SPECIAL FEATURE

Physical Exercise and Depression

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Recently, the US Department of Health and Human Services issued its first ever physical activity guidelines, which were developed because "we clearly know enough now to recommend that all Americans . . . engage in regular physical activity to improve overall health and to reduce risk of many health problems."[1] The current weekly recommendation (2.5 hours of moderate aerobic physical activity, 1.25 hours of vigorous aerobic physical activity, or an equivalent combination of moderate and vigorous aerobic physical activity plus additional muscle strengthening activities on 2 or more days) has increased from the 1995 recommendation issued by the American College of Sports Medicine and the Centers for Disease Control and Prevention of at least 30 minutes of moderate physical activity on most days of the week. The Mayo Clinic lists several medical benefits of regular physical activity on its Web site, including weight management, increased cardiovascular function, prevention and control of chronic diseases, and improvement in sleep.[2] Number 1 on its list is the positive effect of physical activity on psychological well-being.

Major depressive disorder (MDD) is characterized by periods of depressed mood and/or anhedonia (ie, loss of interest or pleasure) that last at least 2 weeks in combination with several somatic symptoms (changes in appetite, sleep, energy level, and psychomotor function) and cognitive disturbances (feelings of worthlessness or inappropriate guilt, trouble concentrating or making decisions, and suicidal thoughts) that cause clinically significant distress or impairment in everyday functioning.[3] Primary care patients often present with a lack of energy and other somatic symptoms rather than with overt psychological symptoms. Indeed, anergia is as common as depressed mood, with both symptoms affecting around 75% of depressed patients.[4]

Feeling tired and fatigued might prevent patients with MDD from engaging in physical activities, including voluntary exercise. In a 2004 study of primary care outpatients, those with severe depression had lower activity levels than those with no to moderate depression.[5] This is an important observation, especially because exercise may reduce symptoms in patients with MDD.[6] In this review, we summarize relevant epidemiological data on the link between depression and physical (in)activity, discuss some of the more recent exercise intervention studies in patients with MDD and in individuals reporting subclinical mood problems, and provide an overview of the biological and psychological mechanisms that may underlie the beneficial effects of exercise on mood.

DEPRESSION AND PHYSICAL ACTIVITY: EPIDEMIOLOGICAL DATA

Depression has been found to affect more than 340 million people worldwide.[7] In the United States, it is estimated that approximately 16% of the population will meet criteria for MDD in their lifetime, with women being 1.7 times more likely than men to develop the disorder.[8] Depression is the leading cause of disability worldwide and is predicted to be the second largest contributor to the global burden of disease by the year 2020.[9]

A negative relationship between physical activity and the symptoms and prevalence of depression has been consistently documented.[10,11] Likewise, physical inactivity has been associated with an

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increased risk for and prevalence of depression. In 2003, Goodwin[12] published findings from the National Comorbidity Survey, a US representative sample of 8098 adults (15–54 years old). She found that regular physical activity, whether in the context of work or recreation, was associated with a significantly reduced likelihood of having current MDD. This association remained after she controlled for differences in sociodemographic characteristics, comorbid mental disorders, and self-reported physical illnesses. Similarly, in 2006, Galper and colleagues[13] reported their findings from the Aerobics Center Longitudinal Study, an ongoing national cohort study of 5451 men and 1277 women (20–88 years old) from all 50 states, who tended to be college-educated Caucasians from middle to upper economic strata. They found an inverse relationship between physical activity and depressive symptom scores. Inactive men and women were found to be more severely depressed than their active counterparts. Furthermore, a dose-response relationship was evidenced, such that those defined as insufficiently active had significantly more depressive symptoms than those defined as sufficiently active.

In 2000, Hassmen and colleagues[14] reported data on a cross-sectional study of 1856 women and 1547 men (25–64 years old) from the Finnish cardiovascular risk factor survey. Data were collected on exercise frequency and depression among other measures. They found that depression scores increased as exercise frequency decreased. Highest depression scores were found for individuals who could not exercise at all because of illness or handicap. Interestingly, they found that those individuals who reported exercising most frequently (ie, daily) had slightly higher depression scores than those who exercised 2 to 3 times or once a week. This was explained by a focus on competitiveness rather than health in this population.

The American College of Sports Medicine defines 3 types of exercise: cardiovascular training (aerobic), resistance or muscular training (anaerobic), and improvement of joint flexibility. In 2001, 6 years after the American College of Sports Medicine and the Centers for Disease Control and Prevention issued their public health recommendation on physical activity,[15] the Centers for Disease Control and Prevention reported that approximately 55% of the US adult population did not meet this recommendation.[16] This may account for the finding that, together with poor diet, physical inactivity is responsible for approximately 15% of all deaths in the United States, and this makes it 1 of the top 2 leading causes of mortality.[17]

Women as a group are not only more likely than men to have a diagnosis of MDD; they are also less likely than men to be physically active. The Centers for Disease Control and Prevention reported in 2005 that 25.9% of women participated in no physical activities at all in the month preceding the survey versus only 21.4% of men.[16] Brown and colleagues[18] reported the results from a prospective study of physical activity and depressive symptoms in women begun in 1996, the Australian Longitudinal Study on Women's Health. A fairly representative sample of middle-aged women (45–50 years), with overrepresentation of Australian-born, employed, and university-educated women, provided self-report data on factors affecting health and well-being at 2- to 3-year intervals. Analyses were conducted on a sample of 9207 middle-aged women who completed all 3 surveys at baseline in 1996 and at 2 follow-ups in 1998 and 2001, reporting on levels of physical activity and completing 2 measures of depressive symptoms. Results indicated that physical activity at any level is associated with decreased risk for depressive symptoms and demonstrated that increasing levels of physical activity are associated with decreasing depressive symptoms.

The association between physical activity and psychological well-being is considered to be well established. However, studies that use cross-sectional data to demonstrate a negative association between physical activity and the prevalence or severity of depression are unable to determine causality. Such an association may exist because depression has an effect on the motivation to exercise, such that people who are depressed may be less likely to engage in physical activity. Likewise, exercise may have an effect on the severity of depression, such that people who exercise are less likely to suffer from MDD. In order to establish causality, longitudinal and intervention studies are needed.

EXERCISE INTERVENTION STUDIES

In 2001, the *British Medical Journal* published a systematic review of the antidepressant effect of exercise treatment. The authors included 14 randomized controlled trials (RCTs) and reported that the effect size of exercise treatment compared to no treatment was large (Cohen's $d = 1.1$).[19] In clinical practice, this can be translated into a significant exercise-induced reduction in people's scores on a depression rating scale and thus presumably into a reduction in the severity of depressive symptoms. However, most studies included in the review did

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not use a dichotomous measure representing the presence or absence of an MDD diagnosis. Although symptom reduction may be considered an important goal of treatment even when symptom remission is not necessarily achieved, additional limitations of this review are that many studies were done in individuals with subclinical mood problems rather than in patients with a clear diagnosis of MDD, and few studies were conducted under adequately blinded conditions.

The idea that exercise treatment is more effective than no treatment is supported by at least 2 other systematic reviews[20–22] as well as several narrative reviews.[23,24] In addition, most reviews conclude that the antidepressant effect size of exercise can be comparable to that of psychotherapy and to that of pharmacotherapy.[19,22,23,25] Moreover, the antidepressant effect of combined treatment may be larger than that of exercise alone.[22,23,26] Given possible acute effects of exercise on mood,[22,27–29] exercise in combination with pharmacotherapy might result in a faster onset of antidepressant action. If confirmed in a well-controlled trial, this idea could be especially important, given that antidepressant medications generally take several weeks before a clinically relevant improvement is seen. Finally, exercise interventions have also been used in combination with other lifestyle changes, such as increased bright-light exposure and vitamin supplementation.[30–32] In general, exercise is thought to constitute a viable combination or augmentation strategy, especially because it is unlikely to interact negatively with other treatments.

Major Depressive Disorder Versus Depressed Mood

Although some researchers have argued that study findings of exercise benefit in subclinical populations with mood complaints do not necessarily generalize to patients with MDD, others believe that these studies are necessary to sufficiently prove the therapeutic benefit of exercise.[6] Adherence to a standardized exercise regimen during an RCT may be problematic for many severely depressed patients. In addition, attempts to motivate or persuade them to participate could be considered a form of psychotherapy, thereby confounding the exercise effect. Studies in individuals with subclinical mood problems are informative, especially if one considers depressive episodes as occurring along continuums of both severity and length. The results from RCTs done in subclinical populations can certainly be extrapolated to predict the potential benefit of exercise in motivated patients with MDD. Exercise is thought to be at least as efficacious in reducing depression symptoms in depressed patients as in healthy individuals who are simply feeling down.[22,33] Also, exercise regimens are thought to have dropout rates that are similar to those for other treatments (eg, pharmacotherapy); in other words, motivation in patients with MDD may be a limiting factor, regardless of the intervention offered.[21,23] Conversely, adherence to an exercise intervention may be as high as adherence to a medication intervention; this supports the use of exercise as a viable treatment strategy for MDD.

Findings of 2 Dose-Response Studies

To reduce the placebo effect caused by people's expectations of the treatment, RCTs in which both the research participants and the investigators are blinded are desirable. However, in exercise RCTs, the blinding of treatments (exercise versus no treatment, exercise versus pharmacotherapy, or exercise versus psychotherapy) has proven difficult. One way in which the expectancy effect can be reduced is direct comparison of different exercise doses in different groups of patients. Because all patients in a trial are exercising, they will all expect the benefit. For example, Dunn *et al.*[34] compared the weekly aerobic exercise (cardiovascular training) dose recommended by the American College of Sports Medicine with a lower dose in a group of patients with mild to moderate MDD. After 12 weeks, the public health dose was found to be effective in reducing depression symptoms at a rate comparable to other antidepressant interventions, whereas the low exercise dose was not. A similar dose-response effect was found for anaerobic exercise (resistance training) in older patients with MDD.[35] In this second study, high-dose resistance training not only reduced depression symptoms but also improved patients' subjective sleep quality and quality of life and increased muscle strength. Although these 2 RCTs had several limitations (eg, group differences in dropout rates and in medical care), they arguably provide the strongest evidence for the antidepressant effect of exercise at the recommended public health dose to date.

The 2 dose-response studies also show that both aerobic and anaerobic exercise can be effective in reducing symptoms of depression; this finding is consistent with earlier reports and especially relevant for clinical practice (eg, for patients who are unwilling or unable to adhere to cardiovascular training, resistance training is a viable alternative).[22,36,37] Furthermore, the results from these 2 studies argue against the idea that social aspects of the exercise treatment (meeting with a trainer and a group setting)

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can fully explain its antidepressant effects: patients in both dosing groups interacted with their trainer and/or group members at a similar frequency. This does not mean that the social interaction associated with many forms of exercise will not benefit mood. The antidepressant effect size of exercise may be larger than that of a social control intervention.[38] On the other hand, there is some evidence that social contact may be as efficacious in reducing core depression symptoms as trainer-assisted exercise.[39] However, exercise may be more likely to also reduce somatic symptoms (eg, improve sleep).[39]

Duration of the Antidepressant Effect of Exercise

The benefit of exercise is known to be greater for longer exercise programs and/or more sessions, although even a single session may be efficacious in acutely reducing symptoms of depression.[22,27–29] It is presently unclear how long the antidepressant effect of exercise may last beyond the end of a program. However, follow-up depression scores might remain low for at least some time.[22] Moreover, individuals who start exercising during a trial may be more likely to continue exercising after the trial than nonexercisers in the trial are likely to start.[40] Sustained adherence to an exercise regimen after a trial has ended has been found to result in fewer depression symptoms when participants are followed up weeks, months, or even years later.[40,41] Together, these data suggest that exercise treatment may have some long-lasting benefits that cannot be explained by its immediate impact on the biology and psychology underlying mood alone.

NEUROBIOLOGY OF EXERCISE

Given that the pathophysiology of MDD is both complex and still poorly understood, it is not surprising that there is no consensus on the putative biological mechanism underlying the positive effect of exercise on the regulation of mood. However, a review of the literature suggests that a number of biological systems may be involved.

Exercise, Opioids, and Cannabinoids

Perhaps the most well-known neurochemical correlate of exercise is the biological change underlying the ''runner's high,'' which is defined as a sense of euphoria and analgesia (pain insensitivity) experienced after strenuous physical activity. The leading explanation for this phenomenon is an increase in endogenous opioids known as endorphins.[42] Proponents of this endorphin hypothesis cite as evidence both raised levels of endorphins measured in blood plasma and cerebrospinal fluid after running and a blunting of the runner's high after administration of naloxone, an opioid receptor antagonist.[43–49] A recent brain imaging study in healthy long-distance runners used positron emission topography to demonstrate increased opioid activity in several frontolimbic brain regions implicated in mood regulation after 2 hours of running.[50] The magnitude of change in opioid binding correlated with the intensity of self-reported euphoria.[50]

Some have questioned the validity of the endorphin hypothesis, noting, for instance, that an increase in endogenous opioid activity should produce not only euphoria and analgesia but also respiratory depression, pupillary constriction, and reduced gastrointestinal motility, effects not observed in runners.[51] Dietrich and McDaniel[51] offer an alternative endocannabinoid hypothesis. Endocannabinoids, like the endogenous opioids, are known to have anxiolytic and analgesic properties and to be present in elevated concentrations in the body following exercise. Hence, Dietrich and McDaniel believe an exercise-induced increase in endocannabinoid activity may also contribute to the runner's high, although they acknowledge the need for further research to determine how these systems and others interact.[51]

The runner's high phenomenon does not occur in every person, nor does it occur consistently or after every run. Nevertheless, the mere existence of the runner's high phenomenon evinces exercise's ability to directly improve mood. Furthermore, there is evidence from animal studies, post-mortem studies in suicide victims, and human brain imaging studies that opioid and endocannabinoid activity may be altered in patients with MDD.[53–60] However, at this time, no coherent model of the pathophysiology of MDD incorporates dysfunction in these particular neuromodulatory systems. Thus, it is presently unclear if and how the physiological processes that precipitate the runner's high might help explain the antidepressant effects of exercise.

Exercise and the Monoamines

Other bodies of research aiming to understand the interaction between exercise and MDD are anchored by preexisting ideas about the pathophysiology of MDD. In particular, the monoamine hypothesis of depression, which originally postulated that inadequate availability of the monoamine neurotransmitters serotonin and norepinephrine

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results in a depressed state, has dominated mechanistic and treatment research since the 1950s, including research investigating links between exercise and mood. Data showing that exercise increases the availability of serotonin and norepinephrine are of particular interest, given that most antidepressant medications currently approved by the US Food and Drug Administration, including the monoamine oxidase inhibitors, tricyclics, selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors, are known to increase serotonin and/or norepinephrine levels.

Several lines of evidence suggest that exercise stimulates brain serotonin function. In experimental animals, physical activity has been shown to increase levels of tryptophan, the amino acid precursor of serotonin, in blood plasma and in cerebrospinal fluid, to boost serotonin neurotransmission, to enhance serotonin metabolism, and to increase the production of various proteins involved in brain serotonin function.[61–66] The idea that exercise may also stimulate serotonin metabolism in humans is largely based on a study that found increased levels of a serotonin metabolite, 5-hydroxyindoleacetic acid, following physical activity.[67] Exercise is also known to decrease plasma levels of the branched chain amino acids valine, leucine, and isoleucine.[68–70] These amino acids compete with tryptophan for uptake into the brain. An exercise-induced increase in the ratio of tryptophan levels to levels of the branched chain amino acids may thus enhance serotonin synthesis by increasing the brain availability of its precursor.

In experimental animals, engaging in an acute exercise trial induces an immediate increase in the activity of the brain cells that produce norepinephrine.[71–73] Chronic exercise also results in increased levels of norepinephrine and its metabolites as well as activation of tyrosine hydroxylase, an enzyme involved in the production of norepinephrine.[62,74–78] This is consistent with norepinephrine's positive effects on mood. Although it should be noted that the norepinephrine surge seen during acute exercise tends to be followed by a depletion of norepinephrine levels, an observation consistent with the idea that exercise can be stressful and exhausting and may lead to a decreased likelihood of or increased threshold for future exercise, norepinephrine depletion is not seen with chronic exercise.

Increases in dopamine activity following exercise have also been found, though less consistently so.[67,79] Nonetheless, a significant body of indirect evidence suggests that exercise does affect dopamine function in the brain. For example, regular exercisers can become addicted to physical activity and may experience withdrawal symptoms when inactive.[80,81] Also, exercise has ameliorative and even protective benefits in patients with Parkinson's disease.[82] Dopamine is known to play a role both in the development and maintenance of addiction and in the pathophysiology of Parkinson's disease.[83,84] Dopamine's role in MDD has largely been described with respect to the motivational problems and anhedonia that many patients describe.[85]

Despite data suggesting a role for the monoamines in both MDD and the effects of exercise on mood, in recent years, scientists have increasingly recognized the inadequacy of the monoamine hypothesis of depression. Many of the currently available antidepressant medications are not at all effective in approximately one-third of individuals who suffer from MDD.[86] As a result, enthusiasm for the monoamine hypothesis has waned. At the same time, a number of supplemental theories of MDD pathophysiology have emerged. Two relevant neurochemical theories focus on a neuroendocrine feedback system consisting of the hypothalamus, pituitary, and adrenal glands [the hypothalamic-pituitary-adrenal (HPA) axis] or on the role of neurotrophic factors such as brain-derived neurotrophic factor. In addition, neuroimaging researchers in particular are concerned with the role of abnormalities in brain circuitry in MDD.

Exercise and the Hypothalamic-Pituitary-Adrenal Axis

The HPA axis, responsible for mounting the body's response to stress by coordinating the release of various stress hormones that determine the state of arousal, is known to function abnormally in the depressed state in some if not all individuals with MDD.[87] A failure of the hippocampus and hypothalamus to inhibit the release of these stress hormones is thought to result in chronic hypercortisolemia, even in the absence of external stressors. The observed effects of physical activity on the HPA axis suggest that exercise may be able to reverse or reduce a potential HPA axis abnormality. Although exercise may acutely increase levels of the stress hormones corticotropin and cortisol (which in terms of mood may mainly help induce a state of vigor), long-term exercise training appears to blunt the body's response not only to the stress of exercise but also to stress in general.[88–90] Interestingly, the effects of acute exercise versus chronic exercise on the HPA axis parallel those on norepinephrine, and this is consistent with the interactions that are known to exist between these 2 systems.[87]

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Exercise and Neurotrophins

The neurotrophic hypothesis of depression has been bolstered by observations that stress impairs, whereas successful antidepressant treatment enhances, the brain's ability to generate new cells and support existing cells. On the basis of these findings, it has been argued that factors regulating the birth and health of neurons across neurotransmitter systems, rather than abnormalities in specific neurotransmitters, underlie the pathophysiology of MDD.[91,92] As summarized in Table 1, exercise is known to increase levels of a number of neurotrophic factors in both experimental animals and humans (see van Praag[93] for a recent review).

Exercise and Neurocircuitry

Human neuroimaging investigations have contributed substantially to the understanding of the neurobiology of MDD. The depressed state is characterized by abnormal functional activity in various brain regions including the prefrontal cortex, amygdala, and hippocampus. In particular, a pattern of altered activity in ventral regions of the anterior cingulate prefrontal cortex has been consistently demonstrated.[94] A reversal is seen with successful antidepressant treatment.[95] Of potential direct relevance to the neurobiology underlying the antidepressant effect of exercise are findings that exercise may induce changes in anterior cingulate prefrontal cortex activity that parallel those associated with the therapeutic response to antidepressant medications.[96]

PSYCHOLOGY OF EXERCISE

Various psychological mechanisms have been proposed to explain, in part, the consistent finding that there is a positive association between physical activity and mental health. For example, the self-efficacy theory, originally proposed by Bandura in 1977,[97] postulates that confidence in one's ability to exercise is very much related to a person's actual ability to exercise. Self-efficacy has indeed been found to be strongly related to both the adoption and maintenance of an exercise program.[98–100] Another hypothesis posits that feelings of success, control, and independence result from an increasing mastery of one's physical skills. It is suggested that exercisers gain a sense of confidence as they become more skillful and that this feeling of mastery is translated into other areas of their lives, including the management of their depressive symptoms and adherence to their exercise program.[43,101,102] Furthermore, although social interaction alone may not fully explain the antidepressant impact of exercise (as discussed previously), social interaction may play an integral role in promoting the mood-enhancing effects of those forms of physical activity that are undertaken in a social context, such as team sports and socially supported physical activity.[103]

On the other hand, in order to effectively encourage people to develop and maintain an appropriate level of physical activity, it is important to be aware of the psychological factors that may act as barriers to being physically active.[104] First, depression itself may pose such a barrier.[105] Symptoms such as loss of energy, fatigue, diminished pleasure, and feelings of worthlessness will make exercise a more difficult undertaking than it would be in the absence of such symptoms. Furthermore, psychological barriers to exercise may include fear, negative experiences with exercise in the past, and a perceived lack of knowledge about available exercise options.[106] There is also some evidence that depressed mood may bias people's perceptions of how strenuous exercise is.[107] In depressed

Table 1. *Levels of Various Neurotrophins Are Increased by Physical Exercise.*

Neurotrophic Factor	Function	Impact of Exercise	References
Brain-derived neurotrophic factor	Factor that promotes cell multiplication, cell survival, and synaptogenesis	*In humans:* increased levels in serum *In rats:* increased gene transcription in hippocampus (specifically the dentate gyrus)	108–111
Insulin-like growth factor 1	Hormone that activates pathways which promote cell growth and multiplication and that inhibits programmed cell death	*In rats:* increased uptake in brain cells and reduced neurogenesis when blocked	112, 113
Vascular endothelial growth factors	Platelet-derived proteins that promote angiogenesis (including new brain tissue)	*In humans:* increased levels in blood serum/blood plasma and increased gene transcription factors *In rats:* reduced neurogenesis when blocked	114–116

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overweight youth, who may benefit in several ways from physical activity, high levels of parent distress and peer victimization are significant barriers to physical activity.[105] For women, who are particularly vulnerable to both depression and physical inactivity, the domain and social context of an exercise program have been found to be important factors influencing the effect of physical activity on mental health.[108] Overall, it is important for clinicians to understand that individual patients will each have their own unique set of circumstances and perceptions that may act as barriers to being physically active. Only when one knows what these are can an appropriate approach to overcoming the resistance to exercise be taken.

Finally, it is important to keep in mind that many if not all of the psychological mechanisms that underlie the effects of exercise on mood not only are interactive but also work bidirectionally. For example, while exercise may improve mood by increasing one's self-worth, mood improvement might in turn increase the likelihood that someone exercises again through its impact on self-worth. The same is likely true for the biological mechanisms that underlie the links between exercise and mood.

CONCLUSIONS AND FUTURE DIRECTIONS

Epidemiologic evidence for the positive effects of physical activity and voluntary exercise on mental health is clearly supported by data from exercise intervention studies showing that the exercise dose recommended by the Centers of Disease Control and Prevention and the American College of Sports Medicine (ie, at least 30 minutes of moderate-intensity physical activity on most days of the week) can be efficacious in reducing symptoms in patients with MDD. The somewhat higher dose recently recommended by the US Department of Health and Human Services (ie, 2.5 hours of moderate aerobic physical activity plus 2 or more days of muscle strengthening per week) will likely be more effective, even though it has not yet been officially studied. Exercise intervention studies continue to show large effect sizes, even though more recent studies have been better controlled and include larger populations. In contrast, the effect size of antidepressant pharmacotherapy in particular seems to taper off as larger, better controlled trials are being conducted.[109]

Nevertheless, in the United States, exercise is still not a first-line or even second-line treatment option for individuals with MDD. In contrast, in the United Kingdom, national guidelines for treating MDD explicitly list physical exercise as a particularly useful and effective intervention for patients with mild depression symptoms and recommend a structured and supervised program of 45 to 60 minutes up to 3 times a week for 10 to 12 weeks. The United Kingdom Department of Health also has an exercise referral system in place for patients consulting their doctors about depressive symptoms.[110] The United States does not currently have national guidelines for an exercise program specifically designed for patients with MDD, even though exercise treatment has few if any adverse effects, is readily available and cost-effective, can be sustained indefinitely (unlike most other treatments for MDD), and has additional benefits for multiple aspects of physical health.[111] In particular, exercise helps improve sleep, increase muscle strength, enhance cardiovascular function, and control hypertension, hypercholesterolemia, and diabetes and can even reduce mortality.[112] Many of these conditions are common in MDD[113,114]; exercise therefore has the potential to improve both mental and physical health in this patient population. Furthermore, although no RCTs of exercise as a preventative strategy have been performed to date, it has been suggested that exercise may help prevent depression in addition to treating it.[115]

It is true that not all questions surrounding the exercise-depression link have been answered at this point. Recent RCT design reports suggest that investigators are currently focusing on eliminating sources of potential bias (eg, selecting a reasonable placebo control, concealing the method of randomization, and adequate blinding of outcome assessments), increasing treatment adherence (eg, involving a social coach, providing a home-based exercise program, individualizing each patient's exercise program, and implementing a behavioral intervention to reduce barriers to exercise), and testing novel hypotheses (eg, exercise as an augmentation strategy and effects on neurobiological measures).[116–118] Nonetheless, on the basis of the current data, exercise deserves to be considered as a viable stand-alone or adjunct treatment for depression in at least some motivated patients with MDD.

On its Web site, the Mayo Clinic also lists how to overcome common barriers to exercising.[119] Doctors may increase their patients' motivation to voluntarily start an exercise program by encouraging them to set aside time to exercise, to make exercise a fun activity, to be creative about how to get physical activity incorporated into their routines, to set realistic goals and expectations, and to talk to their doctors about how to avoid injury. It may be especially

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important to tailor exercise recommendations to individual patients.[104] For example, in overweight individuals, who may tend to focus on weight loss as a distant outcome, clinicians could emphasize mood improvement as an important short-term benefit of exercise. Once a patient is happier, he or she will likely be eager to pursue exercise further. This positive cycle will contribute to a healthy mind in a healthy body.

DISCLOSURES

Potential conflict of interest: Nothing to report.

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