



Editorial

Exercise as antidepressant treatment: Time for the transition from trials to clinic?



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1. Introduction

The notion that exercise may hold promise as an intervention to treat mental health problems has a history of over 30 years. As early as 1984, the National Institute of Mental Health organized a workshop entitled “Coping with mental stress: The potential and limits of exercise intervention” [1]. Since then, this notion has been controversial. In the early days, neither the amount nor the quality of the experimental evidence could withstand serious scrutiny. Hughes [2], for example, after finding no experimental evidence supporting any benefits of exercise for depression, anxiety, or cognitive function concluded that “the enthusiastic support of exercise to improve mental health has a limited empirical basis and lacks a well-tested rationale” (p. 76). Over the years, although experimental evidence started to accumulate, the skepticism persisted. The 1999 Surgeon General’s report on mental health [3] acknowledged some evidence for symptom improvement in individuals diagnosed with depression. Nevertheless, physical activity was not recognized as a potential form of treatment but was rather subsumed in an “ever-expanding list of formal and informal interventions to aid individuals coping with adversity,” alongside “religious and spiritual endeavors,” and “complementary healers” (p. 232).

The issue was placed under a new light in the last decade, when exercise or physical activity were explicitly incorporated as treatment options in clinical guidelines in several countries (see Table 1). Two developments were the likely catalysts for this change. First, a comparison of data published in the literature to data held by the Food and Drug Administration revealed that the apparent therapeutic effect of common antidepressants had been manipulated by selective publication to appear larger [10]. Second, several meta-analyses with converging results showed that the therapeutic effect of antidepressants is distinguishable from placebo only for patients with severe initial levels of depressive symptoms [11–13]. Along with the desire to contain costs, these developments provided the impetus for the evolution of “stepped care” or “stepped collaborative care” models for the treatment of depression. According to such models, the use of in-person psychotherapy and antidepressant medication should be limited to cases of moderate and (mostly) severe symptoms. On the other hand, cases of subthreshold symptoms and mild or moderate depression are to be treated with “low-intensity” interventions that include, among other options, exercise or physical activity.

Guidelines in the US do not presently recommend the use of exercise for treating depression at any level of symptom severity. The American Psychiatric Association [14] provided no systematic review of evidence pertaining to exercise and did not mention exercise among its “Recommended Modalities for Treatment.” Physicians were offered guidance only for those cases in which the idea of exercise as antidepressant treatment is raised by the patients themselves: “if a patient with mild depression wishes to try exercise alone for several weeks as a first intervention, there is little to argue against it” (p. 30). This sentence has been interpreted [15] as suggesting that “the clinician should not consider exercise as a first-line intervention even for mild depression” (p. 187). Similarly, the US Preventive Services Task Force and the American College of Physicians [16], following a very limited review of evidence from clinical trials on the effects of exercise, concluded that only cognitive behavioral therapy and second-generation antidepressants should be considered for the treatment of depression. While medical practice in the US is subject to certain fundamentally different processes compared to other Western countries, it is nonetheless striking that guideline development panels in different countries have arrived at different conclusions on the treatments they deem appropriate.

Over the years, several authors have expressed the view that exercise is underutilized in the domain of mental health despite what appears to be a fairly consistent body of evidence [17–26]. In fact, exercise is not utilized in the treatment of subthreshold, mild, and moderate depression even in countries, such as the UK [27] or the Netherlands [28], in which guidelines based on stepped-care models explicitly call for its utilization. This phenomenon points to the possibility that lack of awareness, incredulity, skepticism, or a general reluctance on the part of clinicians might be the main obstacles. Here, we briefly address some of the concerns that have been voiced.

Table 1

Examples of stepped collaborative care guidelines that include exercise or physical activity in the treatment of major depression (in chronological order).

Year	Country	Issuing Authority	Summary
2004	United Kingdom	National Institute for Clinical Excellence [4]	Clinical Guideline 23: “Patients of all ages with mild depression should be advised of the benefits of following a structured and supervised exercise program of typically up to 3 sessions per week of moderate duration (45 min to 1 h) for between 10 and 12 weeks” (pp. 15–16).
2010	United Kingdom	National Collaborating Centre for Mental Health and National Institute for Health and Care Excellence [5]	Clinical Guideline 90: “For people with persistent subthreshold depressive symptoms or mild to moderate depression” (p. 213), a “structured group physical activity program” should be presented among other “low-intensity” treatment options. Such a program should (a) be delivered in groups with support from a competent practitioner, and (b) consist typically of three sessions per week of moderate duration (45 min to 1 h) over 10 to 14 weeks.
2010	Scotland	Scottish Intercollegiate Guidelines Network [6]	“Structured exercise may be considered as a treatment option for patients with depression” (p. 10).
2013	Netherlands	Working Group on Multidisciplinary Guideline Development for Anxiety and Depression [7]	Exercise is recommended for light depressive episodes, as well as for first and recurrent moderate major depressive episodes.
2015	Australia and New Zealand	Royal Australian and New Zealand College of Psychiatrists [8]	Lack of exercise is recognized as an “agent that can potential lower mood.” As such, it is a factor that should be addressed at “step zero” of stepped treatment: “it stands to common reason that for both mood and general medical well-being sedentary patients should be actively encouraged to engage in regular exercise” (p. 1119). “Step one” treatments (psychological therapy or pharmacotherapy) should be initiated only if “step zero” measures prove insufficient.
2016	Canada	Canadian Network for Mood and Anxiety Treatments [9]	Recommended exercise as “first-line monotherapy for mild to moderate major depressive disorder and as second-line adjunctive treatment for moderate to severe major depressive disorder” (p. 579).

2. But how could exercise possibly change mood?

According to a qualitative study on the beliefs of British general practitioners about the potential of physical activity in managing depression [29], “virtually all [general practitioners] felt physical activity would be best utilized as an adjunct treatment for managing depression rather than as a ‘stand alone’ treatment” (p. 17). Likewise, in the Netherlands, physicians report advising their patients to be more physically active but refrain from referring them to exercise specifically for depression [28]. What these findings seem to reflect is the assumption that antidepressants or psychotherapy would treat the underlying pathology, whereas exercise can only play a supportive role in promoting wellness as a behavior that is generally “good for you.”

In the medical literature, mentions of exercise as a possible antidepressant treatment are often intertwined with discussions of complementary and alternative approaches that include acupuncture, herbal medicines, or homeopathy. This peculiar juxtaposition may create the impression that exercise operates via similarly arcane or nebulous mechanisms. For example, it is not uncommon to encounter claims [30] that “any effect of exercise is largely placebo in nature” (p. 536). In the oft-cited Cochrane review on exercise for depression [31], in the section “How the intervention might work,” the authors highlighted such processes as diverting attention away from negative thoughts, encouraging social contact, and improving self-efficacy, none of which is likely to be perceived as “therapeutic” per se.

These portrayals of exercise suggest that a disconcerting gap may have developed between the extraordinarily prolific neurobiological literature examining the effects of exercise on the brain and the clinical literature. This gap is presumably a consequence of the absence of training on exercise in medical curricula in most countries, including the US [32], UK [33], Canada [34], and Australia [35]. In actuality, the evidence on the neurobiological effects of exercise is as voluminous as it is fascinating. While the current understanding of both the neurobiology of depression and the exact mechanisms of action of antidepressant drugs remains incomplete, there is evidence that exercise mimics the postulated effects of antidepressants [36]. Specifically, its actions include robust effects on monoaminergic neurotransmission [37], reliable upregulation of neurotrophic factors [38], and extensively documented neuroplasticity [39]. These effects warrant wider dissemination within the clinical literature than they have received.

3. But there is no evidence!

Given the potentially staggering economic ramifications of the transition from current practice norms to stepped-care models for treating depression, it is perhaps unsurprising that the effects of exercise have been disputed and even misrepresented. Authors have gone as far as to state that “the data on the efficacy of exercise ... are either negative or do not exist” [40] (p. 745) or even “do not exist at all” [41] (p. 113). Whether due to misinformation or ignorance, the perception that the use of exercise for the treatment of depression lacks an evidence base appears prevalent among physicians [29,42,43].

The latest version of a periodically updated Cochrane systematic review [31] included 39 randomized controlled trials (RCTs) totaling over 2000 participants with depression. A summary of this review was published in the *Journal of the American Medical Association* [44]. Therefore, claiming that “data do not exist” cannot be attributed to the data being hidden in obscure outlets.

Claiming that data are “negative” is also false. According to the Cochrane review [31], the pooled standardized mean difference (SMD) from 35 RCTs that compared exercise to a control intervention was 0.62 (95% CI –0.81 to –0.42). However, careful analysis of the review reveals numerous irregularities, such as violations of the specified inclusion criteria (i.e., inclusion of studies in which exercise was compared to a different mode of exercise or to an active stress management intervention) and exclusion of several studies with large effects without providing justification (e.g., studies of postnatal depression). Reanalysis of the data set [45] showed a large pooled SMD (–0.90, 95% CI –1.11 to –0.69). Exercise groups lowered their depression scores more than the control groups by 6.43 units on the Beck Depression Inventory and by 4.07 units on the Hamilton Rating Scale [45]. Perhaps more importantly, the seven studies that included head-to-head comparison to psychotherapy ($N = 189$) and the four studies that included head-to-head comparison to antidepressants ($N = 300$) showed that the benefits from exercise were not different from either

(SMD = - 0.03, 95% CI - 0.32 to 0.26, $I^2 = 0.0\%$, and SMD = - 0.11, 95% CI - 0.34 to 0.12, $I^2 = 0.0\%$, respectively).

4. But, even if there is evidence, it's methodologically weak!

In 2001, a meta-analysis on the effects of exercise on depression, published in the *British Medical Journal*, found a large pooled SMD of 1.1 [46]. Without mentioning this figure, a summary in the first pages of the journal appeared under the title “Effectiveness of exercise in managing depression is not shown by meta-analysis.” The summary emphasized that “the trials are of poor quality.” This early meta-analysis subsequently evolved into the Cochrane review. The criticism of poor methodological quality became a theme that has since transcended all updates of the review: “uncertainties remain regarding how effective exercise is for improving mood in people with depression, primarily due to methodological shortcomings” [31] (p. 33).

Before accepting such wholesale condemnation of this line of research, readers are urged to examine the details, some of which are troubling [45]. For example, starting with the 2001 meta-analysis and continuing with each update of the Cochrane review, the investigators coded all RCTs in which the primary outcome measure was a questionnaire, such as the Beck Depression Inventory, as entailing high risk of bias due to non-blinding of the outcome assessor. This greatly limited the pool of RCTs that could be deemed of “high quality” since this designation required satisfying all criteria for methodological quality, including blinding of the outcome assessors. It is crucial to emphasize that this represents an ad hoc rule rather than standard practice in assessing study quality. For example, in evaluating the methodological quality of RCTs examining the effects of cognitive behavioral therapy on depression, other reviewers designated all trials using self-report outcome measures as having blinded assessment [47] (p. 213).

The authors of the Cochrane review wrote in the *Journal of the American Medical Association* [44] that, when only six high-quality trials were considered (i.e., those with allocation concealment, intention-to-treat analysis, and blinded outcome assessment), there was “no association of exercise with improved depression” (SMD = - 0.18, 95% CI - 0.47 to 0.11). However, this conclusion was also shaped by several erroneous or arbitrary inclusion and exclusion decisions [45]. When these are corrected, the pooled effect from high-quality RCTs is significantly different from zero (SMD = - 0.42, 95% CI - 0.68 to - 0.17).

What is undeniable is that, as with psychotherapy, participants allocated to exercise interventions are aware that they are exercising, making double-blind trials impossible. Because participation in exercise is likely to induce an expectation of benefit, studies comparing exercise to pill placebo would be valuable in promoting internal validity. Two such high-quality RCTs published thus far [48,49] have yielded an average effect that is stronger than those from placebo-controlled RCTs of antidepressants and cognitive behavioral therapy (see Fig. 1). Although more such trials are needed to improve the precision of efficacy estimates, the persistent renunciation of this body of research on methodological grounds is no longer justified.

5. But patients won't do it!

In 1990, a clinical psychologist wrote that the notion of using exercise as antidepressant treatment “must puzzle clinicians who, in treating depressed people, often have to contend with an absence of motivation to tackle much less strenuous features of life's routine” [52] (p. 107). Since then, several authors have argued that the cognitive hallmarks of depression, such as helplessness, hopelessness, low self-esteem, and avoidance of socialization, would probably prove insurmountable obstacles to exercise participation for most individuals with depression [46,53,54]

Certainly, low engagement, nonadherence, and dropout pose challenges for the promotion of exercise not only among individuals with

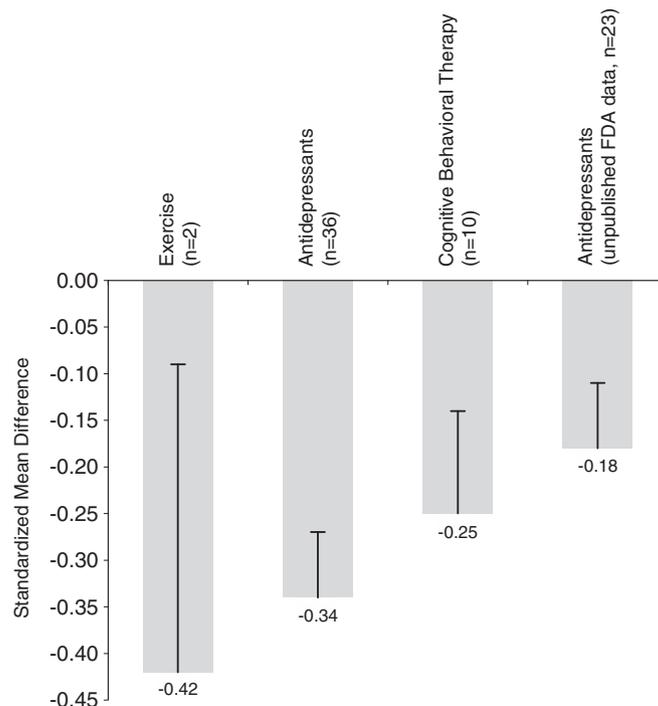


Fig. 1. Standardized Mean Differences associated with exercise [48,49], antidepressants [50], cognitive behavioral therapy [51], and unpublished trials of antidepressants [10] against pill placebo. The error bars represent 95% confidence intervals.

depression but also in the general population. As with any intensive lifestyle modification, behavioral change is difficult. However, prejudging that individuals with depression would not be interested in exercise may be unjustified for several reasons. First, the image of the depressed individual who is completely withdrawn and immobilized by helplessness probably represents patients toward the severe end of the depression spectrum. On the other hand, exercise and physical activity are generally recommended as options for individuals with subthreshold, mild, and moderate symptoms, who generally tend to be more interested in pursuing therapeutic action. Importantly, within stepped-care models of treatment, patients should be offered a choice of treatment among multiple alternatives, of which exercise is only one. Second, although data may be subject to self-selection bias, available RCTs show no difference in dropout rates between exercise and control or comparison groups [55]. Third, early evidence suggests that exercise is regarded as an acceptable and credible form of treatment by at least some individuals with depression [56]. While there is no known comparison of patient preferences for exercise versus pharmacological and psychological treatments for depression, in a large survey of individuals diagnosed with depression, exercise was rated as having the highest benefit-to-burden ratio among thirty, formal and informal, treatments [57]. Thus, among patients willing to pursue treatment, the appeal of exercise may be accentuated once its advantages over alternative options are appreciated. The low cost, virtual absence of adverse side-effects, and presence of numerous salubrious side-effects should compose a particularly appealing set of attributes. As a salient case in point, individuals who become aware of the cardiometabolic and psychoneuroimmune sequelae of depression [58] may be particularly amenable to the option of exercise given its unique multimodal health benefits.

6. In conclusion

Over the past three decades, research on the antidepressant effects of exercise has proliferated and its methodological quality has improved substantially. At this point, clinical guidelines in the United States have fallen behind those of several other Western countries by continuing to overlook exercise and physical activity. Although larger high-quality trials are certainly needed, the extant body of evidence is both larger and stronger than certain claims in the clinical literature may suggest.

To further facilitate the transition from trials to clinic, the following types of studies should be considered. In terms of explanatory trials, larger trials comparing exercise to pill placebo will enable researchers to disentangle the effects of exercise from those of expectancy and will help bring the level of evidence closer to the standards expected of frontline treatments. In terms of pragmatic trials, the focus should be on deciphering not only the most effective dose of exercise but also the types and doses that can facilitate long-term adherence. Furthermore, RCTs examining the potential of exercise as augmentation [43] or switching strategy should be prioritized [59]. Lastly, future trials should incorporate evaluations of cost-effectiveness within the context of healthcare systems and organizations. General practitioners, psychiatrists, and guideline developers are encouraged to take a fresh look at both the neurobiological and the clinical research evidence that pertains to exercise as antidepressant treatment.

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Panteleimon Ekkekakis^{a,*}, Martino Belvederi Murri^b

^a Department of Kinesiology, Iowa State University, Ames, IA 50011, United States

^b Section of Psychiatry, Department of Neuroscience, Ophthalmology, Genetics and Infant-Maternal Science, University of Genoa, L.go Rosanna Benzi 10, Genoa, Italy

E-mail address: ekkekaki@iastate.edu

* Corresponding author at: Department of Kinesiology, Iowa State University, 237 Forker Building, 534 Wallace Road, Ames, IA 50011-4008, United States.