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Exercise in the Treatment of Major Depressive Disorder

Larissa Ann Haug
University of North Dakota

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EXERCISE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

By

Larissa Ann Haug

Bachelor of Science in Psychology & Honors, University of North Dakota, 2015

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Abstract

Objective

The purpose of this research and systematic literature review is to determine how exercise can be incorporated into the treatment of major depressive disorder (MDD) and its efficacy.

Methods

In this review, four databases were searched including SportDiscus, Pubmed, Cochrane Database of Systematic Reviews, and PsycInfo from October 1 to January 5, 2018. A variety of key terms were used when searching. Works chosen for review were published after the year 2000, were peer reviewed, and included randomized control trials (RCTs), pilot studies, systematic reviews, and meta-analyses. Sources that were excluded included those published prior to the year 2000, had poor study design, and included comorbid psychiatric conditions varying from MDD.

Results

For this review, 17 resources were selected. Much of the research presented shows evidence for the use of exercise in the treatment of MDD. Although most of the research points to exercise as more of a beneficial augmentation strategy for MDD versus a first line therapy involving pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) and psychotherapy in disease treatment.

Conclusion

Current research on the topic of exercise as therapy for Major Depressive Disorder (MDD) does show promise; however, more research still needs to be done in order to place exercise as an equivalent treatment to pharmacotherapy or psychotherapy.

Introduction

In the setting of primary care, depression is a disease that is treated and monitored multiple times daily by many different providers. In fact, the prevalence of major depressive disorder (MDD) in the United States is seven percent, while lifetime prevalence is 16.6 percent, and these numbers are only rising (*Dynamed Plus*, 2017). Unfortunately, failure for proper treatment of MDD can have grave consequences for those suffering with depression such as suicidality or even becoming a threat to those around them. According to the Diagnostic and Statistical Manual of Mental Disorder (DSM-V), the diagnostic criteria for MDD includes five or more of the following symptoms that are present for at least two weeks and are a change from baseline function, with one of the first two symptoms required to be present for diagnosis: 1) depressed mood most of the day or nearly every day or irritability in children and adolescents; 2) substantial loss of interest or pleasure in activities most of the day or nearly every day; 3) change in weight and appetite without a conscious effort for weight change; 4) increased or decreased sleep; 5) psychomotor agitation or retardation; 6) decreased energy and fatigue; 7) excessive feelings of worthlessness and inappropriate guilt; 8) decreased concentration or indecisiveness; 9) thoughts of death, suicidal ideation with or without a plan, or suicide attempt (2013). All the listed criteria are by subjective report as well as observable report by others and must cause significant decrease in quality of life in multiple areas including social, occupational, and personal (DSM-V, 2013). The DSM-V also requires that symptoms may not be due to effects of substance or other medical condition (2013).

Categories of MDD range from mild to severe based on symptoms. MDD is a purely clinical diagnosis based on patient history and symptoms. The direct etiology of MDD is not certain, but the pathophysiology is hypothesized to be due to an imbalance in the hormones

serotonin, tryptophan, noradrenaline, and dopamine. The areas of the brain that show functional and structural abnormalities in MDD include anterior cingulate, orbitofrontal cortex, amygdala and basal ganglia, hippocampus, prefrontal cortex, ventral striatum, hypothalamic pituitary adrenal axis, and the nucleus accumbens (*Dynamed Plus*, 2017).

In those with more severe MDD and thoughts of hurting themselves, acute hospitalization with 24-hour surveillance and medication management is often necessary. Current recommendations for initial treatment of mild to moderate depression includes psychotherapy as first line and antidepressants second, while in moderate-to-severe depression it is recommended that antidepressants are used in conjunction with psychotherapy as first line treatment (*Dynamed Plus*, 2017). Newer research has been showing the potential benefit of exercise therapy in initial treatment of mild to moderate MDD or as augmentation therapy with psychotherapy or pharmacotherapy with antidepressants (*Dynamed Plus*, 2017). Currently, pharmacotherapy is the intervention most commonly prescribed for MDD including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and other drugs that selectively target neurotransmitters. Unfortunately, there is a high number of patients who do not respond to pharmacotherapy with about 40 percent, and 70 percent of patients treated with pharmacotherapy do not enter remission (Gartlehener et al., 2016).

From a rural primary care standpoint, pharmacotherapy is the most widely available and used treatment for MDD. Psychologists and counselors trained in psychotherapy are more difficult to come by than drug stores. In a world where a quick fix is what is wanted, many patients would prefer the ease of taking a pill daily over taking time out of their busy life to meet with a therapist for treatment. However, a quick fix with antidepressants such as selective serotonin reuptake inhibitors (SSRIs) does not come without possibility for adverse effects such

as nausea, diarrhea, anorexia, anxiety, headache, insomnia, and sexual dysfunction, not to mention the black box warning of increased suicidality during the first couple months of treatment in young adults (*Dynamed Plus*, 2017). Less scarce, but still time consuming, it would be worthwhile to assess how exercise therapy can serve as a treatment of those with mild to moderate MDD. According to *Dynamed Plus* (2017), there are multiple potential benefits to using exercise are relative affordability, low risk and low likelihood of adverse effects, overall wellness benefits, and availability in comparison to pharmacotherapy and psychotherapy.

An article by Pence, O'Donnell, and Gaynes (2011) stated that of the 12.4 percent of patients with MDD in the primary care setting, only 47 percent are recognized and diagnosed by their primary care provider. Even more shocking is only 24 percent of those recognized are treated and an even lower number of 9 percent are adequately treated. This poses a problem in primary care that needs addressing. In many patients with MDD their only contact with medical professionals is through their primary care provider. This solidifies the importance of finding proper intervention for the wellbeing of such a large primary care patient population.

The question addressed in this literature review is what role exercise may have in the treatment of MDD. Type, duration, and frequency of exercise most efficacious for MDD treatment will be assessed as well as comparing exercise to pharmacotherapy, psychotherapy, and exercise as augmentation to pharmacotherapy and or psychotherapy. It is expected that exercise therapy will have benefits over SSRIs and psychotherapy, but will not necessarily be superior to the latter two. A systematic analysis will look at efficacy of the three therapies in regard to access to adherence, remission, and improvement of symptoms.

Review of Literature

In this review, four databases were searched including SportDiscus, Pubmed, Cochrane Database of Systematic Reviews, and PsycInfo from October 1 to January 5, 2018. A variety of key terms were used when searching. In SportDiscus, an Ebscohost database, keywords searched were exercise and depression and a filter was added to include only peer reviewed articles after the year 2000. A search in PsycInfo yielded works including RCTs as well as systematic reviews. Keywords for the PsycInfo database were exercise, cognitive behavioral therapy, major depression, major depressive disorder treatment, exercise treatment for major depression, and treatment. Again, a filter was added for peer reviewed only and studies were excluded that were published before the year 2000. When searching Cochrane Database of Systematic Reviews, the keyword depression treatment was used, and a filter was selected for only Cochrane Reviews. The final database searched was Pubmed, in which a search was conducted using the MeSH headings primary health care, humans, serotonin uptake inhibitors, exercise therapy, and exercise. Key terms searched in PsycInfo included MDD, depression, and depressive disorder. Sources that were excluded included those published prior to the year 2000, had poor study design, and included comorbid psychiatric conditions varying from MDD.

Pathophysiology of MDD & Mechanism of Exercise as Treatment

MDD is a psychiatric condition related to deficits of neurotransmitters as well as functional and structural changes in the brain. In twin concordance studies, heritability of MDD is about 37 percent, with early-onset and more severe forms of MDD being more heritable (Belmaker & Agam, 2008). No one gene, nor has one theory been 100 percent proven in the pathogenesis of MDD. One of the most widely accepted theories for MDD is the Monoamine-Deficiency Hypothesis, which includes the noradrenergic and serotonergic systems. These

systems are present in many areas of the brain and involve the neurotransmitters serotonin, norepinephrine, tryptophan, noradrenaline, and dopamine. One of the strongest arguments for the monoamine theory is the fact nearly every compound or medication that inhibits norepinephrine or serotonin reuptake works as an antidepressant and has been clinically proven, such as selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors (Belmaker & Agam, 2008).

Another theory endorses structural and functional changes are also associated with MDD in the following areas – anterior cingulate, orbitofrontal, amygdala, basal ganglia, hippocampus, prefrontal cortex, ventral striatum, hypothalamic pituitary adrenal axis, and nucleus accumbens (*Dynamed Plus*, 2017). Decreased neurogenesis in these areas particularly in the hippocampus is a result of MDD (Belmaker & Agam, 2008). Reduction in hippocampal volume and function was shown to be decreased in patients with MDD as evidenced by magnetic resonance imaging (MRI). Reduction was increased with age and with increasing major depressive episodes. In another study, Stockmeier et al. (2004) analyzed tissues from 19 depressed subjects and 21 age matched psychiatrically healthy control subjects. For hippocampal thickness, MDD subjects had significantly thinner sections than control subjects, $p < .002$. Pyramidal neurons had a 17-21 percent decrease in soma size in depressed subjects (Stockmeier et al., 2004). Another study done in 2012 evaluated the hippocampus in 17 depressed subjects and 17 non-depressed control subjects post-mortem. The volume of the hippocampus was linearly decreased with increasing length of depressive illness and increasing depressive episodes, with a p value of <0.026 . Yet another theory that is widely accepted for the pathogenesis of MDD is the inflammatory and oxidative stress hypothesis, which shows that patients with MDD have higher levels of

inflammation and increased peripheral blood biomarkers, including cytokines (*Dynamed Plus*, 2017).

In an article written by Paes, Arias-Carrion, Rocha, Filho, and Machado (2015), researchers recognized that the pathogenesis of depression included monoamine deficiency, loss of neurotrophic factors such as BDNF, and decreased neurogenesis in the hippocampus. From administration of antidepressants, increased BDNF levels were seen. There have also been associated systemic effects that contribute to the pathogenesis of depression including immune system activation, oxidative stress, and inflammation – specifically interleukin-6 and tumor necrosis factor-alpha are increased. Researchers also mentioned how hippocampal neurogenesis is suppressed by pro-inflammatory cytokines. As for exercise in the treatment of MDD, it was stated that it is likely due to the increased cerebral blood flow and perfusion. Exercise has also been shown to increase vascular endothelial growth factor in the brain, leading to increased neurogenesis and an antidepressant effect (Paes, Arias-Carrion, Rocha, Filho, & Machado, 2015).

The mechanism of action of pharmacotherapy is understood and proven, but how can exercise be used to treat MDD? An animal study looked at two groups of rats and measured their physical activity by wheel running and level of depression by the forced swim test. Interestingly, this study found an increase in cell proliferation in the hippocampus in the running group of rats (Bjornebekk, Mathe, & Brene, 2005).

Introduction to Themes

Three themes or categories were identified in the use of exercise for the treatment of MDD and include the following – type of exercise for therapeutic benefit, exercise compared to pharmacotherapy and psychotherapy, and exercise as adjunctive treatment. The type of exercise

evaluated aerobic versus strength training, group exercise versus individual exercise, number of sessions of exercise per week, and intensity of exercise needed to provide optimal therapeutic benefit for MDD treatment. Most studies that were found comparing exercise to pharmacotherapy and psychotherapy used sertraline, an SSRI, and cognitive-behavior therapy (CBT) respectively. These studies compared the three methods of treatment mostly by remission of MDD, quality of life, and reduction of depressive symptoms. Some studies also looked at adherence among the different therapies. Finally, meta-analyses and studies looked at exercise as adjunctive therapy for MDD for first line therapy as well as for resistant, refractory MDD. All studies included adult participants with a diagnosis of MDD and no other psychiatric comorbidities.

Theme One: Type of Exercise, Intensity, and Dose for Therapeutic Benefit

In this RCT performed by Doose et al. (2015), researchers were searching for the effect physical exercise may have on patients with depression. The trial lasted eight weeks and one group of participants performed physical activity throughout, while a control group did not perform physical activity. Unique to this study, the group performing exercise got to choose their own preferred intensity of exercise. Both groups of participants were kept on their previous medical management and all participants had to have a previous diagnosis of mild to severe depression. Multiple scales were used to measure fitness and depression, including the Hamilton Rating Scale for Depression (HRSD-17) and Beck Depression Inventory. According to researchers, results did show a large reduction of depression symptoms as rated by participant self-report and scale measurement with the HRSD-17 scores *p value of* <0.0001 (Doose et al., 2015).

Nystrom, Neely, Hassmen, and Carlbring (2015) completed a systematic overview of 12 randomized control trials that assessed the treatment of depression in otherwise healthy patients with physical activity, which included aerobic activity, anaerobic activity, or both. The goal of the overview was to determine what type and dose of physical activity would provide the best efficacy for treating depression. Ten studies were selected that had patients diagnosed with major depression based on the DSM-IV and the other two studies had participants who were either diagnosed with dysthymia or mild depression. The studies included all ages from 12 to 84 and both sexes. Most of the studies did not have a control group as they compared two different therapies including pharmacotherapy, psychotherapy, and two groups that were offered health education. Physical activity was graded measuring frequency, intensity, length of intervention, and effect of intervention. Results showed neither aerobic or anaerobic activity were superior, and it was concluded that it should be up to the patient preference and ability. The therapeutic effect of physical activity is seen at minimum dose three or more times per week for at least 30 minutes (Nystrom, Neely, Hassmen, & Carlbring, 2015).

Some limitations to this overview include the lack of control groups, as well as the lack of consistency of comparison therapy. The goal of the study was to find what type and “dose” of activity practitioners should prescribe, which was not specifically met. With only ten studies being reviewed, it is a rather small review. Also, all studies included participants that were not already physically active, limiting recommendations to only sedentary individuals suffering from depression. Another pitfall, is that not all studies had patients who were diagnosed with major depression by the criteria of the DSM-IV. It would have been a better overview had they not included the patients with dysthymia and mild depression. More research needs to be done on this topic. It is useful to know the “dose” of exercise that is needed to see an effect from a

provider standpoint. Also useful is the fact that neither anaerobic or aerobic exercise were found to be superior in the treatment of depression (Nystrom, Neely, Hassmen, & Carlbring, 2015).

The Cochrane Review performed by Cooney et al. (2013) of 39 studies assessed what type of exercise had a stronger clinical evaluation and indicated that mixed aerobic and resistance exercise and resistance exercise alone had stronger clinical effects. Mixed ($SMD -0.85$, $95\% CI -1.85 to .15$), resistance ($SMD -1.03$, $95\% CI -1.52 to -.53$), and aerobic exercise ($SMD -0.55$, $95\% CI -0.77 to -0.34$). The review also compared intensity of exercise and clinical effect. The largest effect size indicated for vigorous intensity ($SMD -0.77$, $95\% CI -1.3 to -0.24$) and light/moderate intensity ($SMD -0.83$, $95\% CI -1.32 to -0.34$). This is not very conclusive being a large effect is seen with vigorous and light/moderate intensity. Also, duration and frequency of exercise was analyzed, which showed large effect sizes were seen for more sessions such as 13 to 24 sessions ($SMD -0.70$, $95\% CI -1.09 to -0.31$) and 25 to 36 sessions ($SMD -0.80$, $95\% CI -1.30 to -0.29$). While a moderate effect size was seen for 0 to 12 sessions ($SMD -0.42$, $95\% CI -1.26 to 0.43$) and 37 or more sessions ($SMD -0.70$, $95\% CI -0.69 to -0.23$). These results suggest that more sessions have a larger effect, to a certain point, at which then the effect drops off (Cooney et al., 2013).

In the SMILE study completed by Hoffman et al. (2011), a controlled clinical trial was done where 202 participants were randomized to four of the following interventions for four months; supervised exercise, home-based exercise, sertraline, or placebo pill. Participant outcome was measured by the Hamilton Depression Rating Scale score and status of MDD in terms of depression, partial remission, or full remission. At four months patient progress was assessed which revealed similar benefits between participants treated with exercise and sertraline. Twelve months post study, 66 percent of participants had remitted. In follow up,

continued self-reported exercise was directly associated to lower depression scores and improvement of depressive symptoms. However, the study found that the anti-depressant activity of exercise drops after exceeding three hours per week. Results suggest that much similarly to antidepressant pharmacotherapy, exercise must continue to be performed in order to see antidepressant effects. When participants discontinued exercise, they had worsening of symptoms (Hoffman et al., 2011).

Theme Two: Exercise Compared to SSRIs and Psychotherapy

Cooney et al. (2013) performed a meta-analysis on 39 studies of adults with depression comparing exercise to standard treatment, psychological treatment, or other active treatment. Pharmacological and psychological therapy were compared with exercise and found to have no significant difference in depression treatment. Seven trials with 189 participants compared exercise with psychological therapies. Results showed a *SMD of -0.03 (95% CI -0.32 to 0.26)*, which indicated that there was not a significant difference between the two groups – an argument for the use of exercise. Four trials in this meta-analysis compared exercise with pharmacological treatments. Results indicated no significant difference between the two groups with *SMD -0.11 (95% CI -0.34 to 0.12)*. Results were inconclusive due to the few number of studies done as well as the limitations to those studies. However, authors did conclude that based on review, exercise is not a more efficacious treatment for depression than antidepressants or psychotherapy, however, at the same time, it did not conclude a major difference among the different groups treated with exercise versus other therapies. Adverse effects of exercise were reported by a small number of trials, but these were not consistent among trials; such effects included chest pain, worsening depression, arthralgias, joint swelling, myalgias, and falls (Cooney et al, 2013).

In another large review completed by Gartlehenr et al. (2016), 45 studies were assessed in regard to primary care treatment of major depression. Therapies included in comparison were antidepressants, psychological, complementary and alternative medicine (CAM), and exercise treatment in adults with acute MDD. Authors of the review were critical and analytical of the current research to date comparing all therapies. Remission rates of MDD were statistically similar in those treated with sertraline and aerobic exercise in two trials assessed, however this was low quality evidence. CBT and antidepressants had similar response rates ($RR, .90$ [95% CI, $.76$ to 1.07]) and remission rates ($RR, 0.98$ [CI, $.73$ to 1.32]). However, antidepressants did have higher risks for adverse effects (Gartlehenr et al., 2016).

A final meta-analysis of 13 studies completed by Jonefsson, Lindwall, and Archer (2014), studies were collected that compared physical exercise to usual care (which was not defined by most of the studies) as well as compared to placebo. As for exercise versus placebo or no treatment, exercise showed a large effect in improvement of depressive symptoms ($p < 0.001$) in participants with mild to moderate depression. There was not a significant effect found between exercise and usual care. Usual care was not defined because many of the studies did not include a definition of what usual care meant (Jonefsson, Lindwall, & Archer, 2014).

From this analysis, it is suggested that exercise is only effective in those with mild to moderate depression. In the primary care setting, that is the patient population that is mainly being treated as those with more severe depression are often sent to specialists. Using exercise therapy in those who are not severely suffering may be an appropriate approach especially considering the low risk in comparison with anti-depressant medications. Authors of this analysis also pointed out other advantages of exercise compared to usual care such as stress reduction, decreased blood pressure, reduced risks for coronary artery diseases, weight reduction, increased

oxygenation, and an increase in cognitive functioning as shown in animal studies (Jonefsson, Lindwall, & Archer, 2014).

Theme Three: Exercise as Adjunctive Therapy for Depression

In this study completed by Greer et al. (2016), a group of participants were selected who were considered “partial responders” to antidepressant therapy with SSRIs. They were assigned either a high or low dose exercise regimen for 12 weeks and monitored at 6 and 12 weeks by 5 different scales assessing quality of life along with measurement of depressive symptom severity by a clinician and self-report. Completing the study was 101 participants. Results found significant improvement in quality of life and functioning in both doses of exercise therapy, and an insignificant difference among the two doses. Areas of improvement included physical and mental health, social relationships, work, and general life satisfaction (Greer et al., 2016).

In this study, there are many limitations. First, they did not have a control group. Also, they had a rather small group of participants at 101. The population was rather specialized – having to be only partially responsive to anti-depressant therapy; although, this is commonly seen in the primary care setting. Another limitation is the participants could not have engaged in physical activity over the past month, which is leaving out a large group of people who are active and do already exercise but still have MDD. Positives to this study is that all participants were on the same class of antidepressants and dosing changes were not made throughout the study (Greer et al., 2016).

As mentioned above, depression treatment in the primary care setting is often met with some resistance. It is common to see patients who are not completely responsive to antidepressant therapy and still have residual depressive symptoms. From a primary care

perspective, it is useful to know that adding on exercise to the current medication regimen may be sufficient before considering switching medications or increasing dosage (Greer et al., 2016).

An article in the *British Journal of Sports Medicine* looked at 12 patients with a known diagnosis of major depressive disorder ages 20 to 65. These participants current depressive episode lasting an average of 35 weeks and had seen no improvement in the last four weeks of being treated with two antidepressants at high doses. Participants were both inpatient and outpatient and had a Hamilton Rating Scale for Depression (HAM-D) of 15 or more. Participants were not allowed to have an associated comorbidity or schizophrenic symptoms. During the study, no changes were made to their current depression regimen other than the augmentation of exercise. Exercise included interval training on a treadmill for a duration of 10 days. Patients rated their exertion and other parameters were measured such as lactate concentration and heart rate. Results showed a great improvement in 5 participants, with their HAMD scores dropping to less than 10, while 4 participants showed no improvement (Dimeo, Bauer, Varahram, Proest, & Halter, 2001).

Seiquior et al. performed a RCT with 57 participants with a diagnosis of moderate to severe MDD and a HAM-D score of at least 15. All participants were given sertraline 50 milligrams daily and had no use of antidepressants for the last five weeks. Twenty-nine participants were randomized to the exercise intervention, while 28 participants were given sertraline alone (Siqueira et al., 2016).

Results of the study did not show a statistically significant difference between reduction in depressive symptoms between the two arms, with a *p value of <0.001*. However, participants in the exercise group had a lower final dose of antidepressants with only 17 percent of the

participants in the exercise group taking 100 mg, while 54 percent in the control group (medication alone) taking 100 mg of sertraline (Siqueira et al., 2016).

A study by Murri et al. (2015) included primary care patients 65 to 85 years old whose health was compatible with exercise and used the HAM-D. Exercise was scheduled three times per week for 60 minutes per session for 24 weeks. Non-progressive exercise worked on strength, balance, respiration and motor coordination, and used both mat work and instrumental exercise. The progressive exercise used exercise bicycles working on improving cardiopulmonary function and increasing intensity. Remission was defined as a HAM-D score of less than 10. Mean baseline HAM-D score was 20 (Murri et al., 2015).

Both non-progressive exercise plus sertraline (SNPE) and progressive exercise with sertraline (SPAЕ) had higher remission rates than sertraline alone, with the following percent remission respectively: SPAЕ 36 percent, SNPE 40 percent, and sertraline 7 percent at 4 weeks, ($p=0.001$). At the end of the study remission rates were the following, SPAЕ 81 percent, SNPE 73 percent, and sertraline 45 percent ($p=0.001$), showing a substantial and statistically significant improvement in both groups who participated in exercise. Sertraline 50 milligrams 45 percent response, sertraline plus supervised non-progressive exercise 3 times per week 54 percent remission, and sertraline plus supervised higher intensity progressive aerobic exercise three times per week, 85 percent. $P = 0.001$. At 24 weeks, sertraline only 45 percent, sertraline plus progressive exercise 73 percent, and sertraline plus higher intensity aerobic exercise 81 percent, $p = 0.001$ (Murri et al., 2015).

Hallgren et al. (2016) looked at 945 adults with mild to moderate depression in the primary care setting in Sweden. For 12 weeks, three of the following interventions were assigned randomly – supervised group exercise, clinician supported internet-based cognitive-behavioral

therapy (ICBT), and usual care for depression. Participants had to have a Patient Health Questionnaire (PHQ-9) score greater than nine and participants were included for comorbid substance abuse or psychosis (Hallgren et al., 2016).

Participants were followed up at 3 months post intervention and again at 12 months. Multiple scales were used to measure depression and outcomes including the Montgomery-Asberg Depression Rating Scale (MADRS), the EuroQol EQ-5D to measure overall health, employment, Alcohol Use Disorders Identification Test (AUDIT) for alcohol abuse, and tobacco use. Participants who were selected for the exercise intervention completed 3 sessions lasting 60 minutes for 12 weeks at varying intensities lead by certified personal trainers. The ICBT intervention included an explanation by a psychologist of the program followed by working through self-help modules. Participants were monitored throughout the 12 weeks by a psychologist. Treatment as usual included 45 to 60 minutes of cognitive behavior therapy by a psychologist or counsellor and approximately 8 visits to general to their general practitioner. Results of the study showed that both ICBT and exercise were as effective as usual care as therapy for mild to moderate depression (Hallgren et al., 2016).

A large pitfall to this study is that usual care was not uniformly controlled and was variable in participants. This research is important for the argument of exercise because in the rural primary care setting, ICBT and exercise are much more accessible to patients than a trained psychologist or counsellor. Also, this implies that exercise therapy is as effective as ICBT or usual therapy, but as stated above, usual therapy was not well-defined (Hallgren et al., 2016).

Discussion

Type of Exercise, Intensity, and Dose for Therapeutic Benefit

In the study completed by Cooney et al. (2013), conclusions were unable to be made on what type, frequency, duration, level of supervision, or location of exercise offers patients the most benefit. Again, this must be looked at from a patient by patient basis. Authors were quick to recognize the inclusiveness of the review, including that studies only included those patients with depression who were willing to participate in an exercise program, which many only represent a small amount of the MDD population – the true number is not known (Cooney et al., 2013).

The RCT completed by Doose et al. (2015) allowed participants to choose their own intensity of exercise. Although this study cannot help the primary care provider on the exact dose of exercise needed to see benefit, it is useful because it showed that leaving the intensity of exercise up to the participant may still result in considerable improvement in depressive symptoms (Doose et al., 2015).

The review completed by Nystrom, Neely, Hassmen, and Carlbring (2015) looked at which form of exercise was beneficial in the treatment of depression – comparing aerobic activity, anaerobic activity, and a combination. Also assessed, was the dose needed for therapeutic benefit. It was concluded from this review that no form of activity was superior to another when treating depression, which makes it easier as a clinician in terms of prescribing exercise. The most effective dose was seen at a minimum of three or more times per week for at least 30 minutes. Allowing the patient to pick their desired form of exercise as well as only needing to complete the exercise three times per week for 30 minutes make exercise a more attractive option in the treatment of MDD (Nystrom, Neely, Hassmen, & Carlbring, 2015).

A thorough meta-analysis done by Cooney et al. (2013) looked at the level of intensity, the type of exercise (aerobic, resistance, and mixed), and the number of sessions that provided the most benefit in the treatment of MDD. It was concluded that mixed aerobic and resistance

exercise was the most effective, in contrast to the analysis completed by Doose et al. (2015), which said that there was no difference. For intensity of exercise, it was not very conclusive because both vigorous and light/moderate intensity had large effect sizes. Of note, was that the number of sessions that were most effective in MDD treatment were 13 to 36 sessions, while 0 to 12 and greater than 37 sessions were not as effective. Conclusions that can be drawn by this analysis that moderation is more beneficial (Cooney et al., 2013).

Another study completed by Hoffman et al. showed that the efficacy of exercise drops after exceeding three hours per week, which reinforces the findings of Cooney et al. indicating that moderation of exercise in MDD treatment is key. This study also concluded that in order to see the antidepressant effects of exercise, it must be continued (Hoffman et al., 2011)

Exercise Compared to SSRIs and Psychotherapy

In the analysis completed by Cooney et al. (2013) exercise was not shown to be statistically different in the efficacy of MDD treatment compared to psychotherapy or pharmacotherapy. Conclusions that were drawn from this review are that CBT and antidepressant therapy have similar efficacy, and the latter may have more adverse effects. Unlike other reviews that showed a benefit to combining psychotherapy and pharmacotherapy, this review did not. Recommendations were made that CBT and antidepressant therapy are both sufficient first line choices in the treatment of MDD and should be chosen on a patient by patient basis. Important take home points from this review are alternate methods to pharmacotherapy may show promise in the treatment of mild to moderate MDD. When approaching the patient with mild to moderate depression, it is important to acknowledge patient expectations, goals, and demographics when deciding on initial treatment (Cooney et al., 2013).

Gartlehenr et al. (2016) performed a large review comparing antidepressants, psychological, complementary and alternative medicine (CAM), and exercise treatment in adults with MDD. Although there were similar remission rates seen in those treated with sertraline and aerobic exercise, this was not high quality evidence. One important note made by this review was that antidepressants had more adverse effects than aerobic exercise. This review is important for the argument of exercise in the treatment MDD (Gartlehenr et al., 2016).

Exercise as Adjunctive Therapy for Depression

The study completed by Siqueira et al. (2016) looking at the antidepressant efficacy of aerobic activity using biomarkers is important because with increasing dosing of antidepressants comes increasing side effects. Antidepressants such as sertraline are given a warning that they take weeks to months to take effect. Starting patients on an exercise regimen at the same time as medication administration may result in a quicker improvement of depression symptoms. This also helps understand the physiology of exercise and how it may improve depressive symptoms by laboratory measures (Siqueira et al., 2016).

This study by Dimeo, Bauer, Varahram, Proest, and Halter (2001) makes a good point that this would be a good initial approach in combination to medical therapy because antidepressants typically take two to four weeks to start working, while aerobic activity has a quicker onset. A pitfall to this study was that only 12 patients were followed, and 33 percent showed no improvement in their depression with therapy. This research is useful for the question of physical activity as an adjunctive initial therapy to the heavily prescribed anti-depressants. Starting those patients on an exercise regimen while starting medication may further enhance patient well-being and improve depression symptoms more quickly (Dimeo, Bauer, Varahram, Proest, & Halter, 2001).

Applicability to Clinical Practice

As mentioned earlier, MDD is a disease that is very common in the primary care setting and it can have effects on other comorbid conditions and healing, but most importantly on patient well-being and quality of life. Current standard for clinical practice are first line treatment with either CBT or SSRIs. According to *Dynamed Plus*, physical activity may be considered as initial treatment for people with mild MDD or those who are teetering between a diagnosis of MDD or not. However, with this recommendation, *Dynamed Plus* only has a Level 2 or mid-level evidence of recommendation for using exercise in lieu of CBT or MDD. With a lower recommendation and lower evidence, it does not mean that studies have conclusively proven exercise not as effective as CBT or SSRIs, rather that studies are inconclusive. The research presented in this review also reinforces the guidelines from *Dynamed Plus*, encouraging that more research be done to better understand the true potential of exercise for MDD treatment (*Dynamed Plus*, 2017).

Based on the studies in this review, however, it can be suggested that exercise may play the best role as an augmentation treatment to CBT or SSRIs because it may offer a more rapid resolve of symptoms than either of the two alone. SSRIs are especially important because they are given a black box warning of increasing suicidality in the first few weeks of treatment.

One major component to treating a patient is patient empowerment. Having a health condition can leave patients feeling helpless. Giving the patient specific tasks that he or she can do to improve his or her health helps give the patient some responsibility and control of his or her condition. Offering exercise may be a way to empower the depressed patient and give a task or a goal that is easily completed without many side effects or likelihood that it will make the patient's condition worse. Concerns for the use of exercise as a therapy for MDD includes

patient compliance as well as access. It is undeniably easier to spend 60 seconds or less per day taking a pill in contrast to spending at least 30 minutes every other day exercising. Also, not everyone has accessibility to exercise equipment or resides in climates warm enough to participate in outdoor physical activity.

Although research has been done on this topic and MDD, there is still much that is unknown. For example, the true and complete pathogenesis of MDD, much like other psychiatric illnesses, is still unknown. And, though improved from the past, there is still an unfortunate stigma with mental health. More research needs to be done on both MDD as well as the potential for exercise as an effective treatment for the condition. In many of the studies, a large percent of the participants were non-compliant with the exercise control. More RCTs need to be completed before

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