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Effects of physical activity on treatment of schizophrenia

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Summary

The aim of this paper was to describe the effects of physical activity on management of schizophrenia. A critical review of literature was made and current state of knowledge presented. In line with contemporary research trends and based on available evidence, a panel of experts from the European Psychiatric Association issued a guidance on exercise interventions in the treatment of severe mental illness.

Elevated premature mortality rates in schizophrenia patients are linked largely to the effect of antipsychotic treatment, low physical activity, and/or increased somatic comorbidity, mainly of cardiometabolic origin. Physical exercise combined with psychological and dietary interventions are reported to improve parameters of the metabolic syndrome, cardiovascular fitness and cognitive performance. Moderate and high intensity training are deemed attractive forms of adjunctive therapy of schizophrenia, adjustable to patients' age, performance and preferences.

Future research and high-quality clinical trials investigating the effects of exercise on early presentation of the disease, its pragmatic efficacy, potential adverse events, financial burden and neurobiological underpinnings could help create specific recommendations for training programs of optimal format, dose and duration.

schizophrenia, physical activity, aerobic exercise, high-interval intensity training, endurance training

INTRODUCTION

Lifetime prevalence of schizophrenia is calculated as approximately 1 %, affecting mainly young adults between 20 and 30, with symptoms persistent throughout adult life of 30-50% of patients [1]. Apart from symptom-related impairment in social functioning, schizophrenia leads to high hospitalization rates and occupational incapacity, generating socioeconomic burden exceeding that of most widespread somatic conditions, and thus stands among the 10 most costly diseases worldwide [2], not to mention being one of the leading causes of years lived with global disability. Schizophrenia-related premature mortality rates, high prevalence of somatic comorbidity and pronounced cognitive impairment are especially challenging in light of the limited treatment options [3]. Rising somatic health burden in this population calls for novell treatment approaches, and add-on physical activity interventions seem to be a promising augmentation to existing forms of therapy.

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Mortality and comorbidity in schizophrenia

Negative effects of schizophrenia on daily functioning and subjective well-being have been well

documented [4]. Among some of its other characteristics remain reduced physical activity, poor physical health, and limited daily activity [5]. Both illness-related health outcomes and unhealthy lifestyle translate into a 12-fold higher mortality rates than those observed in the general population [6]. High incidence of somatic comorbidities, habitual cigarette smoking and/or low physical activity, and high suicide rates are all considered accountable for elevated mortality and reduced life expectancy (by approximately 10-20 years) in schizophrenia [7]. According to research findings, mortality due to unnatural causes, such as suicide, is higher compared to natural causes, such as cardiovascular diseases (CVD). Still, the relative risk of the latter is estimated to be higher in schizophrenia patients than those with depressive disorders or patients with multiple diagnoses [8]. In general, psychiatric patients with severe mental illness (SMI) are at a higher cardiovascular risk of developing coronary heart disease, hypertension, diminished heart rate variability, alterations of the QT interval, abnormal lipid pattern and autonomic nervous system dysfunction [9]. Interestingly enough, the relative risk of mortality due to diabetes or heart disease within the first 12 months from diagnosis of first-episode psychosis does not seem to differ significantly from the rates recorded in the general outpatient group [10], suggesting that the observed disparity in all-cause mortality may be linked to either unnatural causes (like suicide) or fatalities due to somatic comorbidities developed later, as the illness progresses, or the two combined.

Factors found to be linked with greater ratio of suicide ideation in first-episode patients include higher incidence of depressive symptoms, longer period without treatment and presence of positive symptoms (ie. hallucinations and delusions) [11]. Other predictors of suicidal behaviors seem to be lower severity of negative symptoms, reduced global cognitive performance and poor visual memory [12]. Different factors are associated with suicide attempts and completed suicide, the former being somatic comorbidity, family history of mental illness, history of alcohol abuse, depressive symptoms and history of depression, with the latter comprising history of attempted suicide, higher IQ, poor compliance with treatment, hopelessness, and being male [13].

Around 70% of premature deaths recorded in psychiatric patient populations are estimated to occur as a consequence of somatic comorbidities, largely of metabolic, respiratory and cardiovascular origin [14]. Contemporary standards dictate the use of pharmacotherapy and/or psychotherapeutic interventions as first-choice treatment of mental disorders. Although both these approaches, alone and in combination, show confirmed treatment efficacy towards psychiatric symptoms, psychotropic medication may lead to poor health outcomes, mainly of metabolic nature [15]. The metabolic syndrome (ie. increased waist circumference combined with low HDL cholesterol, high blood pressure, elevated triglycerides and fasting glucose levels), which is linked with a 4-fold increased risk of type 2 diabetes and a 2-fold risk of CVD (such as stroke and coronary heart disease) [16] in the general population, has a 4 times higher prevalence in schizophrenia patients [4], leading to a 2-3-fold higher risk of CVD, and thus also increased cardiac mortality [17]. Such data are consistent with findings reporting elevated risk of the metabolic syndrome (MS) in all patients with SMI [17]. Older age, illness duration, waist circumference [18] and negative symptoms [19] turn out to be the strongest predictors of MS in schizophrenia patients, whereas factors like treatment setting (in – vs. outpatient), country of origin or gender do not seem to affect its rates [18]. Research reports also suggest higher incidence of cardiovascular risk in multi-episode patients compared to the first-episode ones [20], possibly attributable to longer treatment with antipsychotics and their side effects.

Comparisons of mortality rates between antipsychotic medication users vs. non-users show that both first – and second-generation antipsychotics lead to more frequent cardiac deaths, with atypical antipsychotics further known to negatively affect such features as the length of the QT interval and resting heart rate [21], to lead to weight gain and increased sedation, but also to cause fewer extrapyramidal side effects compared to the first-generation medication [22]. Consequently, due to the adverse effects of long history of antipsychotic treatment, both cardiovascular and metabolic risk is calculated to be significantly higher in multi-episode patients, especially those on polypharmacotherapy, com-

pared to their antipsychotic-naïve counterparts [17, 20]. As regards cognitive function, antipsychotic medication has been linked with reduced grey matter volume in schizophrenia patients [23]. All above evidence deems lifestyle changes crucial, notably in multi-episode patients with substantial treatment history.

Physical activity in schizophrenia

In the general population, physical inactivity has been estimated to be responsible for various adverse health conditions, including approximately 6% of the worldwide burden of disease from coronary heart disease (CHD), 7% from type 2 diabetes, 10% from breast and colon cancer, and 9% of premature mortality overall [24]. Postulated benefits of physical activity include reduced incidence of MS, CHD, type 2 diabetes, cancer, stroke, or depression. There is also strong evidence for higher cardiorespiratory and muscle fitness, healthier body mass and composition, enhanced bone health and improved cognitive functioning [24].

Evidence suggests that only <50% of schizophrenia patients [25] meet the recommended physical activity levels of 150 min. weekly of moderate-to-vigorous exercise [26], which is consistent with findings that SMI generally correlates with highly sedentary lifestyle [26] and low cardiorespiratory fitness [27]. Medication side effects, poor general health [28], lack of professional support or sufficient resources, and various motivational aspects [29] are just some of the obstacles to engaging in physical activity that this population experience.

Sedentary behavior is evidenced to be significantly higher in schizophrenia patients compared to healthy controls. Even when they do engage in physical activity, its intensity seems to be less moderate and vigorous, mainly in connection to depressive symptoms and older age [30]. Decreased rates of physical activity in this patient population are also linked with lower quality of life, motivation, poorer social functioning, higher social withdrawal, and lower employment. What is more, low physical fitness tends to correlate with illness duration, cigarette smoking, incidence of the MS, and greater severity of schizophrenia symptoms [5].

Even among those enrolled in sports activities, the dropout rates seem somewhat staggering. In their meta-analysis, Vancampfort et al. [31] reported that 26.7% of the analyzed 594 schizophrenia patients dropped out of the administered physical activity interventions, which constituted more than double of the figures demonstrated in the non-active controls. Lower dropout rates were recorded when training was supervised by a professional sports scientist and combined with a motivational intervention.

Effects of physical activity interventions in schizophrenia patients

Research results suggest improvement in symptoms and enhanced cognitive performance in response to supervised exercise interventions in schizophrenia patients [32]. Better cognitive function resulting from physical activity was observed within domains of social cognition, working memory and attention/vigilance in schizophrenia patients [33]. To magnify the pro-cognitive effects, recent designs have shifted toward combining exercise interventions with cognitive rehabilitation [34]. However, some data suggest that better physical fitness may not necessarily ensure improved cognitive performance in people with established schizophrenia and baseline evidence of cognitive dysfunction [35]. A systematic review [36] investigating the pro-cognitive effects of exercise in schizophrenia patients suggested their increased brain volume, though with no specific mention of any particular brain region, while data on physical activity's effects on BDNF levels was somewhat inconclusive. The results concerning potential hippocampal growth also proved inconsistent [37], suggesting that the neurobiological underpinnings of the observed effects still remain unclear.

Systematic reviews analysing how strength training alone [38] or in combination with aerobic interventions [39] affect schizophrenia-spectrum disorders indicate that they may lead to improvement in general muscle strength and reduced schizophrenia symptoms. Elsewhere, aerobic exercise was also found to improve cardiorespiratory fitness [40].

It is postulated that new treatment options, like aerobic exercise, might reduce the risk and

incidence of cardiovascular and metabolic diseases in schizophrenia. Still, research on the effects of endurance training on MS-related parameters in schizophrenia patients appears somewhat inconclusive. According to findings from different studies, exercise has no effects on weight loss, BMI, body fat ratio, or MS-related factors [41]. There is, however, some evidence suggesting that aerobic exercise might improve overall physical activity, blood pressure levels and body composition [42]. What findings to date seem to indicate is that exercise interventions alone are less likely to elicit weight loss in schizophrenia patients, while combining them with other psychosocial or dietary interventions might constitute a promising strategy to impact body weight reduction. Following this approach, there is evidence that 12-week physical activity in combination with motivational interventions reduced body weight in schizophrenia patients [43]; a 3-month program involving psychosocial interventions, behavior therapy, and aerobic exercise led to a reduction in waist circumference, body weight, and BMI [44]; a 24-week aerobic exercise program significantly reduced patients' weight and BMI [45]; or that personalized diet and exercise interventions of at least one month induced a weight reduction in this patient population [46].

An alternative to aerobic exercise, expected to potentially increase its somewhat insufficient efficacy is high-intensity interval training (HIIT), ie. a new form of intensified endurance activity [4], considered a time-efficient method to improve body composition [47]. There is good evidence that in mentally healthy populations with obesity and cardiometabolic risk factors, this type of intervention can elicit stronger beneficial effects on metabolic parameters, including waist circumference, body mass, HDL cholesterol, fasting glucose and blood pressure [48]. However, studies comparing HIIT and continuous training bring different results, some suggesting HIIT's significant superiority [49], while others reporting no difference between these two forms of physical activity [50]. Given the positive health outcomes observed in mentally healthy populations, there is good chance that HIIT can be an efficacious strategy to improve MS-related parameters also in psychiatric patients, including those suffering from schizophrenia-spectrum disorders. Despite a relative paucity of evidence investigating its application in schizophrenia patients, research to date indicates positive effects of using this type of intervention [51, 52].

When it comes to CVD and mortality prevention, a key strategy in the general population lies in improving cardiorespiratory fitness [53], which, amongst others, can be achieved through aerobic exercise [54] or HIIT. Group exercise [55] or continuous training [37, 42, 45, 56, 57] have been found to provide cardiorespiratory benefits also in schizophrenia patients, exceeding those offered by other forms of intervention, eg. occupational therapy or table soccer. Some evidence confirms positive effects of HIIT on cardiovascular parameters when applied in therapy of schizophrenia [51, 58, 59]. In addition, cardiorespiratory fitness reportedly correlates with an increased hippocampal volume [37, 60], and may attenuate brain volume changes in schizophrenia patients [57].

The collected body of evidence (see above) clearly indicates that modern therapeutic approaches should include physical activity as part of an intervention programme to improve cognitive functioning, psychopathology and health outcomes in schizophrenia. Interestingly, following Stubbs et al. [25], relatively few authors comment on the potential harms of exercise in schizophrenia patients, all but one [61] reporting no physical activity-related adverse events [36, 38, 39, 41].

Practical recommendations and future research directions

Recommendations on the optimal amount of physical activity for healthy individuals to improve cardiorespiratory fitness dictate 150 min of moderate training per week [62]. However, in contrast to healthy population, schizophrenia patients are characterized by features which decrease their motivation to engage in physical activity (ie. treatment-induced sedation, schizophrenia symptoms, poorer education, lacking experience with exercise; or social withdrawal) [63], which implies that they might benefit from external motivational interventions or supervision from a sports scientist to increase their mo-

tivation to participate, making training both effective and feasible [64].

Various systematic reviews and meta-analyses report the benefits of physical exercise in therapy of schizophrenia-spectrum disorders [35, 36, 39, 40, 41], regardless of the observed variation in frequency, intensity, type or time of the interventions. Findings suggest that 90 min of weekly physical activity (ie. a minimum of 30 min per session at least three sessions per week [65]) of moderate-to-vigorous intensity is associated with alleviating general, positive and negative symptoms of schizophrenia and improving quality of patients' life [41].

Population-based research demonstrates that prevention of metabolic deterioration, including lifestyle changes is in fact a more effective approach than any attempts to reverse the negative cardiovascular or metabolic health outcomes [66]. Compared physical health outcomes of pharmacological versus non-pharmacological interventions targeting patients with schizophrenia-spectrum disorders [26] demonstrate that among the most effective strategies inducing weight reduction are, subsequently, individual lifestyle counseling and physical activity, psychoeducation, aripiprazole augmentation, topiramate, d-fenfluramine and metformin. In contrast, superior effects for MS-related parameters such as waist circumference, glucose, triglicеride, total, LDL – and HDL-cholesterol levels, and insulin resistance are yielded by various pharmacological interventions.

Early research on aerobic exercise in therapy of schizophrenia had a number of methodological limitations, some of the major concerns including lacking (healthy and/or patient) control groups, insufficient sample sizes, and non-controlled or – randomized research models. There are still certain areas that seem somewhat neglected in the scientific investigation of the effects of exercise on schizophrenia management. Establishing whether physical activity interventions have a similar positive effect on somatic and mental health outcomes in first-episode schizophrenia patients still requires more evidence. It is expected that further research might also elucidate whether early intervention including exercise in first-episode psychosis or even its prodromal phase could either reduce the risk of long-term functional disability, or lead to a full and sustained remission

Future research directions regarding the actual delivery of physical activity interventions should also focus on their pragmatic efficacy. Namely, it is postulated [25] for their form to be accessible, interesting and effective enough so as to reach and involve large patient populations. According to the existing body of evidence, this entails their sufficient intensity and delivery by exercise professionals (as opposed to e.g. qualified mental health personnel).

Establishing what exactly constitutes the optimum frequency, intensity, time and type of interventions for each SMI, while accepting some degree of individual variance with regard to patient preferences and disease characteristics, is another area to be further explored. What is more, in light of a relative paucity of research commenting on physical intervention-related adverse events, it is recommended for future studies to carefully analyze this very issue, especially with respect to cardiovascular risk.

European Psychiatric Association (EPA) experts [25] also postulate further investigation of the underlying neurobiological pathways of exercise interventions in therapy of psychiatric patients, as the existing theories seem insufficient to fully explain the implicated mechanisms. Of particular note are lacking long-term trials (ie. >12 month long) that could evidence sustainable effects of implemented exercise-based interventions.

Last but not least, though there is convincing evidence of the efficacy of physical activity in treatment of SMI, the cost-effectiveness of those remains largely unknown.

CONCLUSION

There is quite ample evidence to support the notion that physical activity, especially in combination with other psychosocial or dietary interventions may improve various aspects of functioning in schizophrenia patients, positively affecting their cognitive performance, somatic health outcomes (especially cardiometabolic parameters) and elevated mortality rates. Aerobic training has proved feasible and effective in psychiatric patient populations, but due to certain illness-related limitations observed in these particular groups (eg. sedation, low internal mo-

tivation, negative symptoms), it is especially recommended under professional supervision. To date, there are no established adverse effects of physical activity interventions. Despite confirmed benefits of both continuous and high-intensity interval training models, specific therapy recommendations can be formulated only after the optimal format, dose and duration or the potential supremacy of either intervention have been determined in the course of clinical trials. Given the still limited research on application of physical activity interventions in treatment of schizophrenia, more trials are called for to further investigate the effects of exercise on early presentation of the disease, their pragmatic efficacy, potential adverse events, durable and sustainable effects of training, as well as financial requirements and neurobiological mechanisms underlying this form of therapy.

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