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Exercise Compared to SSRIS in the Treatment of Major Depressive Disorder

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EXERCISE COMPARED TO SSRIS IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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Abstract

Major Depressive Disorder (MDD) is a common disease seen every day by primary care providers across the United States. According to the Centers for Disease Control and Prevention (CDC, 2018), eight percent of all adults over the age of 20 suffer from depression, and a study by the American Psychological Association found depressive disorders to cost roughly $71 billion annually. Today, psychotherapy is the recommended first-line therapy for treating MDD, but pharmacotherapy is more commonly used. Alternative forms of therapy are also being researched in order to avoid the use of medication while adequately treating the symptoms of MDD.

For this review, seven databases were searched including PubMed, Cochrane Database of Systematic Reviews, PsycInfo, Cinahl, DynaMed, ClincalKey, and ScienceDirect from September 1 to November 21, 2018. Works chosen for review were published after the year 2000 and included randomized controlled trials (RCTs), systematic reviews, and meta analyses. This review found several benefits of using exercise to treat MDD while reducing risks, but exercise alone is not superior in effectiveness to psychotherapy or pharmacotherapy. Overall, exercise offers the greatest benefit in reducing MDD symptoms when used as an augmented therapy to either psychotherapy or pharmacotherapy. Limitations of this literature review include lack of studies with longevity or large sample sizes.

Key Terms *pathophysiology, exercise, depression, SSRIs, selective serotonin reuptake inhibitors, Major Depressive Disorder, MDD*

Introduction

On any given day, patients with the diagnosis of Major Depressive Disorder (MDD) show up at least once on the schedule of primary care providers across the United States. According to a recent study by the Centers for Disease Control and Prevention (CDC, 2018), eight percent of all adults over the age of 20 suffer from depression within a given two-week period, with women being twice as likely as men to be affected by the disorder. Of these individuals, 80 percent reported at least some difficulty with completing daily activities due to depressive symptoms. More specifically, 50 percent of them noted mild difficulty with home, work, or social activities while 30 percent admitted to moderate or extreme difficulty based on evaluation with the Patient Health Questionnaire-9 (PHQ-9). Researchers involved in the study believe this is a conservative estimate, as there are more patients with depression who are unwilling to participate in the survey (CDC, 2018). However, even when patients are evaluated by a primary care provider for depressive symptoms, it has been found that the diagnosis of MDD is all too commonly missed. DynaMed (2018) completed a study of 2,321 participants in a primary care setting with 304 patients who screened positive for depression with the PHQ-9. Of those 304 patients, only 31 percent were diagnosed with depression by the provider. To further expand, 175 of those patients displayed significant depressive symptoms on the PHQ-9 and yet only 37.7 percent were diagnosed with MDD at that visit (DynaMed, 2018).

The PHQ-9 is a screening tool commonly used in clinics when there is a concern for depression in an individual, as it addresses the diagnostic criteria which must be met for the diagnosis of MDD. To further expand, the diagnostic criteria is defined by the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-V) which states in order for a patient to be diagnosed with MDD, he or she must have a change in baseline causing significant impairment

in daily activities due to experiencing at least five of the following symptoms most of the day, nearly every day for a minimum of two weeks with at least one of the first two symptoms present: 1) depressed mood; 2) decreased interest or pleasure in activities; 3) unintentional change in weight or appetite; 4) insomnia or hypersomnia; 5) psychomotor agitation or retardation; 6) fatigue; 7) excessive feelings of worthlessness or guilt; 8) decreased concentration or indecisiveness; 9) recurrent thoughts of death or suicide. The DSM-V also requires that symptoms may not be attributable to any other condition or substance. If the above criteria are met, the diagnosis is then further classified based on the severity. Mild MDD can be defined as the minimum number of symptoms present with symptoms causing distress that is manageable. Moderate and severe MDD include an increased number of symptoms present as well as increased impairment and difficulty managing symptoms. Due to the difficulty with managing the symptoms of moderate or severe MDD, primary care providers will typically refer these patients to a specialist for further evaluation and treatment (DynaMed, 2018).

If proper treatment is not initiated for those with depression, high societal costs and greater functional impairment than associated with other chronic diseases such as diabetes and arthritis can occur according to the CDC (2018). In fact, a study by the American Psychological Association found depressive disorders to be the sixth-most-costly health condition overall with $71 billion being spent annually, falling shortly behind conditions such as diabetes mellitus, ischemic heart disease, low back and neck pain, hypertension, and injuries related to falls (Winerman, 2017). Therefore, it is imperative that primary care providers across the United States understand and implement proper treatment for their patients suffering from mild MDD. Today, first line therapy for mild MDD is psychotherapy. The modality of psychotherapy with the best evidence for efficacy according to DynaMed (2018) is cognitive behavioral therapy

(CBT) which focuses on modifying behavior and functioning by refocusing dysfunctional beliefs through social skills training, relaxation, coping skills, and behavioral activation. Although CBT is recommended as first-line therapy, MDD is more commonly treated with medications such as Selective Serotonin Reuptake Inhibitors (SSRIs). This tendency seems to occur for two reasons with the first being pharmacotherapy appears to be more readily available especially from a rural primary care standpoint, and secondly, many patients today want the "quick fix" they believe a pill can offer rather than participating in the lengthy process that CBT involves. DynaMed (2018) reported CBT has been found to reduce both symptoms and relapse rate more than SSRIs in patients with mild MDD, but Jesulola, Micalos, and Baguley (2018) also reported up to 80 percent of patients with depression fail to respond to antidepressant therapy in clinical trials. Recent research, however, shows treating patients with mild MDD with alternative therapies, including exercise, may be just as beneficial as traditional therapies, while providing further significant benefits, avoiding side effects, and limiting the use of medication (DynaMed, 2018).

The purpose of this scholarly project is to determine the role of exercise in treating adult patients diagnosed with mild MDD in the primary care setting. Exercise will be assessed as a stand-alone therapy compared to pharmacotherapy with SSRIs, as well as reviewed as an augmented therapy to SSRIs. It is anticipated that exercise will provide benefits over SSRIs and it will be useful as an augmented therapy, but it will not be superior alone. Further research will be required to support the use of exercise as a sole therapy over SSRIs. A systematic analysis will look at the efficacy of the two therapies regarding benefits, risks, and improvement of symptoms.

Statement of the Problem

With the increasing cost of medications and potential for high risk side effects, some providers are recommending alternative therapies to SSRIs for adult patients diagnosed with mild MDD in hopes of providing an option that is safer and more cost effective while providing the same benefit. Further research is needed to show if exercise and SSRIs are equal in efficacy in the reduction of symptoms associated with mild MDD in adults.

Statement of the Research Question

In adult patients diagnosed with mild MDD in a primary care setting, does treating with exercise as a stand-alone therapy compared to treating with SSRIs adequately improve symptoms while minimizing side effects?

Review of Literature

In this review, seven databases were searched including PubMed, Cochrane Database of Systematic Reviews, PsycInfo, Cinahl, DynaMed, ClinicalKey, and ScienceDirect from September 1 to November 21, 2018. Many key terms were searched in PubMed: Major Depressive Disorder, exercise, SSRI, MDD, and pharmacotherapy. Cochrane Database of Systematic Reviews was searched using the key terms exercise, depression, and SSRI. A search of PsycInfo yielded results based on the key term SSRI. Key terms utilized in a search of CINAHL included depression, exercise, Major Depressive Disorder, SSRI, and MDD. DynaMed results were obtained by searching the key term MDD. A search of ClinicalKey yielded results based on the key terms MDD, depression, and SSRI. Lastly, key terms used to search ScienceDirect included depression and pathophysiology. Filters were applied to include only peer reviewed articles published after the year 2000. Works chosen for review included randomized controlled trials (RCTs), systematic reviews, and meta analyses. Sources excluded

were those published prior to the year 2000, had poor study design, and those focused on severe MDD or child and adolescent populations

Pathophysiology of MDD

MDD is a very common but serious chronic mental health disease characterized by changes in mood, thoughts, behavior, and physical health that can take away a patient's ability to enjoy life and perform even the simplest daily tasks (Fekadu, Shibeshi, & Engidawork, 2016). Even with years of extensive research on MDD, the exact pathophysiology remains unknown. There are many theories that may answer the question of the underlying pathophysiology including theories of neural circuitry, stress response circuits, genetic vulnerability and environmental interaction, biogenic monoamine, inflammation, hormones, and circadian rhythm (Fekadu et al., 2016). One of the most commonly accepted theories is the biogenic monoamine theory which is the basis for pharmacologic treatment for MDD. In fact, this theory was developed after the unexpected discovery of the first antidepressant drugs which were created for other conditions but were found to increase the amount of monoamine neurotransmitters in the brain by either blocking monoamine oxidase inhibitors (MAOI) or the reuptake of neurotransmitters such as serotonin (Fekadu et al., 2016). Serotonin is involved in pain sensation, appetite regulation, aggression, and mood, and the increased available amounts of serotonin activity in the brain were found to decrease depressive symptoms. Later this knowledge was used to create SSRIs which then became one of the primary treatment options for MDD.

Another potential theory discussed by Jesulola et al. (2018) considers the theories listed previously as a combined source of pathogenesis rather than each theory individually, stating that MDD is a complex disorder with multiple etiologies. To further expand, Jesulola et al. reported environmental stress combined with genetic factors act on immunologic and endocrine responses

to cause structural and functional changes in the brain leading to dysfunction of neurogenesis and neurotransmission which ultimately causes the symptoms of depression.

Exercise in the Treatment of MDD

In the SMILE study completed by Blumenthal et al. (2007), 202 adults with the diagnosis of major depression participated in a RCT with groups assigned to supervised group exercise, home exercise, sertraline, or placebo pill for 16 weeks. Upon the completion of the 16 weeks, outcomes were evaluated by the Hamilton Depression Rating Scale (HAM-D). Forty-one percent of the participants were considered to be in remission as they no longer met the criteria for MDD based on the HAM-D score. In fact, 45 percent of patients assigned to supervised group exercise achieved remission, 40 percent of home exercisers, 47 percent of those on medication, and 31 percent of those with a placebo pill ($p = 0.057$). Results were not statistically significant ($p = 0.23$) when comparing patients treated with exercise or SSRIs compared to those with placebo treatment. Due to the nature of the study, a double-blind set up was not possible. However, the treatment team and outcome assessors were not aware which patients were participating in each treatment group to minimize bias (Blumenthal et al., 2007).

A Cochrane Review by Cooney et al. (2013) pooled together results of 39 RCTs to compare exercise versus control and pharmacological treatments in treating MDD. For the purpose of this Cochrane Review, exercise was defined as "planned, structured, and repetitive bodily movement done to improve one or more components of physical fitness" (Cooney et al., 2013) and control interventions included no intervention, placebo intervention, and those in which exercise was augmented to an already established treatment option such as CBT in both exercising and non-exercising groups. Thirty-five of the studies focused on a comparison between exercise and control, and exercise was found to be moderately more effective (*SMD* -

0.62, 95% CI [-0.81, -0.42]). More specifically, type, intensity, duration and frequency of exercise were all reviewed to determine the best form of exercise to treat MDD. This research indicated either resistance (*SMD* -1.03, 95% [CI -1.52, -0.53]) or resistance combined with aerobic exercise (*SMD* -0.85, 95% CI [-1.85, 0.15]) at a vigorous intensity (*SMD* -0.77, 95% CI [-1.30, -0.24]) for 13 to 24 (*SMD* -0.70, 95% CI [-1.09, -0.31]) or 25 to 36 sessions (*SMD* -0.80, 95% CI [-1.30, -0.29]) produced the largest clinical effect on reducing depressive symptoms (Cooney et al., 2013).

Additionally, the outcomes of the four trials included in the review that compared exercise to pharmacological treatments indicated no statistically significant difference (*SMD* -0.11, 95% CI [-0.34, 0.12]) between the two treatment options. A weakness of this review lies in the fact that not all RCTs included used the same evaluation tool, instead, Beck Depression Inventory (BDI), HAM-D, and a variety of other scales were used to measure depression symptom outcomes. Many of the RCTs included were also small and had many methodological weaknesses. The review also touched on potential biases and noted while they try to avoid any biases, the authors mentioned a certain degree of bias was inevitable due to “asymmetrical funnel plot” with more positive trials being published than negative trials, therefore, more positive trials were included in the research (Cooney et al., 2013).

A systematic review by Danielsson, Noras, Waern, and Carlsson (2013) examined the quality of evidence available for using exercise in the treatment of MDD through a compilation of statistics from fourteen RCTs. The RCTs included compared exercise to antidepressants, exercise to physical activity, and exercise as an augmented therapy to traditional treatment versus traditional treatment alone. Exercise was again defined as “planned, structured, and repetitive bodily movement done to improve one or more components of physical fitness” (Danielsson et

al., 2013). The comparison between exercise and antidepressants was reviewed in two trials and two long-term follow-up studies. The results showed no statistically significant difference between exercise and antidepressants regarding depression severity in either the short (*SMD* -0.06, 95% CI [-0.36, 0.23]) or long term (*SMD* -0.19, 95% CI [-0.68, 0.31]). Exercise versus physical activity was reviewed in eight studies with the result indicating there is no difference in the effect of the two (*SMD* 0.01, 95% CI [-0.23 to 0.24]). Lastly, four studies included data on exercise as an augmented therapy versus traditional treatment alone. This data indicated there was a small effect on those treated with exercise as an augmented therapy compared to those who were not (*SMD* -0.44, 95% CI [-0.79, -0.09]) (Danielsson et al., 2013).

The positive effects of exercise on depressive symptoms are proposed to include both psychological and neurobiological mechanisms (Danielsson et al., 2013). Psychological effects proposed include diversion from depressive thinking as well as increased self-efficacy and self-confidence. Neurobiological effects proposed include changes in endorphin and monoamine levels similar to those in patients treated with antidepressants. Recent studies also suggest exercise stimulates hippocampal neurogenesis to improve depressive symptoms. The weaknesses noted in the study design include variations in the methodology of each RCT, small and varying sample sizes, and lack of standardized outcome measuring tool (Danielsson et al., 2013).

A RCT by Dunn, Trivedi, Kampert, Clark, and Chambliss (2005) aimed to address the efficacy of exercise in the treatment of depression, specifically whether there is a dose-response relationship. The study contained 80 adult patients diagnosed with mild to moderate MDD who were evaluated before the study with the 17-item Hamilton Rating Scale for Depression (HRSD17) and then again after 12 weeks of treatment. During treatment, there were four exercise groups and a placebo group. The first two groups exercised at a low dose energy

expenditure of 7 kcal/kg/week, with one of the low dose (LD) groups exercising 3 days per week and the other 5 days per week. The second two groups exercised at a higher energy expenditure of 17.5 kcal/kg/week which was consistent with the public health recommendations. One of the public health dose (PHD) groups exercised 3 days per week and the other for 5. Lastly, the placebo group performed stretching and flexibility exercise for just 15 to 20 minutes 3 times per week. All exercise was performed in a supervised laboratory for 12 weeks (Dunn et al., 2005).

Dunn et al. (2005) found that HRSD17 scores steadily decreased with each week of exercise. At 12 weeks, the scores of the PHD groups significantly improved (-47% from baseline, $p<0.001$) and LD groups were less effective, but still improved (-30%, $p=0.006$). Groups exercising 3 and 5 days per week both improved with relatively equal efficacy (-39%, $p<0.001$ and -38%, $p<0.001$), and the control group improved only slightly (-29%, $p=0.02$). Overall, PHD exercise was significantly more effective than LD exercise in improving HRSD17 scores at 12 weeks ($p=0.04$ and $p=0.03$ respectively). In fact, those in the PHD group exercising 5 days per week had the greatest response in reducing HRSD17 scores and a total of 20 participants were able to achieve remission, defined as HRSD17 score of less than or equal to 7 (Dunn et al., 2005).

Another RCT by Bartholomew, Morrison, and Ciccolo (2005) consisted of 40 participants already diagnosed with and receiving treatment for MDD. The study aimed to determine if "a single bout of moderate-intensity aerobic exercise would improve mood and well-being" in these patients (Bartholomew et al., 2005). Participants were randomly assigned to an exercise or control group with the exercise group participating in 30 minutes of exercise at 60 to 70 percent of age-predicted maximal heart rate, while the control group simply participated in a 30-minute period of quiet rest. Outcomes of mood improvement were measured by both the

Profile of Mood States (POMS) and Subjective Exercise Experiences Scale (SEES) 5 minutes prior to treatment as well as 5, 30, and 60 minutes following treatment. Effect size was then labeled as "d" to indicate mean differences in the change scores. Overall, no significant differences were noted between the exercise and control groups regarding improvement of depressive symptoms (all $p>0.15$). The only statistically significant difference noted was the change in positive well-being in the exercise group over the resting group at 5 and 30 minutes after treatment ($p<0.01$, $d=1.13$ and 1.06 respectively) (Bartholomew et al., 2005).

SSRIs in the Treatment of MDD Including MOA, Benefits, and Risks

A review by Garnock-Jones and McCormack (2010) on the use of escitalopram, a commonly used first-line SSRI, in the treatment of MDD included both short and long-term trials. Only well-designed trials with at least 100 patients were included, and each trial utilized randomization, double-blind, and multiple approaches to comparisons between escitalopram and placebo or another medication. The review not only compared trials for efficacy of the drug, but also provided background information on the pharmacodynamics, side effects, and benefits of the SSRI. Garnock-Jones and McCormack (2010) stated escitalopram provides antidepressant effects by selective, dose-dependent inhibition of the serotonin transporter (SERT) which causes inhibition of serotonin reuptake into presynaptic nerve terminals ultimately leading to increased extracellular serotonin levels.

The results concluded that in the short-term trials escitalopram was more effective than placebo and just as effective as other SSRIs or antidepressants in treating MDD. Escitalopram was found to have a rapid onset and significant antidepressant effects with 35.2 percent of escitalopram treated patients compared to 21.5 percent of placebo patients reporting a 20 percent decrease in the HAM-D17 score ($p=0.008$). In fact, escitalopram produced a significantly higher

response rate than placebo in all but two trials included in the review (Garnock-Jones & McCormack, 2010).

Moreover, escitalopram showed greater efficacy in preventing relapse in the long-term trials over placebo and was just as effective as other antidepressants. Outcomes in long-term studies included in the review were based on change in MADRS score from baseline or time to relapse. In two long-term studies comparing escitalopram to placebo, those treated with escitalopram had significantly longer timeframes to relapse than those in the placebo treatment group (*ESC:* 252 and 188 days versus *PL:* 130 and 56 days respectively, $p<0.05$) and rate of recurrence was also significantly higher among placebo participants (*ESC:* 27 and 26 percent versus *PL:* 65 and 40 percent respectively, $p<0.05$) (Garnock-Jones & McCormack, 2010).

Garnock-Jones and McCormack (2010) noted the most common side effects found in the two fixed-dose trials in the review were mild to moderate in severity and included nausea, ejaculation disorder, insomnia, diarrhea, somnolence, dry mouth, rhinitis, fatigue, influenza-like symptoms, dizziness, and increased sweating. Occurrence rates of adverse effects among patients treated with escitalopram 10 and 20 mg daily versus those in the placebo group were 66 percent and 86 percent versus 61 percent. Overall, it is a well-tolerated medication with a rapid onset. It has a low risk for drug interactions and side effects and may provide the benefit of cost effectiveness over many other antidepressants (Garnock-Jones & McCormack, 2010).

Strengths of the study lie within the various inclusion criteria. Only studies on adult populations were included and those including patients with severe MDD or suicidal ideations were excluded from the review. Outcomes were evaluated based on either the MADRS or HAM-D17. However, variety amongst the individual studies makes it difficult to directly compare results to compile a review (Garnock-Jones & McCormack, 2010).

A meta-analysis by Li, Shen, Lou, and Li (2017) pooled together the results from four clinical trials examining the efficacy of escitalopram in the treatment of MDD. The four clinical trials included 649 participants with a formal diagnosis of MDD who were started on escitalopram as monotherapy and again evaluated for depressive symptom improvement at the end of a two-week period. Average change in HAMD17 score was most significant in patients with moderate-severe depression, but scores also significantly improved in those with mild and moderate depression (15.0+/-7.9, 12.4+/-5.0, and 12.9+/-6.8 respectively). In those with only mild depression, the response rate was 76.9 percent and remission was 64 percent. Overall, the authors found that the more severe the depressive symptoms were at the beginning of the study, the less responsive the patient will be to escitalopram as monotherapy (Li et al., 2017).

Adverse effects and safety of the drug were also evaluated during the trials. Amongst the four trials included, there were 479 adverse events with the most common being mild to moderate gastrointestinal symptoms such as nausea, dry mouth, and dyspepsia. No serious adverse events were noted. The group of participants as a whole showed promising data for escitalopram being a suitable and safe treatment option for patients with MDD (Li et al., 2017).

Strengths of the analysis lie within the study design as only trials with similar methodology of randomization, double-blind, and active control were included. Only adult patients were included and those who were not in good physical health or had a recent history of substance abuse were excluded. This helped control the participant sample for a more consistent finding. Additionally, Li et al. (2017) graded outcomes of depressive symptoms with the HAMD17 score for a more consistent grading of the outcome. One weakness of the analysis according to the authors was the inability to fully complete a high-quality meta-analysis due to

the missing information including raw data and unpublished versions of the studies reviewed (Li et al., 2017).

A Cochrane Review by Arroll et al. (2009) pooled together results of 14 RCTs with a total of 2283 participants to compare antidepressants to placebo in the treatment of MDD. Of the studies included, four RCTs examined SSRIs compared to placebo while the others focused on different antidepressants. Within these four studies, the rate of beneficial outcomes associated with SSRI use was significantly greater than that of placebo (1.28, 95% CI [1.15, 1.43]) and risk for harm was quite low (1.03, 95% CI [0.87, 1.21]) (Arroll et al., 2009).

A weakness of the study lies in the short duration of the studies, as most lasted for only 6 to 8 weeks which is hardly enough time for the medications to become fully effective. A variety of outcome tools were also used to measure depressive symptoms throughout, although most commonly used were the HAMD17 and MADRS, therefore the authors chose to only include data based on these two scores to create a SMD. A strength, however, comes from the inclusion criteria applied in the reviewing process. Studies with the majority of participants over the age of 65 were excluded and studies including patients with co-existing conditions were also excluded (Arroll et al., 2009).

Discussion

As knowledge of the underlying pathophysiology of MDD continues to develop, recommended treatment also continues to evolve. Alternative therapies such as exercise are being considered in the treatment of mild MDD, but each treatment plan must be individualized to maximize benefits while minimizing risks. The next section is a discussion of the review of

literature of exercise compared to SSRIs in the treatment of adult patients with mild MDD in the primary care setting.

Exercise in the treatment of MDD

Dunn et al. (2005) and Bartholomew et al. (2005) both concluded exercise alone was effective at improving depressive symptoms. However, the degree of improvement varied. Dunn et al. found the effects of exercise to be dose dependent. When it was completed at a higher dose and intensity, effects were greater. Specifically, exercise at a PHD, or 17.5 kcal/kg/week, was found to be an effective option for mild MDD by reducing HRSD17 scores by 47 percent from baseline. This improvement in depressive symptoms was significantly greater than that found in the LD and control groups. In fact, Dunn et al. concluded exercise at a PHD 3 or more times per week was just as effective as traditional therapy options for treating mild MDD, although the various treatment options were not directly compared in the RCT. Bartholomew et al. concluded 30 minutes of either exercise or rest equally reduced depressive symptoms, but only exercise improved positive well-being. Unfortunately, the increase in positivity was short-lived as it returned to baseline by the 60-minute post-exercise evaluation.

Dunn et al. (2005) also noted the benefits of exercise over medication or CBT include the reduction of risk for mortality from diseases such as cardiovascular disease and obesity which further supports the recommendation to use exercise to treat MDD by primary care providers. Unfortunately, the studies by Dunn et al. and Bartholomew et al. (2005) were not without weaknesses as participants were unable to be blinded to treatment assignment due to the nature of the treatment. The sample sizes were also small, and the studies lacked longevity. Lastly, all exercise in the RCT by Dunn et al. was completed in a supervised lab which weakens the ability to apply the findings to the general population. Overall, the studies indicated exercise can be a

beneficial treatment option for MDD once further research is completed to correct for weaknesses (Dunn et al., 2005).

SSRIs in the treatment of MDD including MOA, benefits, and risks

Garnock-Jones and McCormack (2010), Li et al. (2017), and Arroll et al. (2009) all found SSRIs to be an effective treatment for mild MDD. Garnock-Jones and McCormack (2010) and Arroll et al. both concluded SSRIs are more effective than placebo in treating MDD. Garnock-Jones and McCormack (2010) specifically focused on escitalopram and found it to be more effective than other SSRIs and antidepressants. Li et al. also found escitalopram to be an effective monotherapy in treating MDD, although it was not compared to other medications, and the effectiveness was based on the severity of the MDD with the greatest effects found in those with mild MDD. Garnock-Jones and Mccormack (2010) also reviewed long-term studies in order to develop a better understanding of escitalopram. Escitalopram showed greater efficacy in preventing relapse in the long-term trials over placebo and was, again, just as effective as other antidepressants.

All three studies found SSRIs to be relatively safe. Garnock-Jones and McCormack (2010) did note a variety of side effects throughout the studies included, but the only side effects noted were mild to moderate in intensity and incidence increased with a higher dose of the medication. Overall, escitalopram was found to have a rapid onset, provide effective anti-depressant effects, and be more cost effective than other antidepressant medications. Unfortunately, not all participants responded appropriately to the use of the medication. Li et al. (2017) also found escitalopram to be safe. Throughout the four studies included in their research, the most common adverse effects were mild gastrointestinal symptoms, and therefore the drug was found to be favorably safe. Lastly, Arroll et al. (2009) found the risk for harm of SSRIs to be

minimal. The results indicated SSRIs are an appropriate choice for treating MDD in primary care, although the number needed to treat (NNT) was seven for SSRIs, meaning it is likely that one patient will benefit from treatment with the drug while six will not.

The review by Garnock-Jones and McCormack (2010) comparing escitalopram to both placebo and other antidepressants minimized bias and weaknesses by only including well-designed trials with larger sample sizes. Li et al. (2017), however, included small sample sizes and lacked longevity, and additional research is needed to better understand predictors of therapeutic response. Likewise, no specific recommendations regarding dose and duration of SSRI treatment were formulated through the review by Arroll et al. (2009). Additional studies on the use of SSRIs need to be completed to further specify the recommendations for SSRI use in MDD.

Exercise compared to SSRIs in the treatment of MDD

Blumenthal et al. (2007) found exercise to be comparable to antidepressant medication in treating patients with MDD. This study corrected for weaknesses found in previous studies by comparing exercise not only to antidepressants, but also to a placebo pill. This helped ensure effects with antidepressant medication was not just based on the placebo of taking a pill. Blumenthal et al. saw higher remission rates in both those treated with supervised or at home exercise (45 and 40 percent respectively) and antidepressants (47 percent) compared to those in the placebo group (31 percent) after 16 weeks of treatment. The exact mechanism as to how exercise produced the anti-depressive effects remains unknown, although Blumenthal et al. suggested numerous psychological factors that may contribute including “increased self-efficacy, a sense of mastery, positive thoughts, distraction from negative thoughts, and enhanced self-concept” as well as biologic pathways including “increased central norepinephrine

neurotransmission, alterations in the hypothalamo-pituitary-adrenocortical axis, and increased secretion of amine metabolites as well as serotonin synthesis and metabolism" (Blumenthal et al., 2007).

On the contrary, Cooney et al. (2013) found exercise to be less effective than antidepressants or psychological therapy and only moderately more effective than control in improving depressive symptoms. When only high-quality studies were included in the review, the effects of exercise over control were further reduced. Similarly, Danielsson et al. (2013) concluded there was no significant difference in the antidepressant effects of exercise compared to antidepressants through the four studies included reviewing the two. Eight trials comparing exercise to physical activity, such as stretching or meditation, found no statistical difference in the effects between the two, and results obtained by both methods was proposed to be a result of increased self-efficacy, coping skills, social support, or encouragement during the activity. However, Danielsson et al. did conclude that exercise is beneficial as an augmentation to medication in treating MDD, which is useful information for primary care providers in recommending treatment options.

Unfortunately, each of the studies presented with weaknesses that need to be corrected for in future research. The RCT by Blumenthal et al. (2007) concluded findings consistent with many other previous meta-analyses, but it contained methodological barriers and lacked longevity which makes it impossible to conclude the exact efficacy of using exercise to treat MDD. Likewise, Danielsson et al. (2013) noted grade of evidence for their findings was low secondary to many methodological weaknesses noted in the trials included. Future studies with sound methodology and large sample sizes can correct for this deficit and help support the use of exercise as an alternative to antidepressants.

Cooney et al. (2013) noted a slightly different weakness. This review included 39 trials which gave a variety of results to develop a summarized conclusion, but the variety also provided a source of weakness as many evaluation tools were used throughout the 30 trials to determine outcomes of the treatment methods. The authors noted there is an inevitable bias in the results as more positive than negative trials are published and therefore included in the research. Overall, the authors conclude extensive research is still needed to recommend exercise as an alternative therapy over traditional treatments for MDD (Cooney et al., 2013).

Applicability to Clinical Practice

With depression being one of the most common illnesses seen by primary care providers today, understanding all current treatment options available is essential. CBT is the recommended first-line treatment for mild MDD, but the convenience of pharmacotherapy has appealed to the majority of patients and SSRIs have become first-line in treating MDD. These medications, however, do not come without risks. Therefore, it is important that primary care providers be educated on the alternative forms of therapy that may be of equal benefit without the added risks of medication. The information provided in this literature review allows clinicians to make an educated decision on the recommendation for alternative forms of treatment for MDD based on clinical evidence. Benefits of using exercise in the treatment of MDD include, but are not limited to, minimizing medication use, avoiding side effects, reducing cost, improving self-confidence, aiding in weight loss, and improving overall health.

Research on this topic is becoming very popular, but unfortunately, current research includes more women than men and lacks longevity. At this point in the research, exercise is noted to have a moderate effect on depression, but after correcting for the bias found in current research, the effect may only be small (Cooney et al., 2013). There is not enough data to

recommend specific type and intensity of exercise to produce the best results, and long-term anti-depressive effects after exercise has concluded has not been studied sufficiently. Future research should correct for these aspects to further the knowledge on this potential alternative therapy. Overall, while exercise cannot be reported as a superior therapy over traditional options such as pharmacotherapy or psychotherapy, it can be recommended as a beneficial augmented therapy option in addition to the traditional treatments for all patients with MDD.

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