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Physical Exercise and Geriatric Depression: An Opinion**Actividad Física y Depresión Geriátrica: Una Opinión****Atividade Física e Depressão Geriátrica: Uma Opinião***Sergio Machado¹**João Lucas Maciel de Lima**Flávia Paes**Salgado de Oliveira University**Diogo Monteiro**João Moutão**Luis Cid**Polytechnic Institute of Santarém**Eric Murillo-Rodriguez**Anáhuac Mayab University**Tetsuya Yamamoto**Tokushima University***Abstract**

Depression represents a common public health problem in the world. Depression in the elderly appears to follow a vulnerability-stress model, with an interaction between individual vulnerabilities, including genetic factors, age-related cognitive and neurobiological changes, and a variety of stressful events that occur more frequently in advanced ages, such as grief, financial problems, and reduction in autonomy/functionality. In the last decades, several studies have indicated that exercise can be effective in preventing or reducing depressive symptoms, both in healthy and psychiatric populations. Due to the scientific community's interest in the efficacy and safety of physical exercise as complementary therapy for depressed elderly patients, we conduct an opinion study on the subject. Despite the researchers' efforts, in the last decades little progress has been made in verifying the efficacy of exercise in geriatric depression.

Keywords: depression, elderly, exercise, functionality

Resumo

A depressão representa um problema comum de saúde pública no mundo. A depressão em idosos parece seguir um modelo de vulnerabilidade-estresse, com uma interação entre vulnerabilidades individuais, incluindo fatores genéticos, mudanças cognitivas e neurobiológicas relacionadas à idade, e uma variedade de eventos estressantes que ocorrem mais frequentemente em idades avançadas, como luto, problemas financeiros e redução da autonomia/funcionalidade. Nas últimas décadas, vários estudos indicaram que o exercício pode ser eficaz na prevenção ou redução dos sintomas depressivos, tanto em populações saudáveis como psiquiátricas. Devido ao interesse da comunidade científica na eficácia e segurança do exercício físico como terapia complementar para idosos deprimidos; realizamos um estudo de opinião sobre o assunto. Apesar dos esforços dos pesquisadores, nas últimas décadas pouco progresso foi feito na verificação da eficácia do exercício na depressão geriátrica.

Palavras-chave: depressão, idosos, exercício, funcionalidade

Resumen

La depresión representa un problema común de salud pública en el mundo. La depresión en los ancianos parece seguir un modelo de vulnerabilidad-estrés, con una interacción entre las vulnerabilidades individuales, incluidos factores genéticos, cambios cognitivos y neurobiológicos relacionados con la edad, y una variedad de eventos estresantes que ocurren con mayor frecuencia en edades avanzadas, como el duelo, problemas financieros y reducción de la autonomía/funcionalidad.

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En las últimas décadas, varios estudios han indicado que el ejercicio puede ser eficaz para prevenir o reducir los síntomas depresivos, tanto en poblaciones sanas como psiquiátricas. Debido al interés de la comunidad científica en la eficacia y seguridad del ejercicio físico como terapia complementaria para pacientes ancianos deprimidos, realizamos un estudio de opinión sobre el tema. A pesar de los esfuerzos de los investigadores, en las últimas décadas se ha avanzado poco en la verificación de la eficacia del ejercicio en la depresión geriátrica.

Palabras clave: depresión, ancianos, ejercicio, funcionalidad

Introduction

Depression represents a common public health problem with a prevalence of 15% to 20% (Kessler et al., 2005; Moussavi et al., 2007), which rose from 15th to 11th position (37% increase) in the 1990-2010 among one of the main causes of disability in the world (Murray et al., 2012). Although the prevalence of depression apparently decreased with age (Scott et al., 2008), with a prevalence in samples from adult communities aged 65 years and older ranging from 1 to 10% in most large-scale epidemiological studies (Hasin, Goodwin, Stinson, & Grant, 2005; Park et al., 2012), rates of depression are higher in certain elderly subgroups, such as clinical outpatients (5 to 10%), hospital outpatients (10 to 12%), and residents of care institutions for elderly (asylums) (14 to 42%) (Blazer, 2003). Depression in the elderly appears to follow a vulnerability-stress model, with an interaction between individual vulnerabilities, including genetic factors, age-related cognitive and neurobiological changes, and a variety of stressful events that occur more frequently in advanced ages, such as grief, financial problems, and reduction in autonomy/functionality (Carta, Balestrieri, Murru, & Hardoy, 2009; Fiske, Loebach Wetherell, & Gatz, 2009).

Due to the high prevalence of depression, the efficacy of antidepressants and their low side-effect profile, these drugs have become one of the most common drugs in Europe with 6% of users in France (Gasquet et al., 2005) and 4.7% in Italy (Carta et al., 2010). Randomized clinical trials involving depressed elderly have shown moderate to large effect sizes for selective serotonin reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors (Beyer, 2007). However, only a small proportion of depressed elderly (around 20%) received adequate treatment (Barry, Abou, Simen, & Gill, 2012; Zhang et al., 2010). Lack of treatment among older adults may partly reflect the difficulty of detecting depression in older adults because of the age-specific presentation of the disease, compared to young adults, older patients tend to present less emotional symptoms of depression, such as sadness, uselessness/guilt, worry and fear, and are less accurate in identifying general symptoms of depression (Wetherell et al., 2009). Finally, response rates to antidepressant monotherapy are only 30% to 45% with single-acting or double-acting monotherapy with antidepressants (Smith, Dempster, Glanville, Freemantle, & Anderson, 2002). Therapies of augmentation or combination with two antidepressants increase the percentage of responsive patients by up to 75%, but these strategies increase the risk of side effects and treatment cessation (Thase, Howland, & Friedman, 1998; Rush et al., 2006). Finally, the presence of severe comorbidities may contribute to depression and complicate the choice of treatment. In addition, elderly patients are likely to use a wide variety of medications, some of which may worsen depression and/or interact with antidepressants and metabolize medications slowly, as they are more sensitive to side effects than young people (Alexopoulos, Katz, Reynolds, Carpenter, & Docherty, 2001).

In the last decades, several studies have indicated that exercise can be effective in preventing or reducing depressive symptoms, both in healthy and psychiatric populations (Tsutsumi et al., 1998; Mortazavi et al., 2012; Anderson, 2001; Barbour & Blumenthal, 2005; Sjösten & Kivelä, 2006). However, these studies present many methodological flaws, such as the lack of an adequate method of randomization and blinding procedure, small samples, and poor quality in data analysis (Sjösten & Kivelä, 2006). However, due to the scientific community's interest in the efficacy and safety of physical exercise as complementary therapy for depressed elderly patients, we conduct an opinion study on the subject.

Exercise as an Adjunctive Therapy on Elderly Depression: Methodological Differences

Only a few studies had intervention groups with supervised exercise programs, compared to health lectures or short groups of health advice as a control (Singh, Clements, & Singh, 2001; Mather et al., 2002; Sims, Hill, Davidson, Gunn, & Huang, 2006). Matthews et al. (2011) combined health lectures with stretching. Teri et al. (2011) had a two-arm control group, one with a health promotion education program or a health care routine. McNeil, LeBlanc, & Joyner (1991) had two groups of control, one with social contact and another with waiting list. Singh et al. (2001) had as control an attention group, while Singh et al. (2005) performed a two-arm treatment (supervised anaerobic training at high or low intensity) in comparison to a 'care group' as a control group. In the present study, the use of antidepressants in combination with antidepressants (Kerse et al., 2010) was performed by a group of patients with antidepressant sertraline therapy (Mather et al., 2002) a reasonable percentage of participants undergoing antidepressant therapy in both the treatment group and the control group.

Treatment assignment was adequately conceived in four studies (Singh, Clements, & Fiatarone, 1997; Singh et al., 2001; Mather et al., 2002; Kerse et al., 2010). The intention-to-treat analysis was performed in five studies (Singh et al., 1997; Blumenthal et al., 1999; Singh et al., 2001; Mather et al., 2002; Sims et al., 2006). The double-blind evaluation of the main outcome was not performed in any study. The main result was a significant reduction comparing the initial moment of GDS assessment in three studies (Sims et al., 2006; Kerse et al., 2010; Teri et al., 2011), BDI score in one study (Mcneilet al., 1991), the score of the HAM-D score in two studies (Mather et al., 2002; Singh et al., 2005). Two studies evaluated participants with both an observation questionnaire (HAM-D) and BDI (Singh et al., 1997; Blumenthal et al., 1999).

Due to the variety of samples, the characteristics of the intervention and control groups, the duration of the trials, main assessment and follow-up, a direct comparison between studies is difficult. In addition, lack of appropriate randomization, intention-to-treat analysis and double-blind design affected the studies.

The latest guidelines from the National Institute for Health and Clinical Excellence (NICE) included physical activity as a treatment strategy for depression, recommending structured programs of supervised exercise, 3 x week (45 min to 1 hour) over 10-14 weeks, of low intensity as an intervention for mild to moderate depression. In addition, guidance for the promotion of mental health prescribes an accumulation of a minimum of 150 minutes of exercise in moderate intensity or a minimum of 75 min of vigorous intensity per week in sessions of at least 25 min over 3 to 5 days per week (Otto & Smiths, 2009). In this sense, the studies do not

follow completely the parameters of NICE (Mcneil et al., 1991; Singh et al., 1997; Singh et al., 2001; Mather et al., 2002; Singh et al., 2005; Matthews et al., 2011; Teri et al., 2011).

Exercise as an Adjunctive Therapy on Elderly Depression: Clinical Evidence

Physical exercise has been considered as adjunct therapy to act on depression, promoting a variety of neurobiological effects, such as increased monoamine and endorphin levels or reduced levels of cortisol in the brain (Duclos, Gouarne, & Bonnemaïson, 2003; Helmich et al., 2010). Since it has been hypothesized that depression may be linked to decreased neurogenesis (Duman, Heninger, & Nestler, 1997; Bjornebekk, Mathe, & Brene, 2005), researches have shown that exercise promotes adult neurogenesis in the hippocampus (Elder, De Gasperi, & Gama Sosa, 2006; Lucassen et al., 2010; Lieberwirth & Wang, 2012), and dendritic remodeling (Yau et al., 2011), and such exercise-related effect was found to be stronger than that determined by antidepressant drugs (Marlatt, Lucassen, & van Praag, 2010).

Exercise improves subjective quality of life in the physical domain of depressed patients (Carta et al., 2008; Martin, Church, Thompson, Earnest, & Blair, 2009; Blake, 2012), with higher doses of physical activity associated with greater improvements, both in physical and mental domains of quality of life. In addition, exercise may promote other cognitive mechanisms related to subjective well-being, such as negative thinking drift and sense of purpose (Hardoy et al., 2011; Searle et al., 2011).

A series of literature reviews and meta-analyses, carried out in the recent past, highlighted the researchers' interest in establishing the efficacy of exercise on elderly depression (Lawlor & Hopker, 2001; Barbour & Blumenthal, 2005), but did not carry out specific analyses of the efficacy of exercise as an additional treatment in depression of elderly people who underwent antidepressant therapy, which may probably be more useful in clinical practice. For example, Forsman, Nordmyr, and Wahlbeck (2011), reviewing the literature on psychosocial interventions for mental health among elderly concluded that physical activity did not have statistically significant effects when compared to no intervention.

The question is the small amount of randomized clinical trials conducted, which could provide experimental evidence of the effect of exercise, excluding confounding factors. Other frequently overlooked evidence is a dose-response effect, and minimal dose-effect (Ruberg, 1995). A consensus conference between experts pointed out for the experimental evidence of a dose-response between physical activity and health (Kesaniemi et al., 2001; Oja, 2001). Dunn, Trivedi, and O'Neal (2001) confirmed the lack of studies but stated that the dose-response relationship remains plausible.

Ströhle, in a recent review, argued for the lack of ideal parameters of exercise, intensity, frequency and duration of treatments, highlighting the need for knowledge on how best to deal with symptoms related to depressions, which are likely to prevent patients from engaging in physical training (Ströhle, 2009). In addition, many studies on the subject are scarce from a 'placebo' condition as a control. Klein (1996) assumes that researchers comparing non-pharmacological interventions for antidepressant drugs should include a placebo control group in order to exclude confounding factors. Walsh and Sysko (2005) reported that the proportion of patients responding to placebo in the studies with elderly were slightly higher compared to studies with younger adults, leading to a reduction in effect size. Interestingly, a

higher response rate for placebo was predicted by the low severity of the disease at the start of the study (Stein, Baldwin, Dolberg, Despiegel, & Bandelow, 2006), and in clinical practice, patients with mild to moderate depression are likely to have a better placebo response in clinical trials (Sneed et al., 2008). On the other hand, only a few studies have focused on the effect of exercise compared to anti-depressant therapy. Thus, in order to show the effect of common confounding factors on exercise and “control” condition, choosing an activity such as relaxation exercise, flexibility or stretching as “control” seems to be acceptable rather than a “no treatment” group (Carta et al., 2008).

Another important point is that exercise can act on depression through other elements other than itself, such as socialization, learning new skills, weight loss, everything related to psychosocial skills, usually reduced in patients with depression (Barton, Griffin, & Pretty, 2012). In addition, elderly generally have low levels of social interaction, which are also related to depression (Prince, Harwood, Thomas, & Mann, 1998), determining the time spent on anti-depression activity programs. Consequently, social contact also seems to be accepted as a control for the social component of physical activity programs (Kerse et al., 2010).

As noted by Lawlor and Hopker (2001), the use of disease-free volunteers and the lack of intention-to-treat analyzes suggest that the results may overestimate what would be likely in real life. Among other studies, Singh et al. (2005) focused on the effect of different exercise intensities, showing that the high intensity exercise was superior to the control treatment, with no effects for low intensity training. In a study of exercise as adjuvant treatment to antidepressants in the treatment of resistant depressive patients, Trivedi, Greer, Grannemann, Chambliss, and Jordan (2011) showed that although high and low doses of exercise combined with SSRI treatment produced a decrease in depressive symptoms, there was a tendency to reach a remission rate at the highest dose compared to the lower dose group. However, participants assigned to the low-dose exercise group had better adherence than those assigned to the high-dose exercise group, showing that low-dose exercises may be more tolerable and acceptable for depressed patients and suggesting that patients being treated with antidepressants, even performing low doses of physical activity can get reduction of depressive symptoms effectively.

Thus, although the authors’ findings fail to generalize the results, they attract attention to really important issues, which are the prescription of exercise as an adjuvant to pharmacological treatment. Interestingly, a growing body of evidence links the neuropathological correlates of depression, such as hippocampal atrophy, and the effect of physical activity on brain plasticity. Minor hippocampal volumes are associated with depression in both young and elderly populations (Steffens et al., 2000), and also predict more unfavorable long-term outcomes of antidepressant therapies (Hsieh et al., 2002). There is strong evidence that BDNF protein expression plays an important role in the pathophysiology of depression (Hashimoto, 2010), supporting the notion that clinical improvement in depression is associated with neuroplasticity. Both antidepressants (Brunoni, Lopes, & Fregni, 2008) and exercise (Erickson, Miller, & Roecklein, 2012) have been shown to block or even reverse depression-related hippocampal atrophy by increasing BDNF. Vascular disease in the elderly is closely associated with depression (Alexopoulos, Bruce, Silbersweig, Kalayam, & Stern, 1999). The presence of sub-limbic manic symptoms, which is very difficult to identify in the elderly, also with screening methods (Angst et al., 2010), increases the risk of vascular dysfunction (Fiedorowicz, Coryell, Rice, Warren, & Haynes, 2012) and therefore it is possible

that among people with more severe depression they are cases that are more vulnerable to switching mania during antidepressant therapy.

Previous research has suggested that combined treatment with more antidepressant exercise produced significant increases in BDNF levels while the antidepressant alone failed, and the combination between exercise and reboxetine led to rapid increases (detectable at 2 days) and sustained at 20 days in the hippocampus expression of BDNF mRNA (Russo-Neustadt, Alexandre, Garcia, Ivy, & Chen, 2004). It is noteworthy that this effect was demonstrated in both young and elderly rats (Garza, Ha, Garcia, Chen, & Russo-Neustadt, 2004). Very few studies have been conducted in this promising field; however, physical activity has been recommended in combination with other treatments (Daley, 2008) and, in a pilot study, was proposed as a lower cost-raising strategy to improve the residual symptoms of depression and prevent relapse (Trivedi, Greer, Grannemann, Chambliss, & Jordan, 2006). Thus, while more research is needed to confirm this hypothesis, physical activity may be considered of interest as augmentation strategy to treat treatment-resistant depression at the end of life.

Final Considerations

Despite the researchers' efforts, in the last decades little progress has been made in verifying the efficacy of exercise in geriatric depression. This is due in part to the methodological flaws, the difficulty of establishing the actual effectiveness of physical activity, both qualitatively and quantitatively, as a management strategy for depressive symptoms, and the specific characteristics of geriatric depression. In addition, some promising findings on physical activity combined with antidepressants in depressed patients resistant to antidepressant therapy should be carefully considered considering the low cost, overall health benefits, and acceptable risk in elderly patients.

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