

Q. What is exercise?

A. The American College of Sports Medicine (ACSM) defines exercise as “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (2001). This definition encompasses a wide variety of activities, such as walking, aerobic and nonaerobic movement, and strength training. The concept of exercise as medicine has been discussed in relation to a wide variety of health conditions, such as cognitive decline, cancer, cardiac rehabilitation, mental health disorders, and addiction (Netz, 2017). Exercise has been investigated as a potential add-on to pharmacological treatment of depression, as well as a non-pharmacological option for treatment in patients who do not respond to antidepressant medications or experience side effects (Netz, 2017).

Q. What are the potential mechanisms of underlying exercise?

A. A number of pathways are thought to be associated with the etiology of depression, including hormones, neurotrophins, inflammation biomarkers, oxidative stress, and cortical plasticity and activity (Schuch et al., 2016a). As the etiology of depression is likely explained by a combination of these hypotheses, the antidepressant effects of exercise are likely multi-factorial as well (Schuch et al., 2016a). A number of studies have examined the effects of exercise on specific domains associated with major depressive disorder (MDD), but the exact nature of the mechanisms behind the antidepressant effects of exercise is still unclear.

Q. Is exercise recommended in the Military Health System (MHS)?

A. **Yes.** The 2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder gives a “Weak For” recommendation for the use of exercise, and suggests offering patient education on the benefits of exercise as an adjunct to other evidence-based treatments for depression or as monotherapy when patients are unwilling or unable to engage in first-line evidence-based psychotherapy or pharmacotherapy.

The MHS relies on the Department of Veterans Affairs (VA)/Department of Defense (DoD) clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

Q. Do other guidelines and evidence reviews recommend exercise for MDD?

A. **Yes.** Other authoritative reviews have substantiated the use of exercise for treating MDD, though the quality of evidence is low.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) Systematic Review Repository and the Cochrane Database of Systematic Reviews.

- AHRQ: A comparative effectiveness review of nonpharmacological versus pharmacological treatments for MDD found no significant differences in remission or response between patients treated with exercise therapy and those treated with second-generation antidepressants (SGAs), with low strength of evidence (Garthlehner et al., 2015). The review also found no significant differences in effectiveness between patients treated with SGAs versus those treated with SGAs plus exercise, with low strength of evidence.
- Cochrane: A 2013 systematic review of exercise for depression found moderate clinical benefit of exercise versus no treatment or control (Cooney et al., 2013).

Q. Is there any recent research on exercise as a treatment for MDD?

A. A search conducted in September 2017 identified a number of studies on the efficacy of exercise for the treatment of depression published in the time period since the search conducted for the 2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Recent randomized controlled trials (RCTs) look at the effect of exercise, either as an adjunct therapy or monotherapy, in both inpatient and outpatient samples, on a variety of outcomes related to depression, including depressive symptoms (Nyström et al., 2017; Schuch et al., 2015; Kerling et al., 2015; Hallgren et al., 2015), neurocognitive function (Olson, Brush, Ehmann, & Alderman, 2017), brain-derived neurotrophic factor (BDNF) levels (Kerling et al., 2017), monoamine neurotransmitter and cortisol levels (Carneiro et al., 2017), cardiorespiratory fitness and metabolic syndrome factors (Siqueira et al., 2016; Kerling et al., 2015), and quality of life (Schuch et al., 2015).

A 2017 systematic review and meta-analysis of 35 trials assessing the effect of exercise on depression found that exercise significantly reduced depression severity compared to controls, though many of the trials were assessed as having a high risk of bias (Krogh, Hjorthøj, Speyer, Gluud, & Nordentoft, 2017). When including only the four trials assessed as having less bias, the difference was no longer significant. A 2016 meta-analysis of 25 RCTs compared exercise interventions to control conditions for depression, finding that exercise reduced depressive symptoms significantly more than control conditions (Schuch et al., 2016b). A critical review points out that exercise interventions vary widely, and there is substantial heterogeneity in study samples, interventions, and control groups between studies (Schuch, Morres, Ekkekakis, Rosenbaum, & Stubbs, 2017).

Q. What conclusions can be drawn about the use of exercise as a treatment for MDD in the MHS?

A. While there is a great deal of research on exercise interventions for the treatment of MDD, much of the research suffers from methodological flaws and significant heterogeneity between studies, making it difficult to make conclusions from syntheses of the existing research. Despite these shortcomings, exercise interventions are safe, acceptable, and show good adherence in MDD patients. Exercise for MDD is recommended by the current VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder, either for use adjunctively with a first-line evidence-based treatment, or as monotherapy with patients who are unwilling or unable to engage in first-line evidence-based psychotherapy or pharmacotherapy.

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