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A commentary on ‘Exercise and Depression’ (): And the Verdict

Is... Mead et al., 2008

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In 2001, Debbie Lawlor along with co-author Stephen Hopker, published an influential and highly cited meta-analysis in the *British Medical Journal* in which they examined the effectiveness of exercise as an intervention to treat depression (Lawlor & Hopker, 2001). They identified 14 studies, all of which had what they considered important methodological weaknesses. Nevertheless, in studies that compared exercise to no treatment controls, the pooled standardized mean difference in effect size was -1.1 . Pooling the nine studies that used the Beck Depression Inventory (BDI) yielded a weighted mean difference score of -7.3 . However, despite this relatively large effect (i.e., most drug and psychotherapy trials report less than a -4.0 mean difference score; Lesperance et al., 2007; Schneider et al., 2003) the authors concluded that the effectiveness of exercise in reducing symptoms “cannot be determined because of a lack of good quality research on clinical populations with adequate follow up” (Lawlor & Hopker, 2001, p. 763)..

Gillian Mead and colleagues (2008; see Cochrane Corner, this issue) have now performed a new meta analysis in which they compare exercise to “no treatment” (which actually includes comparisons of exercise to exercise combined with established treatments such as cognitive therapy or antidepressant medication) and exercise compared to established therapies such as antidepressant medication or alternative therapies such as ‘light’ therapy. In the present analysis, 28 trials were included for review of which 25 provided sufficient data for meta analysis. For the 23 trials (including 907 participants) that compared exercise to no treatment or to a control condition, the pooled standardized mean difference (SMD) was -0.82 , indicating a large treatment effect; however, the authors note that most of the studies had serious methodological weaknesses, and only 3 trials (Blumenthal et al., 2007; Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; Mather et al., 2002) including 216 participants had adequate allocation concealment, intention to treat analysis, and blinded outcome assessment. In these better quality studies, the pooled SMD was reduced to -0.42 , with a point estimate that was half the size of that with all trials included. Some methodological issues are indeed critical (e.g., intention to treat [ITT] analysis, multiple imputation for missing data, and blinded assessments), while other criteria seem less important and arbitrary (e.g., the requirement of drawing of sealed and opaque envelopes that are sequentially numbered for ‘proper’ randomization). This estimate represents a moderate effect size that is greater than the effect sizes reported from recent meta analyses of clinical data from the US Food and Drug

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Administration of placebo-controlled trials of antidepressants (SMD = 0.32 and 0.31, respectively, Kirsch et al., 2008; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). Nevertheless, results achieved only “borderline statistical significance” when studies that failed to use ITT or blinded assessments, which are critical design features of randomized clinical trials, were excluded from the analysis. As a result of their analysis, the authors concluded that “outstanding uncertainties remain about how effective exercise is for depression, mainly because of methodological considerations” (Mead et al., 2008, p. 13).

While the conclusions of the present meta analysis appear similar to those of their prior review, it is of interest to examine the results from the new studies that were published since the 2001 *BMJ* review: a large study by Blumenthal et al. (2007) enrolled 202 participants in a placebo controlled trial of exercise and antidepressants and found positive results, but only a modest treatment effect (0.20) using ITT; a carefully designed study by Dunn et al. (2005) showed positive results but was limited by high attrition (only 66% of 80 participants completed the study); Mather et al. (2002) reported positive findings in 85 patients but did not perform an ITT analysis; Singh et al. (2005) reported positive results in 60 participants, but involved non-aerobic exercise (unlike virtually all of the other studies that employed aerobic exercise); Chou et al. (2004) reported positive findings in a study using Tai Chi, but included only 14 geriatric outpatients; Knubben et al. (2007) reported positive results in 38 psychiatric inpatients with affective disorders, but the intervention was brief (i.e., walking on a treadmill for 10 days) and a quarter of the sample also received concurrent sleep deprivation therapy; Nabkasorn et al. (2006) reported positive results in 59 female participants, but did not perform an ITT analysis and the outcome assessors may not have been blinded; Pinchasov et al. (2000) reported positive findings in 63 participants with seasonal and nonseasonal depressive disorder, but the treatment of daily cycle ergometry lasted for only one week and it is unclear whether outcome assessors were blind to treatment; and Tsang et al. (2006) examined the effect of Qigong (meditation, breathing exercises, and body movement) in 82 participants and reported positive findings, but stopped recruitment prematurely when an interim analysis found that the main outcome measure was significant. One trial (DEMO) classified as “Ongoing” in the Cochrane review was recently published, but found no exercise benefit (Krogh, Saltin, Gluud, & Nordentoft, 2009). Taken together, the majority of studies since the initial Lawlor and Hopker analysis report positive exercise-related outcomes, but small samples, weak exercise interventions, and improper data analyses diminish the credibility of the findings and as a result, there remains continued skepticism regarding the value of exercise as a treatment for depression. Although we can appreciate the basis for this skepticism, we believe that the weight and consistency of the evidence clearly demonstrates the therapeutic value of exercise as an additional treatment option for some patients with clinical depression.

In their 2001 analysis, Lawlor and Hopker also reported that the length of follow up was significantly negatively associated with the size of the effect. This relationship was not addressed in the current analysis, but the authors plan to examine this issue in future updates of their review, which would be a welcome addition. Although follow-up data are limited for most trials, 6-month follow up of participants in a study comparing exercise with sertraline (Babyak et al., 2000; Blumenthal et al., 1999) revealed that relapse rates were significantly lower among those remitted patients assigned to the exercise condition compared to medication, and that patients who reported exercising over the follow up interval exhibited a 50% reduction in the risk of being diagnosed with major depression (MDD); medication use provided no such benefit. There is no reason to believe that exercise training would continue to benefit patients after they discontinued exercise any more than patients who stopped taking their anti-depressant medication would continue to benefit from medication if they discontinued their medication. There also is no reason to believe that exercise for 10 weeks is superior to a longer 12–16 week intervention in reducing depressive symptoms.

Although the authors conducted several subgroup analyses that investigated the impact of exercise modality and intensity on outcomes, the potential moderating effect of depression severity was not included in their meta analysis and could be informative. Exercise is widely believed to be helpful for mild depression, but may be less effective for moderate to severe depression, although data on this issue are limited. It also is noteworthy that the method by which depression is assessed has varied across studies; structured psychiatric interviews are widely considered to be the “gold standard” for diagnosing clinical depression, while psychometric questionnaires provide useful information about the severity of symptoms. Relatively few studies use clinical interviews such as the Structured Clinical Interview for Depression (SCID) or the Diagnostic Interview Schedule (DIS) to diagnose depression, and using standard psychiatric interviews for diagnosis would be an important methodologic advance for the field.

The authors also identify several other key issues including implications for research and clinical practice. In particular, they call for further trials that are large and methodologically robust. Virtually all cited studies are single-site trials, with our most recent study at Duke of 202 patients with MDD representing the largest sample conducted to date (Blumenthal et al., 2007). Because the assessment of depression utilizes well-standardized procedures and exercise prescriptions are highly portable, a multicenter clinical trial would appear to be very feasible and potentially less costly compared to other intervention trials. In addition, examination of mechanisms that may be responsible for the therapeutic benefit of exercise would be very worthwhile, as well as inclusion of participants with other mood disorders including dysthymia, minor depression, and bipolar depression.

The authors also provide recommendations for clinical practice. Despite the limitations of research in this area, the authors surprisingly suggest that exercise can be recommended to people with clinical depression. However, virtually all studies conducted to date have included research volunteers, who may not be representative of patients seeking psychiatric treatment. Generally, research participants are less severely depressed compared to treatment-seeking individuals, and there are limited data regarding the benefits of intensive, supervised exercise compared to home-based, unsupervised exercise. Patients who are volunteers for exercise studies are typically motivated to exercise, which may not be the case in patients seeking psychiatric treatment for depression. Furthermore, data on the optimal frequency and dose of exercise are limited, and probably would be necessary if exercise were a drug and FDA approval was required to prescribe it for depression.

So at the end of the day, what is the verdict? Evidence from 144 potential papers was carefully reviewed but proved inconclusive: Only 28 trials fulfilled criteria for closer review and most studies had significant methodologic limitations. As a result, the authors conclude that further research is needed to adequately determine the effect of exercise on depression. Is exercise a viable treatment for depression? Perhaps, but it would appear that the jury is still out.

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