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A commentary on the importance of controlling for medication use within trials on the effects of exercise on depression and anxiety

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ABSTRACT

The aims of this commentary are to (1) identify the potential interactive effects of exercise with anxiety/depression medications, based on mechanistic or observational studies, (2) describe how studies dealt with use of antidepressant or anxiolytic participants' medications in their study design and analyses, based on a narrative review of Randomized Controlled Trials (RCTs), and (3) consider the implications for future research for assessing the use of medications within trials and using this information in analyses.

Meta-analyses have shown that exercise interventions reduce depressive (Ekkekakis, 2015; Herring, Puetz, O'Connor, & Dishman, 2012) and anxiety symptoms (Herring, O'Connor, & Dishman, 2010) among patients with a clinical mental health condition and also among those with physical health conditions (e.g., COPD (Coventry et al., 2013), heart failure (Tu et al., 2014), multiple sclerosis (Dalgas, Stenager, Sloth, & Stenager, 2014), and breast cancer (Carayol et al., 2013), but the role of medication use in understanding these effects is not clear.

The aims of this commentary are to (1) identify the potential interactive effects of exercise with anxiety/depression medications, based on mechanistic or observational studies, (2) describe how studies dealt with use of antidepressant or anxiolytic participants' medications in their study design and analyses, based on a narrative review of Randomized Controlled Trials (RCTs), and (3) consider the implications for future research for assessing the use of medications within trials and using this information in analyses.

1. Which types of interaction could occur between exercise and medications?

Mechanistic or observational studies indicate four types of interactive effects of exercise with anxiety and depression drugs that could bias effect estimates of exercise on psychological symptoms in RCTs:

(a) A synergistic/additive effect

An animal investigation has suggested that antidepressants and exercise could act synergistically to upgrade brain-derived neurotrophic factor level which has been negatively associated with depression (Russo-Neustadt, Beard, & Cotman, 1999). Based on murin and humans models, repeated physical exercise and prolonged antidepressant treatment could be considered to engage the same neuroprotective pathways (see details in Chen, 2013), suggesting an additive effect of exercise and antidepressant. In addition, a reduction in blood serotonin could occur after exercise among healthy adults, suggesting a higher retention of serotonin in the brain and then a decrease of depression level after exercise (Wipfli, Landers, Nagoshi, & Ringenbach, 2009).

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(b) An antagonistic effect

In contrast, an antagonistic effect may also exist between exercise and antidepressants. Indeed, Selective Serotonin Reuptake Inhibitor (SSRI) could be decreased with motor activity (based on murin studies) (Marlatt, Lucassen, & van Praag, 2010). In humans, an increased risk of muscle injuries has been reported with SSRI treatment (Labotz et al., 2006).

(c) A behavioral effect

Antidepressant and anxiolytics could moderate the efficacy of exercise through exercise adherence. Although a high depression score is a well-identified predictor of poor adherence (Jette et al., 1998), findings about the relationship of antidepressant and anxiolytic treatments with exercise adherence are scarce and inconsistent. Prescribed antidepressant medication was a major predictor of poor adherence rate or drop-out in individuals participating in an exercise cardiac rehabilitation program (Laustsen, Hjortal, & Pertersen, 2013; Marzolini, Brooks, & Oh, 2008), whereas in an interventional RCT designed for weight loss in postmenopausal women, exercise intervention adherence did not differ between antidepressant users and non-users (Imayama et al., 2013). Comorbid conditions (i.e., higher anxiety and poorer life satisfaction) were also associated with higher dropout rate in middle-aged adults with MDD (Herman et al., 2002).

(d) Health status of participants

The use of antidepressant and or anxiolytic drugs may also reflect differential health status. In the Australian population, the individuals who take one of these two medications were likely to have more comorbidities (e.g., diabetes, cardiovascular disease, cancer, arthritis) than non-users (Atlantis, Sullivan, Sartorius, & Almeida, 2012). Such comorbidities have been associated with greater functional limitations (Sevick et al., 2007) and poorer exercise adherence rates (Tobi, Estacio, Yu, Renton, & Foster, 2012). Furthermore, these medications may impair the efficacy of concomitant treatment. For instance, Breitbart (2011) suggested that antidepressants (inhibitors of CYP2D6) used concurrently with tamoxifen may reduce the clinical efficacy of tamoxifen among cancer patients.

2. Did RCTs testing the effects of exercise on depression and anxiety considered these possible interactions?

We performed a narrative review of literature to examine whether a potential interaction effect of antidepressant/anxiolytic medication with exercise has been identified in previous RCTs. Studies cited in published systematic reviews were included in the present review if they met the following PICOS criteria. Participants were adults with or without depressive/anxiety disorders. Interventions examined the effects of physical exercise (supervised or home-based) and reported a medication arm or antidepressant/anxiolytic medication use during exercise intervention. Control groups were usual care, exercise (other form), other treatment or active control condition. Outcomes were depression/anxiety score (using psychometric instruments) or results from standardized psychiatric interview. Only published RCTs were included.

2.1. Antidepressants in exercise RCTs

Six systematic reviews with meta-analyses focusing on the effects of exercise interventions on depression were identified. The reviews with 39 (Cooney et al., 2013), 90 (Herring et al., 2012), 14 (Perraton, Kumar, & Machotka, 2010), 8 (Robertson, Robertson, Jepson, & Maxwell, 2012), 58 (Rethorst, Wipfli, & Landers, 2010), and 13 RCTs (Mura, Moro, Patten, & Carta, 2014) were screened, and 24 were selected. The studies identified are presented in the following sections: (a) RCTs with exercise and medications arms, (b) RCTs with an exercise arm including only participants with antidepressant treatment, (c) RCTs with an exercise arm describing participants' use of antidepressant at baseline.

(a) RCTs with exercise and medications arms

A 3-armed RCT compared a 16-week intervention involving exercise combined with sertraline (i.e., SSRI) vs. exercise vs. sertraline in older adults ($N = 156$) with MDD (Blumenthal et al., 1999). Patients in combined treatments received simultaneously the same medication and exercise described below. Sertraline was provided by psychiatrists and was initiated with 50 mg daily. Participants were evaluated (therapeutic responses and sides effects) five times during the treatment. Participants in exercise arms attended three weekly supervised aerobic exercise sessions of 45 min. Twenty percent of included patients dropped out before the end of intervention. The exercise adherence rates were nearly 90% of sessions in exercise or combined condition. The depression score did not differ between groups at the end of treatment period (Blumenthal et al., 1999). However, some differences between groups were seen for the timing of depression decrease. Participants in the sertraline arm exhibited a faster therapeutic response within the first few weeks compared to other groups and, participants with initial mild depressive symptoms (Hamilton Rating Scale for Depression, HAMD score between 13 and 18) receiving the combined intervention showed an earlier decrease of depression level compared to exercise or medication only.

Three other 3-armed RCTs compared exercise vs. SSRI vs. placebo/usual care among adults with depressive disorders (Blumenthal et al., 2007, Blumenthal, Sherwood et al. 2012; Brenes et al., 2007). Two studies found a significant superiority of the aerobic exercise and SSRI conditions over pill placebo (without difference between exercise and SSRI arms) to decrease depression level or remission rate (Blumenthal et al., 2007, Blumenthal, Sherwood et al. 2012). The findings suggested also a possible superiority of exercise over sertraline in the context of more baseline exacerbate depression severity. However, in the study of Brenes et al. (2007) including 37 older adults with elevated depressive symptoms, intervention conditions (i.e., exercise vs. SSRI) were not significantly superior to placebo (i.e., usual care) on HRDS and Geriatric Depression Scales scores; a lack of power due to small size sample could be responsible for this negative result. In a 4-armed RCTs, Blumenthal et al. (2007) assessed the efficacy of aerobic exercise (home based vs. supervised) vs. sertraline vs. pill placebo on depression among 202 adults with current MDD. They found a significant superiority of active treatments over placebo for remission rates but not for HAMD continuous scores. For both outcomes, no differences were obtained between aerobic exercise (home based and supervised) and sertraline interventions. A more recent RCT compared supervised aerobic exercise vs. sertraline vs. pill placebo in 101 patients with coronary heart disease and elevated depressive symptoms (Blumenthal, Sherwood et al. 2012). Exercise and sertraline treatment were found to be superior over placebo to decrease HRDS scores at the end of intervention. No statistical differences were found between active treatments. Sub-analyses among patients initially meeting the criteria for MDD suggested a possible superiority of exercise over sertraline and placebo for remission rates (40%, 20%, 0% respectively).