

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 action underlying exercise as a treatment for major depressive disorder (MDD)?

A. Because a combination of biological and psychosocial pathways are thought to be associated with the etiology of depression, the antidepressant effects of exercise may be dependent on a number of factors (Schuch et al., 2016a). A 2019 review of the antidepressant mechanisms of physical activity presented a conceptual framework that included neuroplasticity, inflammation, oxidative stress, the endocrine system, self-esteem, social support, and self-efficacy (Kandola, Ashdown-Franks, Hendrikse, Sabiston, & Stubbs, 2019).

Q. Is exercise recommended as a treatment for MDD in the Military Health System (MHS)?

A. **Yes.** The 2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder 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, with a “weak for” strength of recommendation.

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 authoritative reviews recommend exercise as a treatment for MDD?

A. **Yes.** Other authoritative reviews have identified some evidence substantiating the use of exercise for the treatment of MDD, although 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) and Cochrane.

- 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 May 2020 literature search identified several recent systematic reviews and meta-analyses evaluating the effect of exercise, or physical activity more broadly, on depression. A 2017 systematic review and meta-analysis of 35 randomized controlled trials (RCTs) assessing the effect of exercise on depression found that exercise significantly reduced depression severity compared to controls, although a majority of the trials were determined to have a high risk of bias (Krogh, Hjorthøj, Speyer, Gluud, & Nordentoft, 2017). The finding was no longer statistically significant when those high-bias trials were excluded. A 2016 meta-analysis of 25 RCTs of exercise interventions for depression found that depressive symptoms were reduced significantly more in exercise conditions than in control conditions (Schuch et al., 2016b). A 2018 meta-analysis of 49 prospective cohort studies examining the relationship between physical activity and depression found that individuals with high levels of physical activity had lower odds of depression than people with low physical activity (Schuch et al., 2018).

A critical review of exercise interventions for depression pointed 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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