positive emotions called *runners high*. Raised endocannabinoid levels also seem to modulate mood by affecting striatal dopamine release and pain perception. In addition, CB1 receptor activation is proven to down-regulate cortisol production, therefore directly affecting body stress response. Results of a study by De Chiara *et al.* (2010) on mice point at a protective effect of 15 days of regular physical activity with regard to stress, which is described as being caused by exercise-related CB1 receptor modulation.

Inflammation hypothesis

There is strong evidence pointing to impaired transmission of serotonin and noradrenaline as the

primary neurobiological basis of major depression (Schiepers *et al.* 2005). Proinflammatory cytokines are suspected to be causally involved in the disruption of monoaminergic transmission, primarily by altering the activity of presynaptic serotonergic neurons, but also by affecting synaptic cleft re-uptake and postsynaptic serotonergic receptor activity. In addition, pro-inflammatory cytokines, including interferon- γ and tumour necrosis factor- α , induce the process of tryptophan degradation through the kynurenine pathway. Kynurenine is a major metabolite of tryptophan because over 95% of its dietary intake is processed by the liver through the kynurenine pathway, while only a small percentage of tryptophan is degraded to serotonin (Dantzer *et al.* 2009). Overactive kynurenine pathway decreases the bioavailability of tryptophan as a serotonin precursor, potentially affecting development of depressive symptoms. Impaired concentration and sustaining fatigue are also symptoms of proinflammatory cytokine hyperactivity, and they overlap with primary symptoms of major depressive disorder. Physical activity is pointed out as a potentially effective behavioural intervention for patients with chronic inflammatory disorders. Exercise is reported to increase plasma tryptophan levels in both animal and human models, therefore affecting tryptophan availability for serotonin synthesis (Badawy 2017).

Myokine hypothesis

The term myokines refers to cytokines and other peptides released by muscle fibres, which have an endocrine (associated with long-distance hormonal cellular communication) or paracrine (short-distance hormonal communication) effects. Contracting skeletal muscles by performing physical activity releases myokines, which aside from a number of endocrine and paracrine effects also mediate anti-inflammatory processes (Pedersen 2011). According to the myokine paradigm, muscular inactivity negatively affects muscular endocrine functioning, which may result in increased risk of developing cancer, dementia, cardiovascular diseases, and major depression. A systematic review by Howren *et al.* (2009) reports that depressive symptoms are positively correlated with the presence of such inflammatory myokine markers as interleukin 1 and interleukin 6, implicating a possible bidirectional or unidirectional relationship between depression and inflammation. There is no convincing evidence for a causal relation between depressive symptoms and other myokines, such as irisin (Hofmann *et al.* 2016). However, an

animal model study by Wang and Pan (2016) reports that irisin is involved in energy metabolism regulation in the prefrontal cortex, a process crucial for inducing antidepressant effects.

Psychological and social hypotheses

One of the simplest dependencies observed in people with depression, who have started physical activity, was an increased focus on external and body-related stimuli that acted as distractors for people over-focused on negative thoughts, ruminations, and unpleasant emotions, which is a characteristic trait of depression, as stated in the article by Craft and Perna (2004). The study, however, does not provide a clear answer to the question of whether for people suffering from depression physical exercise is a more effective distractor than other techniques. What is proven is the positive effect of physical exercise on the ability to feel positive emotions, which is a skill often impaired by depressive disorders. Craft's 2005 study on a small group of depressed individuals also demonstrated the benefits of physical activity on self-efficacy and self-image, which may confirm the suspicions of other researchers (Brosse *et al.* 2002). Although previous sections of this paper describe the lack of differences between physical activity exercised independently and in group activity, the importance of social aspects of group training is not negligible. Interaction with others, joint exercise, physical contact, and the ability to meet new people can help to reduce the symptoms of depression and prevent their relapse, but only if one continues to attend the training sessions.

Summary

Generalising, insufficient physical activity and overly static lifestyle can promote the development of a number of mental disorders, including depression (Carek, Laibstain, and Carek 2011). Optimal intervention in the form of physical activity therapy seems to overlap in terms of intensity and frequency with recommendations (but not with the minimum WHO recommendations) for maintaining health (Physical activity. Fact sheet 2017). Studies also confirm the NICE recommendations for professional therapists working with individuals affected by depression, according to which systematic physical activity alone may be beneficial for people suffering from mild to moderate depression, but also that it could be used as an effective addition to conventional therapies when treating severe forms of depression.

Studies have shown that not the length of a single training session nor the intensity measured by HRmax percentage, but total weekly energy expenditure reached during workout sessions may be a more related measure of physical activity that correlates with the level of depressive symptoms reduction. Also, there seems to be no significant relationship between the type of conducted activity and the degree of depression remission. It should be added that a regular physical activity regimen for patients who have already ended therapeutic intervention seems to be a protective factor against the relapse of depression.

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