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The Effect of Physical Exercise as an Adjunctive Treatment to the Usual Treatment for Major Depressive Disorder: An Integrative Review

Eman S. Alsolami[1,2]
[1]*School of Nursing and Midwifery, The University of Sydney,Sydney, Australia*
[2]*Faculty of Nursing, Umm Al-Qura University, Makkah, Saudi Arabia.*

Abstract
Major depressive disorder (MDD) is a leading cause of disability around the world. The current treatment approach for MDD is limited. Physical exercise is a suggested treatment for depression and the use of exercise as an adjunctive therapy to the usual treatment of depression has received significant attention. The aim of this thesis is to evaluate whether physical exercise as an adjunctive therapy leads to an extra reduction in depressive symptoms compared with using the usual treatmentsalone. An integrative review was conducted by a systematic search in Scopus and PsycINFO databases. The search yielded100articles, which were narrowed to 15 articles based on inclusion and exclusion criteria. The review found that using exercise as an adjunctive therapy to the usual treatment of depression decreased depressive symptoms more than using the usual treatment alone. It also found that this effect is not influenced by factors such as type of exercise, as aerobic and resistance exercise lead to the same effect. In addition, it found that exercise programs of short- and medium-duration were more effective than programs of a longer duration, and that hospital- and public-based exercise were more effective than home-based exercise. However, this review cannot determine whether the effect of using exercise as an adjunctive therapy to the usual treatments might be different based on the severity of depression and the patient's age. This review suggests that using short and moderate programs of exercise as an adjunctive therapy to the usual treatment of depression can be an effective way to improve the depressive symptoms among adult patients with MDD.

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I. Introduction

Major depressive disorder (MDD or clinical depression) is a leading cause of disability around the world (World Health Organization [WHO], 2017) and is predicted to have a major contribution to the global burden of disease by 2020, as 300 million people worldwide have been diagnosed with depression (WHO, 2017) with risk of recurrent relapse all their life (Segal, Williams, and Teasdale, 2002). In addition, people with chronic diseases are at high risk to develop MDD compared with the normal population (Moussaviet al. (2007). MDDis a complex mood disorder with an unknown pathophysiology (Cichonet al. (2009). Based on the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition; DSM-IV), MDD is characterised by loss of interest in usual activities for 2 weeks or more. It also comes with physiological, emotional or cognitive symptoms, such as poor concentration, disturbed sleep and suicidal thoughts and acts (DSM-IV; American Psychiatric Association, 1994). It affects women more than men, and a patient's condition can be classified as mild, moderate or severe based on the severity of the symptoms (WHO, 2017).

As the pathophysiology of MMD and the leading cause of depression remain unknown, the current treatment approach for MMD is to treat a patient's symptoms (Kurian, Greer, and Trivedi, 2009). Treatment options for depression include antidepressant medication, electroconvulsive therapy (ECT), psychological treatments and interpersonal psychotherapy (WHO, 2017). Antidepressant medication is often the first treatment approach used to manage depression symptoms (Nemeroff, 2007). However, 60% of patients have been shown to be resistant to antidepressant medication, and patients who improve by taking antidepressant medication are at risk of relapse during the first year after treatment (Trivedi and Daly, 2008). Antidepressant medications also have many side effects, such as withdrawal symptoms (Ebmeier,Donaghe, & Steele2006). ECT which is the most effective treatment option for patients with severe depression has also many side effects such as memory impairment, headaches and confusion, decrease patients' willingness to accept this treatment (Nemeroff, 2007). Because of the difficulties associated with managing depression according to the current treatment approach, calls have increased for the development of alternative treatments for depression (Trivedi et al. (2011). Physical exercise has been suggested as a non-pharmacological approach for treating MDD (Krogh, Nordentoft,

Mohammad-Nezhad, and Westrin, 2010), whereby: 'Physical activity (PA) is defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure'(Howley, 2001). Physical exercise is a subclass of physical activity that is usually regular, planned and structured; it is undertaken with the intention of improving or maintaining physical fitness or health (Craft and Perna, 2004). There are many types of exercise, including cardiovascular exercise (aerobic), such as running and swimming, and resistance or muscular exercise, such as weightlifting (Howley, 2001).

Research has shown that physical exercise has the ability to improve the psychological status of healthy people (Scully, Kremer, Meade, Graham, and Dudgeon, 1998). Therefore, the US Department of Health and Human Services recommends 2.5 hours of aerobic exercise for all Americans (Physical Activity Guidelines Writing Group, 2008). In addition, physical exercise provides health benefits for many chronic diseases, such as diabetes and cardiovascular disease; thus, prevention and treatment plans for chronic diseases include regular exercise (Warburton et al. (2006). Further, a negative correlation has been consistently found between physical activity and depression symptoms (Galperet al., 2006; Hassménet al., 2000). This has led the United Kingdom Department of Health to include physical exercise as useful therapy for patients with mild depression (Exercise Referral Systems: A National Quality Assurance Framework, 2001).

Explanations for Antidepressant Effect of Physical Exercise

Many and varied hypotheses exist that might explain the pathophysiology of depression. Following is a discussion that attempts to explain the antidepressant effect of exercise based on these hypotheses.

Exercise and the monoamine hypothesis of **depression.** The monoamine hypothesis of depression, which emerged in the 1950s, proposes that deficiency in monoamine neurotransmitters, including serotonin, norepinephrine and dopamine, lead to MDD (Stahl, 1998). Therefore, antidepressant medications thatinclude the monoamine oxidase inhibitors, tricyclics and serotonin and norepinephrine reuptake inhibitors work by increasing the level of neurotransmitters (Het Rot, Collins, and Fitterling, 2009). In the same way, evidence suggests that physical activity can increase monoamine neurotransmitters, such as serotonin and norepinephrine. For instance, Greenwood et al. (2005) found that physical activity increases tryptophan, a precursor of serotonin, which leads to increased serotonin production and enhanced metabolism. Further, exercise decreases the level of branched chain amino acid that negatively effects the production of serotonin (Blomstrand, 2001). Further, exercise has been shown to increase the production of norepinephrine and trigger particular enzymes, including tyrosine hydroxylase, required for its production(Chaouloff, 1989).

Exercise and a neurotrophic hypothesis of **depression.** The neurotrophic hypothesis argues that MDD occurs because of impairments to the brain's ability to generate new neurons and support existing neurons in neurotransmitter systems (Duman, Heninger, and Nestler, 1997). This hypothesis increases the interest of researchers infinding whetherthere is a link between physical activity and factors that improve the generation and health of neurons. For instance, a review of animal and human experiments found that physical exercise increased neurotrophic factors, which are responsible for promoting cell multiplication and survival (van Praag, 2008).

The psychological consequences of exercise on depressive **symptoms.** Engaging in physical exercise increases a person's confidence about his or her physical skills. This confidence enhances various feelings, particularly feelings of control and independence. This could transfer into other parts of a person's life, including the ability to manage his or her depressive symptoms (Greistet al., 1979).

Reviewof the effect of physical exercise on MDD. Several reviews compared the effect of physical exercise on decreasing depressive symptoms among patients who have MDD or depression and other medical illnesses, such as heart problems. The majority of these studies compared the effect of physical exercise alone with usual treatments (antidepressant medication, ECT and psychotherapy) or with placebo. For instance, Bridle, Spanjers, Patel, Atherton and Lamb (2012) conducted a systematic review to assess the effect of physical exercise on aged patients with depression. It included studies that compared the effect of exercise with usual care or with placebo; it found that exercise led to reduction of depression symptoms among aged clinically depressed patients. Another systematic review was conducted byTu et al. (2014) to assess the effect of physical exercise on depression symptoms among patients with heart failure. This systematic review found that physical exercise led to symptom reduction among depressed patients with heart failure. However, none of these reviewsfocused exclusively on the effect of physical exercise as an adjunctive therapy to the usual treatment of depression. Adding physical exercise as an adjunctive therapy to the usual treatments could lead to an extra reduction in depressive symptoms compared with using the usual treatments alone. However, what evidence is there to support this?

There is a need to search the literature on the effect of physical exercise being added to the usual treatment of MDD or depressivesymptoms. Therefore, this integrative review has been conducted using specific electronic databases to identify whether using exercise as an adjunctive therapy to current MMD treatments would decrease depressive symptoms compared with using the usual treatment of MDD alone.

Aim of the Review

This integrative review aims to critically review the literature studying the effect of physical exercise as an adjunctive treatment to the usual treatment of depression in reducing depressive symptoms. It seeks to evaluate whether using physical exercise as an adjunctive therapy to usual treatments further reduces depressive symptoms compared with using usual treatments alone.

Method

An integrative review method, as described by Whittemore and Knafl(2005), was applied to study the effect of using physical exercise as an adjunctive therapy to the usual treatment of depression and whether it can further reduce depressive symptoms compared with using the usual treatment alone. This method allows for data to be gathered from primary research studies with different research methodologies; the integrative review process includes five steps: 1) problem identification, 2) literature search, 3) data evaluation, 4) data analysis and 5) presentation of the results. The subsequent chapter outlines the review methodology and includes search strategy and outcomes, review findings, review discussion and conclusions.

II. Methodology

Search Strategy

This section describes the search strategy used to identify required studies for this integrative review. It also details the screening process used to find the studies and to critically appraise the selected studies.

The search was conducted using the Scopus database, which includes a wide range of databases, such as Medline, the database with the most studies on treatment and trials, and the Cumulative Literature Index of Nursing and Allied Health Literature (CINAHL). PsycINFO was also used because it concentrates on research in psychology and related fields. The search was limited to English language studies, while there were no other search limits, such as date. The main keywords searched for were physical exercise, exercise therapy, aerobic exercise, adjunctive therapy, add-on therapy, depression, MDD, depressive disorder, major depression, antidepressant drugs and antidepressant agents. These keywords were combined with ‘and’ and ‘or’ to find the most relevant studies in these databases, as shown in Tables 1 and 2.

The search yielded 100 articles, including research studies and non-research papers. To narrow the search and select relevant studies, the following inclusion and exclusion criteria were used. Inclusion criteria were:

- studies comparing the effect of exercise as an adjunct to the standard treatmentof depression with a control group
- participants of studies were diagnosed with depression (by any diagnosis tool and with any severity of depression)
- participants of studies were aged 18 or above (with no upper age limit)
- depressive symptoms were the outcome measure of studies
- studies were in the English language.

The single exclusion criterion was:

- studies have participants with other psychiatric diagnoses, including schizophrenia and bipolar disorder, and medical diagnoses, including heart disease.

The initial search of the databases returned 100 articles. All articles were then screened for duplication; 20 duplicated articles were excluded. Following this, the abstracts of the remaining articles (n = 80) were screened. There were 10 systematic review and meta-analysis papers, 21 articles comparing two types of exercise and 20 articles comparing exercise and standard treatments of depression without exercise being adjunctive to the standard treatment. The full texts of the remaining articles (n = 29) were then assessed for eligibility. Twelve containedparticipants with other psychiatric diagnosis and 2 did not include depressive symptoms as an outcome measure. The remaining 15 studies were selected and appraised for this integrative review. Figure 1.1 summarises the selection process.

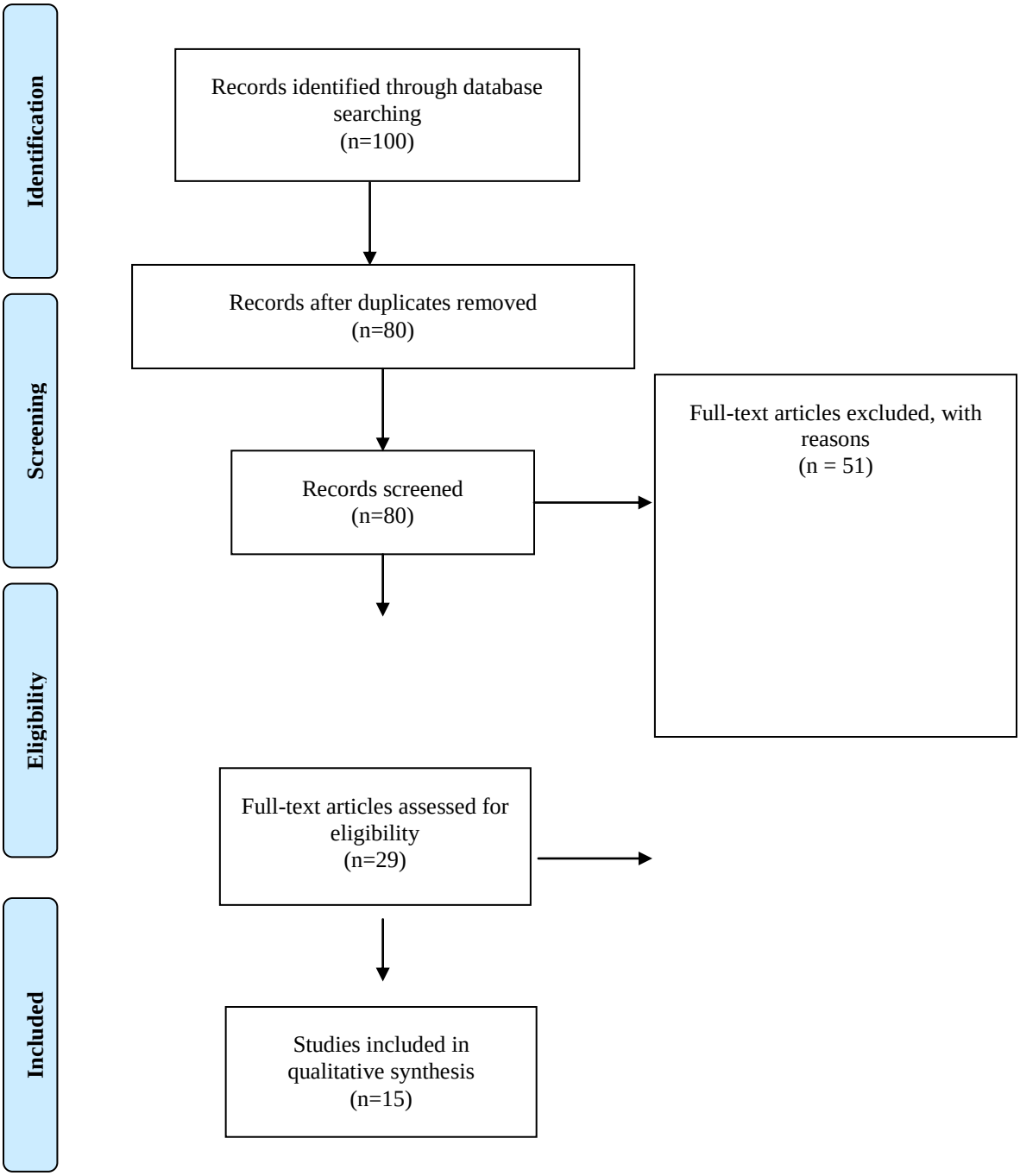

Figure 1.1.PRISMA 2009 flow diagram (adapted from Moher, Liberati, Tetzlaff, Altman, and The PRISMA Group [2009, p. e1000097]).

Quality Appraisal for All Identified Studies

Fifteen studies met the inclusion criteria; of these articles, 14 were RCTsand one was a pre-test/post-test study. Critical appraisal is needed to decide the quality of the identified studies to eliminate the risk of bias and ensure the rigour of these studies (Liberati et al. (2011). Therefore, the Critical Appraisal Skills Programme (CASP) checklist for RCTs was used to assess the quality of the selected studies (see Table 1of the Appendix) and a quality assessment tool for before–after (pre–post) studies was used for pre-test/post-test studies (see Table 2 of the Appendix). All studies had groups with similar basic characteristics, except for Mather et al. (2002), which had more female than male participants (however, there were no differences between the responses of males and females in this trial). In addition, all included RCT studies failed to keep patient blinds for the aim of the studies because of the nature of the intervention (exercise). This issue and other limitations of studies will be discussed in the discussion section of this review. However, all these studies consider with moderate quality studies to be included in this review as it met the majorities of tools criteria. Therefore, there were no excluded studies because of quality issues.

Search outcome

The literature search resulted in 15 studies that met the inclusion criteria and had good to moderate quality. While the integrative review method includes experimental and non-experimental research with different methodologies (Whittemore and Knafl,2005), the studies found by the search were unintentionally experimental, as 14 of these articles were RCTs and one of these studies was a pre-test/post-test study. The details of all these trials, including aims, methods, study participants, sample size and main results are available in Table 5 of the Appendix.

III. Results

Findings

Fifteen studies that met the inclusion criteria were included, and all of these studies were quantitative. Fourteen of these studies were RCTs and one was a pre-test/post-test design. All studies assessed the effect of adding physical exercise to the usual treatment of depression in patients with major depression disorder. The participants aged were different among the studies, as some studies focused only on an older population > 50year old while other studies had patients with ages from 18–60year old. The depression levels were also different; for instance, some studies focused specifically on severely depressed patients and others included populations with different depression levels. While these studies have many outcomes, this review focuses on the reduction of depressive symptoms as the main outcome.

Analytical Approach

The presentation of data in this chapter is based on two main themes: design of the exercise program and the characteristic of patients. The design of the exercise program theme includes four sub-themes: exercise types, duration of exercise program, place of exercise, and the starting time of exercise and the usual treatment. The characteristics of patients'theme includes three sub-themes: patient age group, depression severity and treatment resistance. These themes were selected to analyse the findings regarding whether the effect of exercise as an adjunctive therapy to the usual treatment of depression provides patients with significant symptom reductions compared with the usual treatment. The findings of these themes will be critically discussed below.

Design of Exercise Program Theme

The design of exercise program theme consists of four sub-themes, and the finding regarding the effect of exercise as an adjunctive therapy will be critically discussed among these sub-themes. The sub-themes include the types of exercise used by patients, such as aerobic or resistance, as some studies used aerobic exercise while others used aerobic with resistance exercise. They also include the duration of exercise,which concernshow long the program persists. Among included studies, the duration of the exercise programs included short (equal to or less than 4 weeks), medium (from 8–12 weeks) and long (16 weeks) in other studies. The place where the participants performed the exercise program is the third element, as some performed exercise in hospital, others in public places and other studies used the home as the place of exercise. The last element is the starting time of the exercise program and the usual treatment of depression.

Exercise type.

Mixed exercise: Aerobic and resistance ***exercise.*** Two RCT studies (Mather et al., 2002; Pfaff et al., 2014) examined the effect of adding to the usual treatment of depression for clinically depressed participants a mixed exercise program that consists of aerobic and resistance exercises. While two studies used the same exercise design and same frequency of 5 days per week, there were some differences in the exercise sessions. Pfaff et al. (2014) used exercises in different sessions, as participants had to perform aerobic exercise for 3 days

and resistance exercise for the other 2 days. Mather et al. (2002) used the two types of exercise in one session, as participants were asked to do the aerobic exercise first then the resistance exercise.

In addition, the outcomes of these experimental studies were inconsistent. Mather et al.(2002) found statistically significant differences between the treatment and control group, as 55% of the exercise group had a significant reduction in their depression symptoms score, compared with 30% in the control group. However, Pfaff et al. (2014) found no significant difference between intervention and control groups regarding their depression symptoms scores. The negative result of Pfaff et al. (2014) could be because their participants were not blind to the aim of the study, and so they may haveimproved their physical activity and changed their lifestyle after becoming participants.

Aerobic ***exercise.*** Aerobic exercise was used as an intervention among the remaining 13 studies. Some of these studies focused on one example of aerobic exercise, such as walking or jogging, while others offered a wide range of aerobic exercise examples to their participants and some of them focused on using exercise machines, such as stationary bicycles or treadmills.

Two studies,Schuch et al. (2015) and Schuch et al. (2011), provided three machine types (stationary bicycle, a treadmill or an elliptic) and patients had the opportunity to choose one of these machines to perform their exercise session. These studies were conducted in Brazil and their populations were the same in terms of depression severity (severe level) and age group (adult). The Hamilton Depression Rating Scale (HAM-D) was used to assess patients' depressive symptoms. HAM-Dis a questionnaire with 21 items about depression symptoms, such as suicidal ideation and insomnia; each item will score from 3 to 5 points (Hamilton, 1967). These studies reported a significant reduction in depressive scores on the HAM-D17 in favour of the exercise group. However, there were no significant differences between groups in response, which means 50% reductions in HAM-D 17 score.

Four trials (Carneiro et al., 2015; Danielsson et al., 2014; Martinsen et al., 1985; Siqueira et al., 2016) used a wide variety of aerobic exercise and gym equipment, such as stationary bikes, jumping ropes and treadmills, to evaluate the effect of using exercise as an adjunctive therapy to the usual treatment of depression. The population of each study was adult (young adult, middle-aged and older adult) with different depression levels (mild, moderate and severe). Three of these studies (Carneiro et al., 2015; Danielsson et al., 2014; Martinsen et al., 1985) supported using aerobic exercise as an adjunctive therapy to the usual treatment of depression. Danielsson et al. (2014)usedthe Montgomery-Åsberg Depression Rating Scale (MADRS) a valid and reliable scale (Montgomery and Åsberg, 1979) to assess the severity of depression among patients before and after the trial. This scale contains 10 items that are required to be filled in with psychiatrists after clinical interview with patients. Danielsson et al. (2014) found a significant difference between the treatment and control groups in the MADRS score in favour of the exercise group. In addition, this study used the Self-Reported Montgomery-ÅsbergDepression Rating Scale (MADRS-S) to confirm its result. This is a self-assessment version of the MADRS (Svanborg and Åsberg, 1994), and it also found a significant reduction in MADRS-S score in treatment population.

Further, Martinsen et al. (1985) used the Beck Depression Inventory (BDI; Beck and Steer, 1993b), a tool used for assessing the severity of depression. This scale is reliable and valid, as its reliability and validity have been confirmed among clinically depressed patients (Beck, Steer and Garbin, 1988). Conversely, Carneiro et al. (2015) usedthe Beck Depression Inventory-II (BDI-II; Beck, Steer and Brown, 1996b), which is a developed version of the BDI. The two RCTs reported a significant reduction in depression scores among treatment groups.

On the contrary, Siqueira et al. (2016) found no significant differences between treatment and control groups in depressive symptoms scores. This could be because, unlike the three trials, Siqueira et al. (2016) had a significant difference between groups regarding their medication dose. Indeed, participants in the treatment group received lower antidepressant doses compared with the control group, and this difference in participant characteristics might explain the lack of significant improvement in the treatment group.

Two included studies used walking as an example of an aerobic exercise intervention for an adult population, with mixed severity of depression (mild, moderate and severe). Mota-Pereira et al. (2011) found a significant reduction (> 30% and > 50%) in depression symptoms scores in the intervention group compared with the control group when they assessed the patients using multiple depression scales. Knubben et al. (2007) used the Centre for Epidemiologic Studies Depression (CES-D) Scale, which is a self-reported depression symptoms scale. They also supported using exercise as an adjunctive therapy, as they found a significant improvement in depression symptoms score in CES-D. They also found a significant clinical response regarding treatment groups.

Four studies included in this reviewallowed their participants to select between two types of aerobic exercise—walking or jogging inBabyak et al. (2000), Blumenthal et al. (1999) and Legrand and Neff (2015), and walking or dancing in Cerda, Cervelló, Cocca and Viciana (2011). The frequency and duration of sessions were different among these studies.

Legrand and Neff (2015) and Cerda et al. (2011) usedthree sessions per week and daily sessions for 10 days; these studies supported using exercise as an adjunctive therapy for adult depressed patients. They reported a significant reduction in BDI score and BDI-II score in treatment groups. In addition, a total of 57.1 members of the exercise group in Legrand and Neff(2015) achieved a response (measured as equal to or more than 50 reductions in BDI-II from baseline) compared with 10% of controls. In contrast, Babyak et al. (2000) and Blumenthal et al.(1999) found no statistically significant differences between treatment groups and control groups in DBI score and HAM-D score; they found that both groups experienced the same reduction in depression symptoms.

Duration of **exercise.** The duration of the exercise programs in the included studies varied from less than 1 month to 6 months. Based on this, exercise programs with a duration of 4 weeks or less will be considered short-term, exercise programs from 5 weeks to 12 weeks will be considered moderate-term and studies that used exercise for more than 12 weeks will be considered long-term studies.

Short-term exercise***programs.*** Exercise programs with a duration of 4 weeks or less will be considered short-term programs. Three studies conducted in different countries—France, Germany and Brazil—found that short-term exercise programs were effectiveas an adjunctive therapy to the usual treatment of depression in improving depression among an adult population with different severity levels of MDD. For instance, Knubben et al.(2007) and Legrand and Neff (2015) conducted a trial using a short-duration exercise program (10 days); the frequency of exercise was 30 minutes daily.While these studies used two different depression scales—CES-D in Knubben et al.(2007) and BDI-II in Legrand and Neff (2015)—the two RCTs reported significant improvements in depressive symptom scores in the intervention group. Siqueira et al. (2016) also conducted an RCT that utlised a 4-week exercise program; however, unlike 10-day studies, the frequency of exercise was 30 minutes a day, 4 days per week. This study found a trend towards reduction, as there were large differences between groups in depressive symptoms scores.In addition, thelackof statistically significant difference could be because of the small sample size of the study, as small sample sizes can effect statistical findings.

Moderate-duration studies.Moderate-duration exercise (8–12 week) programs were used in some studies, including in this intergrative review. However, these studies reported inconsistent findings regarding the effect of moderate exercise. For instance, Danielsson et al. (2014) and Mather et al. (2002) evaluted the effect of a four times weekly physical exercise program during 10 weeks on depressive symptoms. The populations of these studies were similar in depression severity, as both studies had patients with different depression severity levels(mild, moderate and severe). They were different in age groups, as Danielsson et al. (2014) had adult participants and Mather et al. (2002) had older adults. The findings of these RCTs support the effect of adding exercise as an adjunctive therapy to the usual treatment of depression, as they reported a significant improvement in depressive scores (> 30% and > 50% in MADRS) in treatment groups.

Additionally, a pre-test/post-test design study with a control group (Cerda et al., 2011) used a medium-duration exercise program (8 weeks) for women with moderate depression levels adds evidence about the effect of medium-duration exercise on depression. The study found that the depressive score of participants in the treatment group reduced signifcantly from moderate (at pre-test) to mild (at post-test) in the BDI depression tool, while the BDI score for the control group was the same pre-test and post-test. However, this study recruited only women and this limits the generalisability of the study's findings to the general population, which includes men.

Further, Mota-Pereira et al. (2011) conducted an RCT usinga 12-weekexercise program; Martinsen et al. (1985) used an 8-week exercise program. Both studies support the effect of using physical exercise as an adjunctive therapy to the usual treatment of depression among an adult population. While the participants of the studies were different, as Mota-Pereira et al. (2011) had treatment resistance and Martinsen et al. (1985)had no resistance to treatment, the participants in the treatment groups in the two studies achieved signifcant reductions in depressive scores. This was confirmed by more than one assessment tool, as each study used two tools to assess depression severity levels, such as BDI and HAM-D17.

In contrast, Pfaff et al. (2014) and Veale et al. (1992) conducted two RCTsthat uses medium-duration exercise programs (12 weeks) to assess the effect of adding a physical exercise program to the usual treatment of depression. While the types of exercise were different in these RCTs(mixed exercise in Pfaff et al. [2014] andaerobic exercise in Veale et al. [1992]), both studies found no significant difference in depressive symptoms scores between treatment groups and control groups.

Long-term studies.In two studies conducted in the United Kingdom (Babyak et al. [2000]; Blumenthal et al. [1999]), long-duration exercise programs (16 weeks) were found to not add any further benefit for depressed patients when usedas an adjunctive therapy to the usual treatment of depression. The sample of these studies consisted of volunteer partients with different severitylevels of MDD and they used similar exercise designs (aerobic exercise). After 16 weeks, these studies found no statistically significant differences between treatment groups and control groups regarding their depressive symptoms scores, as all groups showed improvements in their scores. This could be because these studies were unlike other included studies, as they

had three groups. In addition, participant patients in a combined group in Blumenthal et al. (1999) were unsatisfied with their group.

Place of exercise.

Home-based exercise.Home-based exercise means that patients perform the exercise in their home by utilising simple resources for exercise. Two included studies assessed the effect of home-based exercise among depressed patients with different severity levels: Pfaff et al. (2014) and Mota-Pereira et al.(2011). However, these studies were different in monitoring of their participants regarding their adherence to exercise, and in their findings. For instance, patients inPfaff et al. (2014) performed the exercise alone, without receiving supervision from the researchers; the study reported no significant difference in depressive scores (MADRS scores) between the treatment group and control group at 12 weeks and at 52weeks follow-up. The lack of significant differences between groups could be because participants in this trial did not have ongoing supervision, hence participants might not have performed the recommended exercises or they might have performed these exercises in the wrong way.

In contrast, participants in Mota-Pereira et al.(2011) performed four sessions of walking per week at home and one walk at the hospital gymnasium with supervision from a physical training teacher. Mota-Pereira et al.(2011) reported significant reductions (> 30% and >50%) in HAM-D 17 and BDI-II scores in the treatment group. In addition, there was a trend towards response and remission, as 21% of participants showed a response and 26% showed remission compared with none of the participants in the control group. The part-supervision in this trial ensured the participants' understanding of exercise instruction and increased participants' engagement in exercise, leading to the positive result.

Hospital-based ***exercise.*** Three included studies that used exercise for intervention groups at a suitable place inside hospitals yielded positive results. Schuchet al. (2011) andSchuchet al. (2015) conducted RCTs aimed at assessing the effect of adding structured exercise programs to the usual treatment to decrease depressive symptoms among an inpatient adult population with severe depression. Both studies ran the exercise inside the hospital and offered research staff to describe structured exercise programs for the participants, the proper way to use the exercise machines and to answer participants' questions regarding exercise. In addition, the participants were supervised by research staff to confirm the participants' adherence. At discharge, these studies reported a significant reduction in depressive scores in HAM-D 17 in favour of the exercise groups. However, these reductions did not exceed 50% of the baseline HAM-D 17 scores in the intervention groups, and this could be because of the small sample size, which effects the power to detect statistical difference.

Similarly, Knubbenet al. (2007) ran the exercise inside a hospital to evaluate the effect of an exercise program as an adjunctive therapy to the usual treatments to decrease depressive symptoms among an adult population with different depression levels. The patients were also supervised by study personnel to assess patient performance of exercise and answer participant questions regarding exercise. This study found a statistically significant difference between groups in depressive symptoms (more than 30% and less than 50%). In addition, it found a significantly larger proportion of patients in the treatment group achieved a clinical response.

Public-based ***exercise.*** Two included studies offered exercise for their participants in public areas, such as a faculty of sport or public park, and participants came to these places to perform the recommended exercise.

Carneiro et al. (2015) assessed the effect of adding exercise to the usual treatment of depressive symptomsamong an adult population with different depression levels. The exercise in this trial took place at the Faculty of Sport at the University of Porto. Participants performed the recommended exercise in the presence of a physical training teatcher to ensure participant adherence. The study found that patients located in exercise groups had a significant reduction in BDI-II.

Further, Legrand and Neff (2015) used a public park (outdoor area) as a place where their participants in an intervention group performed their exercise. The patients in this trial were under the supervision of the first author of this trial to ensure patient adherence to exercise and to answer participant questions. This trial found a significant improvement in BDI-II scores and a significant difference between groups in terms of their responses (measured as equal to or more than 50% reduction in BDI-II from baseline).

Starting the exercise and usual treatment at the same **time.** The majority of studies that assessed the antidepressant effects of physical exercise as an adjunctive therapy to the usual treatment of depression asked their participants to start their antidepressant medication before 4 to 6 weeks of the beginning of the trial, as the therapeutic effect of antidepressant medication usually required 4 to 6 weeks to begin. However, participants in Legrand and Neff(2015) used antidepressants for less than 2 weeks before starting the trial. This study found statistically significantdifference between exercise group and control group in response rates (measured as equal to or more than 50% reduction in BDI-II from baseline). This is because 57.1% of the exercise group achieved a response compared with 9.1% of the control group.

Patient Characteristics

Patients in the included studies were different in terms of age, depression severity and their resistance to treatment. Some studies studied the effect of exercise on depression among specific ages and others among specific depression severities. In addition, some of the studies focused on patients who were treatment resistant.

Treatment-resistant **patients.** Patients with MDD are considered resistant to treatment when they do not achieve significant improvements after using at least two types of antidepressant medications in adequate doses and durations (Berlim and Turecki, 2007). This condition is a concern among depressed patients, as the criteria for treatmentfor resistant depression was found to be met by60% of patients (Trivedi and Daly, 2008).

Two included studies, Mota-Pereira et al.(2011) and Mather et al. (2002), focused theirtrials on patients who did not respond to the usual treatment of depression, such as with antidepressant medications, for at least 6 weeks in Mather et al. (2002) and 9 months in Mota-Pereira et al.(2011). While the population ages were different in the two trials, being adult in Mota-Pereira et al.(2011) and only old age in Mather et al. (2002), the two studies supported using exercise as an adjunctive therapy to the usual treatment of depression. These studies reported significant differences between treatment groups and control groups in depressive symptoms scores (more than 30% and less than 50% on the HAM-D17).

Patients with severe depression ***levels.*** The majority of studies had populations with different depression severity levels, as they recruited participants who had mild, moderate and severedepression. However, some studies limited their participants to only one depression level, such as severe depression.

Findings on the effect of using exercise as an adjunctive therapy to the usual treatment among a severely depressed population were available in three studies that used the same methodological design of RCTs (Legrand and Neff, 2015; Schuch, Vasconcelos-Moreno, Borowsky, and Fleck, 2011; Schuch et al., 2015). Although these studies support the antidepressant effect of exercise as an adjunctive therapy, as they found significant reductions in depressive symptoms in treatment groups, the levels of reduction were different in each study. Legrand and Neff (2015) reported a significant difference between groups in terms of response (measured as equal to or more than a 50% reduction in BDI-II from baseline), as 57.1% of the exercise group achieved a response compared with 10% of the control group. However, Schuchet al. (2011) and Schuchet al. (2015) found significant differences between groups in depressive symptoms scores (more than 30% and less than 50% reductions in HAM-D 17). In addition, while 48% of the treatment group achieved remission (a decrease of 50% on the HAM-D 17) compared with 32% in the control group, there were no significant differences between these groups in the response (a decrease of 50% on the HAM-D 17) or remission rate (a score of 7 or less on the HAM-D 17). The lack of significance in response and remission rates in Schuchet al. (2011) andSchuchet al. (2015) could be due to the small sample sizes of these studies,which can affect the statistical power to detect significant differences between groups.

Old age.The majority of studies had a population of adults (18-70-year-old) though without categorising patients into young adult, middle-aged adults and old adult. However, some studies limited their participants to only old patients.

Findings on the effect of adding exercise interventions to the usual treatments to decrease depressive symptoms among an old population were available in four studies, with mixed results. Blumenthal et al. (1999) and Babyak et al. (2000) evaluated the effect of 16weeks of aerobic exercise on old populations with mixed depression levels. The methodological design of these studies were RCTs, with three arms, as each study had three group exercise groups receiving exercise only, a mixed group receiving exercise and usual treatments and a third control group that received the usual treatment. They found no significant differences between the group receiving exercise and the usual treatment and the control group in depressive symptoms scores assessed by HAM-D17. The lack of significant differences between the mixed groups and control group could be because the participants were volunteers interested in performing exercise. Therefore, the control group might have enjoyed physical activity in their lifestyle,meaning no difference between the treatment group and control group in intervention.

In contrast, a two-arm RCT conducted by Mather et al. (2002) to evaluate the effect of adding exercise to the usual treatment among an old population found a positive result. This trial used aerobic and resistance exercise, with patients performing these exercises twice a week for 10 weeks. It found a significant decline in the intervention group, as 55% of patients in the exercise group achieved a greater than 30% reduction in HAM-D 17 compared with 33% of the control group.

IV. Discussion

The included studies that using exercise as an adjunctive therapy to the usual treatment of depression were different in the design of exercise and patients Characteristics. The majority of included studies that using exercise as an adjunctive therapy to the usual treatment of depression found significant reductions of depression

symptoms among their patients. In this chapter, the effect using exercise as an adjunctive therapy will be discussed related to the main theme which were followed in result chapter.

Design of Exercise Program Theme

Type of Exercise

This review included studies that used aerobic and non-aerobic exercise, such as resistance exercise, as an intervention in assessing the antidepressant effects of exercise as an adjunctive therapy to the usual treatment of depression to decrease depressive symptoms. Both aerobic and non-aerobic exercise were found to be effective in reducing the depressive symptoms scores for patients with MDD. Therefore, this effect is not related to specific types of exercise and it may be related to the psychological effects of exercise on a patient, such as enhancing self-confidence, as he/she can learn new skills and this would transfer to the ability to deal with depression symptoms. These findings were also supported by previous research that compared the effect of different types of exercise on depression (see Bosscher [1993] and Sexton, Maere and Dahl [1989]) and by a systematic review that compared the effect of different types of exercise with antidepressants or placebos on depression (Lawlor and Hopker, 2001).

Further, this conclusion offers patients a wide variety of exercise and might enhance patient desire to engage in exercise and also patient adherence to exercise, as they can choose based on their preferences. In addition, because the types of exercise do not affect the antidepressant effect, this gives hospitals the ability to choose suitable exercise based on their patients' preferences and on their economic ability or budget.

The Duration of Exercise

The reviewed papers addressed the effect of exercise as an adjunctive therapy across three different exercise durations: short (equal to or less than 4 weeks), medium (5–12 weeks) and long (equal to or more than 16 weeks). The majority of short- and medium-duration exercise studies reported a significant improvement in depressive symptoms scores, assessed by different reliable and valid assessment tools, such as HAM-D and BDI, among adults with different severity levels of depression.

However, some short- and medium-duration studies failed to support the antidepressant effects of exercise when used as an adjunctive therapy to the usual treatment of depression because of methodology faults. For instance, Siqueira et al. (2016), a 4-week study, found no statistically significant differences between treatment groups and control group. This could be because of the small sample size of the study, whichmay have influencedthe ability to detect statistically significant differences.

In contrast, long-duration exercise (16 weeks) was found not to be effective in decreasing depressive symptoms. Babyak et al. (2000) and Blumenthal et al. (1999) reported no signifcant difference in depressive symptoms scores between treatment and control groups. However, that could be related to factors other than duration. For instance, these studies were three-arm RCTs; each study had threegroups: an exercise group, a medication group, and a combined exercise and medication group.This was not the case with studies of short- and medium-duration. Babyak et al. (2000) mentioned that participants in the combined group were unsatisfied at being in a combined group as they felt that medication might interfere with the effect of exercise. Patient expections could have been a psychological factor that negatively effected the combined group.

While this review found short- and medium-duration exercise to be effective for depression, more so than long-duration exercise, some authors have claimed that longer exercise programs lead to further improvements (Morilla, 2001). In addition, the lack of ongoing assessment during included trials (short-, medium- and long-term) leads to an inability to identify the best duration exercise program in terms of symptom reduction. Therefore, to identify the optimal durition of an exercise program, further studies are required to investigate several assessments during the trial.

Further, MDD is a recurrent disorder, with 50% to 80% of patients experiencing a relapse after achieving recovery (Ciechanowski, Katon, and Russo, 2000; Rush et al., 2006). While short- and medium-duration exercise was found to be effective in decreasing depressive symptoms among clinically depressed patients, the sustainability of this effect is unknown. This is because none of the studies supporting the effect of exercise reported the results of long-term follow-up. They either only assessed patients immediately at the end of trials and did not have a long follow-up period such as Knubben et al.(2007) and Legrand and Neff (2015), or they did not report the results for the follow-up, such as Mather et al. (2002). The lack of long-term follow-up for patients means it is not clear how long this positive effect will continue over time and when patients are likely to relapse. Therefore, future studies with a long-term follow-up period are required to identify how long this positive effect continues.

Place of Exercise

Hospitals and public areas were found to be effective places to perform exercise, as many RCTs using different reliable and valid assessment tools reported significant improvements in depressive symptoms among

theirparticipants after they performed exercise in these places. This is because these places were well prepared for performing exercise. For instance, they had a physical training teacher who assisted patients to understand how to perform the exercises in the best way. It could also provide patients with motivational classes to increase patients' enthusiasm to perform exercise.

In contrast, the results for home-based exercise were inconsistent. Pfaff et al. (2014), a study with totally home-based exercise, failed to fing significant differences between treatment and control groups. This could be due to the lack of ongoing supervision of home-based exercise, meaning patient adherence to exercise is unknown. However, Mota-Pereira et al.(2011), a partly home-based exercise study in which patients performed four exercise sessions alonein their homes and then one session in hospital under supervision, reported positive results regarding the effect of using exercise to improve depressive symptoms. Therefore, home-based exercise could be effective if patients have some exercise sessions ina prepared place, such as the gym in a hospital. These sessions would motivate the patient and increase their adherence to performing exercise. In addition, it provides patients with the opportunity to ask physical training teachers questions regarding exercise and ensures they perform the exercises properly.

The Starting Time of the Exercise and Usual Treatment

Using exercise as an adjunctive therapy to the usual treatment for patients after the first 2 weeks of using antidepressant medication appears to be effective in reducing depressive symptoms quickly after 10 days of exercise. Legrand and Neff (2015) reported a significant reduction in depressive scores in the treatment group among a population using antidepressants for less than 2 weeks. This study could improve the clinical practice, as MMD patients usually show no response rate during the first weeks of using antidepressant medication. Therefore, using exercise as an adjunctive therapy could provide the patients with fast antidepressant effects .However, this is the first study to focus on MMD patients who used antidepressants for less than 2 weeks, and more trials are needed to confirm its findings.

Patient Characteristics

Treatment-resistant patients:

Using exercise as an adjunctive therapy to the usual treatment of depression found to be effective for treatment-resistant patients. This was confirmed by Mota-Pereira et al. (2011) and Mather et al. (2002) as these studies reported significant differences between treatment groups and control groups in depressive symptoms scores. However, the improvement achieved in both trials did not exceed 50% on the HAM-D 17 total score; this could be due to the nature of the patients, as they were treatment-resistant patients.

Severe Depression

The effect of combined treatment on severe depression levels was found to be effective, especially in this group. Three studies that only included severely depressed patients were examined. Based on the findings of these studies, combined exercise and usual treatments add greater benefits for depressed patients, as treatment groups achieved significant reductions in their depressive symptoms scores. In addition, while all studies used aerobic exercise and had participants of the same age group (adult) and depression level (severe), the levels of reduction of depressive symptoms were different among these studies. Schuchet al. (2011) and Schuchet al. (2015) found only significant reduction without achieved response and (Legrand and Neff, 2015) found significant reduction and response rates. This could be due tothe small sample sizeofSchuchet al. (2011) andSchuchet al. (2015).

Further, patients with MDD are categorised by depression tools based on theirsymptomseverityaccording to three levels: mild, moderate and severe. Patient response to the effect of exercise as an adjunctive therapy to the usual treatment could be different according to theirseverity level. However, it is difficult to know whether combined exercise and usual treatments had different effects among different severity levels, because the majority of studies included participants with different levels without separating their populations into groups based on severity level. Therefore, each study reported their findings in general for all participants, without presenting findings based on each depression level.

Older Patients

The effect of using exercise as an adjunctive therapy to usual treatments was inconsistent. This is because two studies found that this did not provide large reductions insymptoms compared with usual treatments. Blumenthal et al. (1999) and Babyak et al. (2000) found no significant difference between combined treatment groups and control groups among old-age populations with mixed depression levels. However, the lack of significance in these studies could be becauseparticipants were volunteers and wereinterested in performing exercise.Therefore, the control group might have enjoyed physical activity in theirnormal lifestyle, resulting in no difference between treatment groups and control groups in terms of intervention.

However, whether the effect of combined treatment will be different based on age group (younger, middle-aged and older adult) is difficult to determine, because the majority of included studies had participants from 18 to 70 years old. They did not differentiate between age groups when they reported their findings to identify whether the effects of combined treatment were different or similar between these groups.

V. Conclusion

MDD is a complex mood disorder and it is predicted to be a major contribution to the global burden of disease by 2020. Current treatment options for depression are limited and have many side effects. Using exercise as an adjunctive therapy to the usual treatment of depression has received significant attention recently. This integrative review was conducted to evaluate whether using physical exercise as an adjunctive therapy to the usual treatments leads to extra reductions in depressive symptoms compared with using the usual treatments alone.

An integrative review was conducted by a systematic search in the Scopus and PsycINFO databases. The search yielded 100 articles, which were narrowed to 15 articles based on inclusion and exclusion criteria. The identified studies were all quantitative, as 14 were RCTs and one was a pre-test/post-test design. Because there were differences in exercise program design and patient characteristics among these studies, the findings and discussion of this review were presented based on two main themes: design of exercise program (including exercise types, duration of exercise program, place of exercise and starting the exercise and the usual treatment at the same time) and the characteristics of patients (including treatment resistance, age and severity of depression).

This review found that using exercise as an adjunctive therapy to the usual treatment of depression provided patients with significant reductions of depression symptoms. This effect was not related to specific exercise types, as both aerobic and resistance exercise decreased patient depression symptoms. However, this effect was different based on factors such as exercise duration and place. In addition, this review was unable to determine whether the effect of using exercise as an adjunctive therapy to the usual treatment might be different based on the severity of depression and patient age.

This review suggests that using exercise as an adjunctive therapy to the usual treatments of depression can be an effective way to improve the depressive symptoms among adult patients with MDD. It can offer beneficial effects for patients with MDD, more so than using the usual treatments alone as It can decrease the severity of patient symptoms and decrease the duration of hospitalisation.

Limitations and future studies:

There were a number of limitations in this integrative review. First, many studies did not follow up their participants after the end of trials, which effects conclusions about the sustainability of the effect of exercise. Therefore, research with longer follow-up periods are recommended to better determine the sustainability of the effect of exercise. Second, some studies included small sample sizes; this can affect the detection of significant difference between treatment groups and control groups. Therefore, large sample size studiesare required. Third, many studies included patients with three levels of depression without putting the participants into groups based on severity. This influences the ability to conclude whether the effect of exercise as an adjunctive therapy would be different among the three severity levels. Therefore, future studies should report findings based on patient severity levels to identify the effect of exercise on each depression level.

Implications

This review provides a reason for mental health hospitals to use short- or medium-duration supervised exercise programsas an adjunctive therapy to usual treatments, as it was found that this significantly reduced patients' depressive symptoms—more so than using the usual treatments alone. Hospitals can adopt such exercise as an adjunctive therapy to the usual treatments. It might also decrease the duration of hospitalisation for inpatients, as it was found to lead to larger reductions of depressive symptoms than using the usual treatments alone. It could also decrease hospital expenses in depression treatment, as exercise is a cost-effective form of therapy compared with other kinds of treatments, such as ECT. Further, it could decrease the need for high doses of antidepressant medicationsto achieve the required effect.

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References

[1]. American Psychiatric Association (APA). (2010). *APA practice guideline for the treatment of patients with major depressive disorder* (3rd ed.).

[2]. Babyak, M., Blumenthal, J. A., Herman, S., Khatri, P., Doraiswamy, M., Moore, K., … Krishnan, K. R. (2000). Exercise treatment for major depression: Maintenance of therapeutic benefit at 10 months. *Psychosomatic Medicine, 62*(5), 633–638.

[3]. Berlim, M. T., & Turecki, G. (2007). Definition, assessment, and staging of treatment-resistant refractory major depression: A review of current concepts and methods. *Can J Psychiatry, 52*(1), 46–54. doi:10.1177/070674370705200108

[4]. Blomstrand, E. (2001). Amino acids and central fatigue. *Amino Acids, 20*(1), 25–34.

[5]. Blumenthal, J. A., Babyak, M. A., Moore, K. A., Craighead, W. E., Herman, S., Khatri, P., … Krishnan, K. R. (1999). Effects of exercise training on older patients with major depression. *Arch Intern Med, 159*(19), 2349–2356.

[6]. Bosscher, R. J. (1993). Running and mixed physical exercises with depressed psychiatric patients. *Int J Sport Psychol, 24*,170–184.

[7]. Bridle, C., Spanjers, K., Patel, S., Atherton, N. M., & Lamb, S. E. (2012). Effect of exercise on depression severity in older people: Systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry, 201*(3), 180–185. doi:10.1192/bjp.bp.111.095174

[8]. Carneiro, L. S. F., Fonseca, A. M., Vieira-Coelho, M. A., Mota, M. P., & Vasconcelos-Raposo, J. (2015). Effects of structured exercise and pharmacotherapy vs. pharmacotherapy for adults with depressive symptoms: A randomized clinical trial. *Journal of Psychiatric Research, 71*, 48–55. doi:http://doi.org/10.1016/j.jpsychires.2015.09.007

[9]. Cerda, P. D. L., Cervelló, E., Cocca, A., & Viciana, J. (2011). Effect of an aerobic training program as complementary therapy in patients with moderate depression. *Perceptual and Motor Skills, 112*(3), 761–769. doi:doi:10.2466/02.15.PMS.112.3.761-769

[10]. Chaouloff, F. (1989). Physical exercise and brain monoamines: A review. *Acta Physiol Scand, 137*(1), 1–13. doi:10.1111/j.1748-1716.1989.tb08715.x

[11]. Cichon, S., Craddock, N., Daly, M., Faraone, S. V., Gejman, P. V., Kelsoe, J., Sullivan, P. F. (2009). Genomewide association studies: history, rationale, and prospects for psychiatric disorders. *The American Journal of Psychiatry*, 166(5), 540-556.

[12]. Ciechanowski, P. S., Katon, W. J., & Russo, J. E. (2000). Depression and diabetes: Impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med, 160*(21), 3278–3285.

[13]. Danielsson, L., Papoulias, I., Petersson, E.-L., Carlsson, J., & Waern, M. (2014). Exercise or basic body awareness therapy as add-on treatment for major depression: A controlled study. *Journal of Affective Disorders, 168*, 98–106. doi:http://doi.org/10.1016/j.jad.2014.06.049

[14]. American Psychiatric Association. (1994).Diagnostic and statistical manual of mental disorders: DSM-IV [Internet] 4th ed. [e-book].Retrieved from http://www.psychiatryonline.com/DSMPDF/dsm-iv.pdf [Accessed 8 May 2017]

[15]. Duman, R. S., Heninger, G. R., & Nestler, E. J. (1997). A molecular and cellular theory of depression. *Arch Gen Psychiatry, 54*(7), 597–606.

[16]. Ebmeier, K. P., Donaghey, C., & Steele, J. D. (2006). Recent developments and current controversies in depression. Lancet, 367(9505), 153-167. doi:10.1016/s0140-6736(06)67964-6

[17]. Greenwood, B. N., Foley, T. E., Day, H. E., Burhans, D., Brooks, L., Campeau, S., & Fleshner, M. (2005). Wheel running alters serotonin (5-HT) transporter, 5-HT1A, 5-HT1B, and alpha 1b-adrenergic receptor mRNA in the rat raphe nuclei. *Biol Psychiatry, 57*(5), 559–568. doi:10.1016/j.biopsych.2004.11.025

[18]. Greist, J. H., Klein, M. H., Eischens, R. R., Faris, J., Gurman, A. S., & Morgan, W. P. (1979). Running as treatment for depression. *Comprehensive Psychiatry, 20*(1), 41–54. doi:https://doi.org/10.1016/0010-440X(79)90058-0

[19]. Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *The British Journal of Social and Clinical Psychology, 6*(4), 278.

[20]. Het Rot, M. A., Collins, K. A., & Fitterling, H. L. (2009). Physical exercise and depression. *Mount Sinai Journal of Medicine, 76*(2), 204–214. doi:10.1002/msj.20094

[21]. Howley, E. T. (2001). Type of activity: Resistance, aerobic and leisure versus occupational physical activity. *Medicine and Science in Sports and Exercise, 33*(6 Suppl.), S364.

[22]. Knubben, K., Reischies, F. M., Adli, M., Schlattmann, P., Bauer, M., & Dimeo, F. (2007). A randomised, controlled study on the effects of a short- term endurance training programme in patients with major depression. *British Journal of Sports Medicine, 41*(1), 29–33. doi:10.1136/bjsm.2006.030130

[23]. Krogh, J., Nordentoft, M., Mohammad-Nezhad, M., & Westrin, A. (2010). Growth hormone , prolactin and cortisol response to exercise in patients with depression. The Journal of Affective Disorders, 125(1-3), 189-197. doi:10.1016/j.jad.2010.01.009

[24]. Kurian, B. T., Greer, T. L., & Trivedi, M. H. (2009). Strategies to enhance the therapeutic efficacy of antidepressants: targeting residual symptoms. Expert Review of Neurotherapeutics Journal, 9(7), 975-984. doi:10.1586/ern.09.53

[25]. Lawlor, D. A., & Hopker, S. W. (2001). The effectiveness of exercise as an intervention in the management of depression: Systematic review and meta-regression analysis of randomised controlled trials. *British Medical Journal, 322*(7289), 763–763.

[26]. Legrand, F. D., & Neff, E. M. (2015). Efficacy of exercise as an adjunct treatment for clinically depressed inpatients during the initial stages of antidepressant pharmacotherapy: An open randomized controlled trial. *Journal of Affective Disorders, 191*, 139–144. doi:10.1016/j.jad.2015.11.047

[27]. Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., . . . Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Medicine, 6(7), e1000100. doi:10.1371/journal.pmed.1000100

[28]. Martinsen, E. W., Medhus, A., & Sandvik, L. (1985). Effects of aerobic exercise on depression: A controlled study. *British Medical Journal (Clinical Research Edition), 291*(6488), 109–109.

[29]. Mather, A. S., Rodriguez, C., Guthrie, M. F., McHarg, A. M., Reid, I. C., & McMurdo, M. E. (2002). Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: Randomised controlled trial. *Br J Psychiatry, 180*, 411–415.

[30]. Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry, 134*, 382–389.

[31]. Morilla, M. (2001). Beneficiospsicológicos de la actividadfísica y el deporte. Educaciónfísica y deportes. *Revista Digital, 7*(43). Extraido el 23 de Noviembre, 2008.

[32]. Mota-Pereira, J., Silverio, J., Carvalho, S., Ribeiro, J. C., Fonte, D., & Ramos, J. (2011). Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. *J Psychiatr Res, 45*(8), 1005–1011. doi:10.1016/j.jpsychires.2011.02.005

[33]. Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., &Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet, 370(9590), 851-858. doi:10.1016/s0140-6736(07)61415-9

[34]. Nemeroff, C. B. (2007). Prevalence and management of treatment-resistant depression. The Journal of Clinical Psychiatry, 68 Suppl 8, 17-25.
[35]. Pfaff, J. J., Alfonso, H., Newton, R. U., Sim, M., Flicker, L., & Almeida, O. P. (2014). ACTIVEDEP: A randomised, controlled trial of a home-based exercise intervention to alleviate depression in middle-aged and older adults. *British Journal of Sports Medicine, 48*(3), 226–232. doi:10.1136/bjsports-2013-092510
[36]. Rush, A. J., Bernstein, I. H., Trivedi, M. H., Carmody, T. J., Wisniewski, S., Mundt, J. C., … Fava, M. (2006). An evaluation of the quick inventory of depressive symptomatology and the Hamilton Rating Scale for depression: A sequenced treatment alternatives to relieve depression trial report. *Biol Psychiatry, 59*(6), 493–501. doi:10.1016/j.biopsych.2005.08.022
[37]. Schuch, F. B., Vasconcelos-Moreno, M. P., Borowsky, C., & Fleck, M. P. (2011). Exercise and severe depression: Preliminary results of an add-on study. *J Affect Disord, 133*(3), 615–618. doi:10.1016/j.jad.2011.04.030
[38]. Schuch, F. B., Vasconcelos-Moreno, M. P., Borowsky, C., Zimmermann, A. B., Rocha, N. S., & Fleck, M. P. (2015). Exercise and severe major depression: Effect on symptom severity and quality of life at discharge in an inpatient cohort. *J Psychiatr Res, 61*, 25–32. doi:10.1016/j.jpsychires.2014.11.005
[39]. Sexton, H., Maere, A., & Dahl, N. H. (1989). Exercise intensity and reduction in neurotic symptoms. A controlled follow-up study. *Acta Psychiatr Scand, 80*(3), 231–235.
[40]. Siqueira, C. C., Valiengo, L. L., Carvalho, A. F., Santos-Silva, P. R., Missio, G., de Sousa, R. T., … Machado-Vieira, R. (2016). Antidepressant efficacy of adjunctive aerobic activity and associated biomarkers in major depression: A 4-week, randomized, single-blind, controlled clinical trial. *PLoS ONE, 11*(5), e0154195. doi:10.1371/journal.pone.0154195
[41]. Stahl, S. M. (1998). Basic psychopharmacology of antidepressants, part 1: Antidepressants have seven distinct mechanisms of action. *J Clin Psychiatry, 59*(suppl. 4), 5–14.
[42]. Svanborg, P. and Åsberg, M. (1994). A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *ActaPsychiatricaScandinavica, 89*, 21–28. doi:10.1111/j.1600-0447.1994.tb01480.x
[43]. Trivedi, M. H. & Daly, E. J. (2008). Treatment strategies to improve and sustain remission in major depressive disorder. *Dialogues in Clinical Neuroscience, 10*, 377–384.
[44]. Trivedi, M. H., & Daly, E. J. (2008). Treatment strategies to improve and sustain remission in major depressive disorder. *Dialogues Clin Neurosci, 10*(4), 377–384.
[45]. Trivedi, M. H., Greer, T. L., Church, T. S., Carmody, T. J., Grannemann, B. D., Galper, D. I., Blair, S. N. (2011). Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. *Journal of Clinical Psychiatry,72*(5), 677–684. doi:10.4088/JCP.10m06743
[46]. Tu, R. H., Zeng, Z. Y., Zhong, G. Q., Wu, W. F., Lu, Y. J., Bo, Z. D., … Yao, L. M. (2014). Effects of exercise training on depression in patients with heart failure: A systematic review and meta-analysis of randomized controlled trials. *Eur J Heart Fail, 16*(7), 749–757. doi:10.1002/ejhf.101
[47]. van Praag, H. (2008). Neurogenesis and exercise: Past and future directions. *Neuromolecular Med, 10*(2), 128–140. doi:10.1007/s12017-008-8028-z
[48]. Veale, D., Le Fevre, K., Pantelis, C., de Souza, V., Mann, A., & Sargeant, A. (1992). Aerobic exercise in the adjunctive treatment of depression: A randomized controlled trial. *J R Soc Med, 85*(9), 541–544.
[49]. World Health Organization. (2017). Depression. Retrieved from http://www.who.int/mediacentre/factsheets/fs369/en/

Appendix

Table 1
Search within Scopus

Search terms		**Document results**
1.	Physical exercise	156,191
2.	Exercise therapy	102,718
3.	Aerobic exercise	28,410
4.	Adjunctive therapy	18,495
5.	Add-on therapy	25,166
6.	Major depressive disorder	72,998
7.	Depressive disorder	132,944
8.	Major depression	178,440
9.	Antidepressant agents	109,710
10.	Antidepressant drugs	91,938
A:1–2–3 combined with or		232,982
B: 4–5 combined with or		34,604
C:6–7–8–9–10 combined with or		330,666
A B C combined with and		60

Table 2:
Search within PsycINFO

Search terms		Document results
1.	Physical exercise	20,500
2.	Exercise therapy	14,000
3.	Aerobic exercise	28,410
4.	Adjunctive therapy	10,000
5.	Add-on therapy	12,000
6.	Major depressive disorder	50,000
7.	Depressive disorder	43,944
8.	Major depression	101,440

9.	Antidepressant agents	70,710
10.	Antidepressant drugs	65,938
A: 1–2–3 combined with or		503,10
B: 4–5 combined with or		12000
C: 6–7–8–9–10 combined with or		262,102
A B C combined with and		40

Table 3

Clinical Appraisal Skills Programme—CASP Tool/RCT Checklist (2013)

	Question										
Author	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Schuch et al. (2015)	Yes	Yes	Yes	Only health workers were blinded.	Yes	Yes	Decrease depressive symptoms	95% Cl	Yes	Yes	Yes
Blumenthal et al. (1999)	Yes	Yes	Yes	Only health workers were blinded	Yes	Yes	Decrease depressive symptoms	Can't tell	Yes	Yes	Yes
Mather et al.(2002)	Yes	Yes	Yes	Only health workers were blinded	No	Yes	Decrease depressive symptoms	95% Cl	Yes	Yes	Yes
Siqueira et al. (2016)	Yes	Yes	Yes	Only health workers were blinded	Yes	Yes	Decrease depressive symptoms in treatment and control group	Can't tell	Yes	Yes	Yes
Martinsen, Medhus, and Sandvik(1985)	Yes	Yes	Yes	Can't tell	Yes	Yes	Decrease depressive symptoms	Can't tell	Yes	Yes	Yes
Pfaff et al.(2014)	Yes	Yes	Yes	Can't tell	Yes	Yes	Decrease depressive symptoms	95% Cl	Yes	Yes	Yes
Knubben et al. (2007)	Yes	Yes	Yes	Only health workers were blinded	Yes	Yes	Decrease depressive symptoms	Can't tell	Yes	Yes	Yes
Mota-Pereira et al. (2011)	Yes	Yes	Yes	Only health workers were blinded	Yes	Yes	Decrease depressive symptoms	Can't tell	Yes	Yes	Yes
Carneiro, Fonseca, Vieira-Coelho, Mota, and Vasconcelos-Raposo (2015)	Yes	Yes	Yes	No	Yes	Yes	Decrease depressive symptoms	95% Cl	Yes	Yes	Yes
Legrand and Neff (2015)	Yes	Yes	Yes	Can't tell	Yes	Yes	Decrease depressive symptoms	Can't tell	Yes	Yes	Yes
Danielsson, Papoulias, Petersson, Carlsson, and Waern (2014)	Yes	Yes	Yes	Only health workers were blinded	Yes	Yes	Decrease depressive symptoms	95% Cl	Yes	Yes	Yes
Babyak et al. (2000)	Yes	Yes	Yes	Can't tell	Yes	Yes	Decrease depressive symptoms	Can't tell	Yes	Yes	Yes
Schuch et al. (2015)	Yes	Yes	Yes	Only health workers were blinded	Yes	Yes	Decrease depressive symptoms	95% Cl	Yes	Yes	Yes

	Question										
Author	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Veale et al. (1992)	Yes	Yes	Yes	Only health workers were blinded	Yes	Yes	Decrease depressive symptoms	Can't tell	Yes	Yes	Yes

Yes = identified in journal article
No = not identified in journal article
Can't tell = authors not clear/not specified
1. Did the trial address a clearly focused issue?
2. Was the assignment of patients to treatments randomised?
3. Were patients, health workers and study personnel blinded?
4. Were groups similar at the start of the trial?
5. Aside from the experimental intervention, were the groups treated equally?
6. Were all of the patients who entered the trial properly accounted for at its conclusion?
7. How large was the treatment effect? (Is the primary outcome clearly measured?)
8. How precise was the estimate of the treatment effect?
9. Can the results be applied in your context?
10. Were all clinically important outcomes measured?
11. Are the benefits worth the harms and cost?

Table 4:
Quality Assessment Tool for Before–After (Pre)Post) Studies

Criteria	**Yes**	**No**	**Other**
Was the study question or objective clearly stated?	Yes		
Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes		
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes		
Were all eligible participants who met the prespecified entry criteria enrolled?	Yes		
Was the sample size sufficiently large to provide confidence in the findings?	Yes		
Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes		
Were the outcome measures prespecified, clearly defined, valid, reliableandassessed consistently across all study participants?	Yes		
Were the people assessing the outcomes blinded to the participants' exposures/interventions?			Unknown
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?		No	
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-topost- changes?	Yes		
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes		
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?		No	

Table 5:
Results Table

Source	**Study aim**	**Study method/design**	**Subject**	**Main findings**
Knubben et al. (2007)	To evaluate the short- term effects of exercise in patients with major depression.	Quantitative—RCT study. PRMS tool and was used to assess patient depressive symptoms before and after the trial.	A total of 38 patients with MDD who scored > 12 on the BRMS, which equals moderate to severe depression, were randomly assigned into two groups: intervention group (n = 20) who received exercise + standard clinical antidepressant and control group (n = 16) who receives standard clinical antidepressant.	A significant reduction in depressive symptoms score (by using BRMS) was found in exercise group. In addition, a significant clinical response (reduction in the BRMS scores by more than six points) was found in treatment group.
Schuch et al. (2015)	To evaluate the effects of add-on exercise on the usual treatment of severely depressed inpatients.	Quantitative—RCT study. HAM-D 17 tool was used to assess patient depressive symptoms	A total of 50 patients with MDD who scored higher than 25 on HAM-D, equal to severe depression, were randomly assigned into two groups:	This study found a significant difference between groups in depressive score in HAM-D 17 in favour of the exercise group. However, none of

Source	Study aim	Study method/design	Subject	Main findings
		before and after the trial.	intervention group (n = 25) who received aerobic exercise + usual treatment of depression (consisting of antidepressant medication and or ECT) and control group (n = 25) who received usual treatment of depression.	these studies found differences between groups in the response (a decrease of 50% on the HAM-D 17) and remission rate (score of 7 or less on the HAM-D 17).
Legrand and Neff (2015)	To evaluate the effects of a short (10-day) add-on endurance-training intervention in hospitalised MDD patients on antidepressant medication for less than 2 weeks.	Quantitative—RCT study. BDI-II was used to assess patient depressive symptoms before and after the trial.	A total of 35 patients with MDD who scored 29 or more on the BDI-II, equal to severe depression, were randomly assigned into three groups: intervention group (n = 14) who received aerobic exercise + usual treatment of depression (consisting of antidepressant medication), control group (n = 10) who received usual treatment of depression and placebo group (n = 11) who received short-time stretching exercise as placebo + usual treatment of depression.	This study found a significant improvement in BDI-II scores in treatment group. It also found a significant difference between groups in terms of response (measured as equal to or more than 50% reduction in BDI-II from baseline) as 57.1% of exercise group achieved response compared with 10 % of control group.
Danielsson et al. (2014)	Evaluates the effects of two different add-on treatments: exercise and basic body awareness therapy.	Quantitative—experimental design RCT study.MADRS was used to assess patient depressive symptoms before and after the trial.	A total of 62 patients with MDD were randomly assigned into three group: exercise groups (n = 22) who received aerobic exercise + usual treatment of depression (consisting of antidepressant medication), basic body awareness therapy group (n = 20) who received basic body awareness therapy + usual treatment of depression and control group (n = 20) who received usual treatment of depression.	This study found a significant improvement in depressive score in treatment group. However, there were no significant differences between groups regarding response and remission rate.
Mather et al. (2002)	To determine whether exercise is effective as an adjunct to antidepressant therapy in reducing depressive symptoms in older people.	Quantitative—experimental design RCT study.HAM-D 17 tool was used to assess patient depressive symptoms	A total of 86 patients with MDD who scored 10 or more on the Geriatric Depression Scale were randomly assigned into exercise group (n = 43) who received aerobic exercise + usual treatment of depression (consisting of antidepressant medication) and control group (n = 43).	This study found a significant ≥ 30% improvement in depressive score in treatment group.
Carneiro et al. (2015)	To measure the effect of a structured physical exercise program as a complement to antidepressant medication in the treatment of women with depression.	Quantitative—experimental design RCT study.BDI-II tool was used to assess patient depressive symptoms.	A total of 29 patients with MDD were randomly assigned into exercise group (n = 9) who received aerobic exercise + usual treatment of depression (consist of antidepressant medication) and control group (n = 10).	A significant reduction in depressive symptoms score (using BDI-II scale) in treatment group.
Siqueira et al. (2016)	To evaluate the antidepressant efficacy of adjunctive aerobic activity in association with pharmacotherapy.	Quantitative—experimental design RCT study. Depression severity was assessed using the HAM-D.	A total of 57 patients with MDD were randomly assigned into exercise group (n = 29) who received aerobic exercise + usual treatment of depression (consist of antidepressant medication) and control group (n = 28).	No significant differences between treatment and control groups in depressive symptoms scores.
Martinsen et al. (1985)	Assess the antidepressive effect of systematic aerobic exercise in depressed patient.	Quantitative—experimental design RCT study.BDI tool was used to assess patient depressive symptoms before and after the trial.	A total of 43 patients with MDD were randomly assigned into exercise group (n = 24) who received aerobic exercise + usual treatment of depression (consisting of psychotherapy + occupational therapy) and control group (n = 19) who received only usual treatment of depression.	A significant reduction in depressive symptoms score (using Beck tool) in treatment group.
Blumenthal et al. (1999)	To assess the effectiveness of an	Quantitative—experimental design	A total of 156 patients with MDD were randomly assigned into mixed	No significant difference was founded between groups.

Source	Study aim	Study method/design	Subject	Main findings
	aerobic exercise program compared with standard medication (i.e., antidepressants) for treatment of MDD in older patients.	RCT study. HAM-D17 and BDI tools was used to assess patient depressive symptoms	group (n = 55) who received aerobic exercise + usual treatment of depression (consisting of antidepressant medication), exercise group (n = 53) who received aerobic exercise and control group (n = 48) who received only usual treatment of depression.	
Pfaff et al. (2014)	To evaluate the efficacy of a home-based exercise programme added to usual medical care for the treatment of depression.	Quantitative—experimental design RCT study.HAM-D17 tool was used to assess patient depressive symptoms.	A total of 200 patients with MDD were randomly assigned into exercise group (n = 108) who received aerobic exercise + resistance exercise + usual treatment of depression and control group (n = 92) who received usual treatment of depression.	No significant difference was found between groups.
Babyak et al. (2000)	Assess the status of 156 adults with MDD after completion of a study in which they were randomly assigned to a 4-month course of aerobic exercise, sertraline therapy or a combination of exercise and sertraline.	Quantitative—experimental design RCT study. HAM-D17 and BDI tools was used to assess patient depressive symptoms	A total of 83 patients with MDD with > 13 in HRSD randomly assigned into exercise group (n = 25) who received aerobic exercise, mixed group (n = 29) who received aerobic exercise + antidepressant medication and control group (n = 29) who receives antidepressant medication.	No significant difference was found between groups.
Cerda et al. (2011)	To assess the effects of an aerobic training program as complementary therapy in patients suffering from moderate depression.	pertest post-test design. BDI tool was used to assess patient depressive symptoms.	A total of 82 adults with MDD divided into two experimental groups: exercise group (n = 41) who received exercise +pharmacotherapy and pharmacotherapy group (n = 41) who received only pharmacotherapy.	This study found that in the treatment groupthe depressive score (using BDI) was significantly lower at post-test than at pre-test. However, the depressive score was still moderate in post-test of control group.
Mota-Pereira et al. (2011)	Assessed the impact on depression and functioning parameters of a moderate intensity exercise program, as an adjunct to pharmacotherapy in treatment-resistant MDD patients.	Quantitative—experimental design RCT study. HAM-D 17 and BDI tool was used to assess patient depressive symptoms	33 individuals with treatment-resistant MDD were randomised to one of two groups: usual pharmacotherapy (n = 11) and usual pharmacotherapy plus aerobic exercise (n = 22)	Significant reduction in HAM-D 17 and BDI-II scores in treatment group. In addition, there was a trend towards response and remission as 21% of participants showed response and 26% showed remission compared with none of the participants in control group.
Schuch et al. (2011)	To evaluate the effects of physical exercise as an add-on treatment for severely depressed inpatients.	Quantitative—experimental design RCT study. HAM-D 17 tool was used to assess patient depressive symptoms.	A total of 26 patients with MDD who scored higher than 25 on HAM-D, equal to severe depression, were randomly assigned into two groups: intervention group (n = 15) who received aerobic exercise + usual treatment of depression (consisting of antidepressant medication and or ECT) and control group (n = 11) who received usual treatment of depression.	This study found significant differences between groups in depressive score in HAM-D 17 in favour of exercise group. However, none of these studies found a difference between groups in the response (a decrease of 50% on the HAM-D 17) and remission rate (score of 7 or less on the HAM-D 17).
Veale et al. (1992)	To determine whether adding aerobic exercise to the treatment of patients suffering from depression produced additional benefit.	Quantitative—experimental design RCT study. BDI tool was used to assess patient depressive symptoms.	A total of 83 adults with MDD were randomly assigned into two groups: exercise group (n = 48) who received exercise +usual treatment for depression and control group (n = 35).	The study found no significant difference in depressive symptoms score between treatment groups.

Eman S. Alsolami et. al. "The Effect of Physical Exercise as an Adjunctive Treatment to the Usual Treatment for Major Depressive Disorder: An Integrative Review." *IOSR Journal of Nursing and Health Science (IOSR-JNHS)*, 9(4), 2020, pp. 27-44