Is the Comparison between Exercise and Pharmacologic Treatment of Depression in the Clinical Practice Guideline of the American College of Physicians Evidence-Based?

Yael Netz*

Behavioral Studies, Graduate School, The Academic College at Wingate, Wingate, Israel

Major depression disorder is most commonly treated with antidepressants. However, due to their side effects clinicians seek non-pharmacologic options, and one of these is exercise. The literature on the benefits of exercise for depression is extensive. Nevertheless, two recent reviews focusing on antidepressants vs. other therapies as a basis for clinical practice guidelines recommended mainly antidepressants, excluding exercise as a viable choice for treatment of depression. The aim of this perspective is to analyze the literature exploring the reasons for this discrepancy. Two categories of publications were examined: randomized controlled trials (RCTs) and meta-analyses or systematic reviews. Based on this reassessment, RCTs comparing exercise to antidepressants reported that exercise and antidepressants were equally effective. RCTs comparing exercise combined with antidepressants to antidepressants only reported a significant improvement in depression following exercise as an adjunctive treatment. Almost all the reviews examining exercise vs. other treatments of depression, including antidepressants, support the use of exercise in the treatment of depression, at least as an adjunctive therapy. The two reviews examining pharmacologic vs. non-pharmacologic therapies as a basis for clinical practice guidelines examined limited evidence on exercise vs. antidepressants. In addition, it is possible that academics and health care practitioners are skeptical of viewing exercise as medicine. Maybe, there is a reluctance to accept that changes in lifestyle as opposed to pharmacological treatment can alter biological mechanisms. Longitudinal studies are needed for assessing the effectiveness of exercise in real clinical settings, as well as studies exploring dose-response relationship between exercise and depression.

Keywords: antidepressants, exercise therapy, monotherapy, combination therapy, adjunctive therapy

INTRODUCTION

The perception of exercise as medicine has been discussed in relation to health conditions such as cognitive decline (e.g., Nagamatsu et al., 2014), cancer (e.g., Lin et al., 2016), cardiac rehabilitation (e.g., Almodhy et al., 2016), schizophrenia (e.g., Firth et al., 2015), alcohol use disorders (e.g., Hallgren et al., 2017), and all-cause mortality (e.g., Eklund et al., 2016). One meta-epidemiological
study on mortality outcomes concluded that in a number of health conditions, such as heart failure, stroke, and diabetes, exercise and various pharmacological treatments are similar in their potential to extend longevity (Naci and Ioannidis, 2013). Thus, exercise interventions should be considered as a viable alternative to, or combination with, drug therapy (Naci and Ioannidis, 2013). It is therefore not surprising that comparative assessments of exercise and drug treatments were performed for some conditions, such as sleep disorders (Buman and King, 2010), chronic pain (Ambrose and Golightly, 2015), and mental health (Firth et al., 2016).

Probably more than for other health conditions, comparative benefits of exercise and pharmacologic treatments have been examined and discussed in relation to depression (e.g., Stubb et al., 2015; Gartlehner et al., 2016). According to the WHO (World Health Organization), depression is the leading cause of disability worldwide (WHO, 2016 http://www.who.int/mediacentre/factsheets/fs369/en/).

Major depression disorder (MDD) is most commonly treated with antidepressant medication, where second-generation antidepressants are the most commonly prescribed drugs (Agency for Healthcare Research and Quality [AHRQ], 2016). However, many patients do not respond to antidepressant medications, or experience side effects (Gartlehner et al., 2016). In addition, increasing evidence indicated a large placebo response, making it more challenging for novel medications to demonstrate their effectiveness (Rutherford et al., 2012). Therefore, clinicians and patients seek non-pharmacologic options for treating depression – and one of them is physical exercise (e.g., Martiny et al., 2012).

The literature on the benefits of exercise for both minor and major depressive symptoms is extensive, with exceptionally numerous reviews perhaps outnumbering randomized controlled trials (RCTs) (e.g., Mead et al., 2009; Rethorst et al., 2009; Krogh et al., 2011; Rimer et al., 2012; Robertson et al., 2012; Cooney et al., 2013; Danielsson et al., 2013; Silveira et al., 2013;Josefsson et al., 2014; Mura et al., 2014; Knapen et al., 2015; Nyström et al., 2015; Stubb et al., 2015; Kvat et al., 2016; Schuch et al., 2016b). In addition to exercise, additional studies (Adaman et al., 2016) and reviews (Zhai et al., 2015; Hallgren et al., 2016; Liu et al., 2016; Schuch et al., 2017) in recent years examined the relationship between sedentary behavior, physical activity, and depression. Interestingly, a recent study has shown that a 1-week of forced sedentary behavior may cause bad mood or depression in active individuals (Edwards and Loprinzi, 2016). Furthermore, it has been found that people with depression are at increased risk of sedentary behavior (Dugan et al., 2015; Schuch et al., 2017), which may cause cardiovascular diseases and metabolic syndromes (Gardner-Sood et al., 2015).

Along with RCTs and reviews examining exercise as a treatment for depression, there have been attempts to explore the mediating biological mechanisms explaining the reduction in depression in MDD as a result of exercise (Kandola et al., 2016; Schuch et al., 2016a). One explanation is hippocampus plasticity (Kandola et al., 2016). It has been shown that the hippocampus in depressed individuals may be affected by neuron atrophy (Mendez-David et al., 2013). Aerobic exercise has the potential to promote neuroplasticity and thus facilitate the function of the hippocampus (Erickson et al., 2011). Through increasing neuroplasticity in the hippocampus, it may be possible to generate structural changes that affect the region's functioning and contribute to the alleviation of cognitive malfunction in MDD (Kandola et al., 2016). It has also been hypothesized that there is a relationship between the decline in neurogenesis and depressed mood (Duman et al., 1997). Based on the above, it was concluded that the anti-depressive effects of exercise are due to physiological changes that result in hippocampal neurogenesis (Eriost et al., 2006).

One mechanisms by which exercise could potentially facilitate this neurogenesis is the brain-derived neurotrophic factor (BDNF). A growing number of studies, performed both on animal models of depression and on depressed humans, have focused on the neurotrophic hypothesis of depression (Neto et al., 2011). According to this hypothesis, several alterations in the levels of neurotrophins, particularly of the BDNF, might produce the structural and neurochemical changes that underlie depression (Neto et al., 2011). Both pharmacological and non-pharmacological interventions for depression have been shown to produce changes in the levels of neurotrophins. BDNF increases have been reported to follow the administration of antidepressant drugs (Czubak et al., 2009), which suggests that BDNF expression may mediate the action of antidepressants. Furthermore, when exercise is combined with antidepressants, BDNF levels were found to increase in as little as two days, compared with two weeks with antidepressants alone (Russo-Neustadt et al., 2001).

Another mechanism for enhancing neurogenesis is serotonin. Adaptations in the serotonergic system may serve as potential facilitators of the antidepressant effects of exercise (Schuch et al., 2016a). As a result, antidepressant medications available today target the release and reuptake of serotonin. Exercise increases tryptophan hydroxylase (Chaueloff et al., 1989), which is necessary for serotonin synthesis. Results of animal studies point to a relationship between serotonin elevation and neurogenesis (Brezun and Daszuta, 2000).

According to Schuch et al. (2016a), it is possible that the antidepressant effect of exercise is caused by the interaction of several neurobiological mechanisms rather than by one mechanism exclusively. It is certain that exercise generates both acute and chronic responses, mainly in hormones, neurotrophines, and inflammation biomarkers (Schuch et al., 2016a).

It is, therefore, not surprising that quite a few attempts have been made to compare the effects of exercise to other treatments, including drug treatments, in various depressive disorders, specifically MDD. Four reviews on this topic were published in 2016. Two meta-analyses examining the efficacy of exercise as a treatment for major depression concluded that exercise as a treatment for depression can be recommended as a stand-alone treatment or as an adjunct to antidepressant medication (Kvam et al., 2016), and that exercise can be considered an evidence-based treatment for the management of depression (Schuch et al., 2016b). On the other hand, two systematic reviews comparing antidepressants to other therapies – including exercise – as a basis for clinical practice guidelines for depression, disregarded...
exercise in their recommendations. One concluded that “The American College of Physicians recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder…” (Qaseem et al., 2016, p. 355), and the other that “given comparable efficacy, cognitive behavioral therapy and antidepressants are both viable choices for initial MDD treatment” (Gartlehner et al., 2016, p. 338). The aim of this perspective is to analyze the available literature on the efficacy of exercise vs. antidepressants in the treatment of depression and to suggest a few explanations for this discrepancy.

Publications Examined
Two categories of publications were examined: RCTs (Table 1) and meta-analyses or systematic reviews (Table 2).

All RCTs published in 1999–2016 that are included in systematic and/or meta-analyses reviews published from 2009 to 2016 were examined, as well as two recent RCTs found in PubMed search. RCTs were excluded if they assessed participants with additional co-morbid diagnoses, such as cardiovascular diseases (e.g., Blumenthal et al., 2012), or if they assessed two kinds of interventions as add-on therapy – for example chronotherapy vs. exercise (Martiny et al., 2012). One group of RCTs compared exercise to antidepressants – monotherapy comparisons, and the other compared exercise combined with antidepressants to antidepressants only – combination comparisons (Table 1).

As a collection of RCTs does not reflect a general effect size, meta-analyses, Cochrane reviews and systematic reviews providing an effect size of exercise vs. antidepressants in the treatment of depression were examined. As a large number of meta-analyses and other reviews were conducted in the last decade, it was decided to screen only reviews from the last seven years (2009–2016). Interestingly, in spite of the large number of reviews, none of them focused solely on exercise vs. antidepressants. One group compared exercise to other treatments of depression, including antidepressants, and the other compared antidepressants to other therapies, including exercise. More specifically, the present review investigated: (1) whether comparisons were conducted specifically between exercise and antidepressants (as opposed to exercise vs. all other treatments together, or antidepressants vs. all other treatments together), (2) which RCTs comparing exercise to antidepressants were included in these reviews, (3) which conclusions were drawn from these comparisons, and (4) whether all published RCTs conducting such comparisons were included in the reviews.

Summary and Conclusions of the Findings
Randomized Controlled Trials
Exercise vs. antidepressants – monotherapy comparisons (Table 1)
Three RCTs compared 4 months of exercise to antidepressants–two for MDD (Blumenthal et al., 1999, 2007) and one for minor depression (Brenes et al., 2007). Two were conducted on older adults (Blumenthal et al., 1999; Brenes et al., 2007). One study (Hoffman et al., 2011) was a follow-up to a previous study (Blumenthal et al., 2007). The Blumenthal et al. (1999, 2007) studies included aerobic exercise, and the Brenes study a combination of aerobic and resistance exercises.

Conclusion: All these studies reported that exercise and standard antidepressant treatments were equally effective.

Exercise combined with antidepressants vs. antidepressants only – combination comparisons (Table 1)
Eleven RCTs compared exercise as an adjunctive treatment to antidepressants (combination comparisons) – 10 for MDD and one for minor depression (Table 1). The duration of the exercise period varied from 10 days (Knubben et al., 2007; Legrand and Neff, 2016), to 6 weeks (Kerling et al., 2015, 10 weeks (Mather et al., 2002), 3 months (Mota-Pereira et al., 2011), 4 months (Carneiro et al., 2015), 6 months (Murri et al., 2015), 8 months (Pilu et al., 2007), 12 months (Chalder et al., 2012), to throughout a hospitalization period (undefined time period) (Schuch et al., 2011, 2015). Control groups included antidepressants only (Mather et al., 2002; Pilu et al., 2007; Mota-Pereira et al., 2011; Schuch et al., 2011, 2015; Chalder et al., 2012; Carneiro et al., 2015; Kerling et al., 2015), light exercise with both exercise groups receiving antidepressants (Knubben et al., 2007; Legrand and Neff, 2016), and antidepressants only (Murri et al., 2015). The exercise mode included mostly aerobics (Knubben et al., 2007; Mota-Pereira et al., 2011; Schuch et al., 2011, 2015; Kerling et al., 2015; Murri et al., 2015; Legrand and Neff, 2016) or aerobic and strength (Pilu et al., 2007); aerobic, strength, and stretching exercises (Mather et al., 2002); aerobics and strength exercises, games and dancing (Carneiro et al., 2015), and facilitated physical activity chosen and performed individually by participants (Chalder et al., 2012). The studies using exercise in a control group used light stretching (Knubben et al., 2007; Legrand and Neff, 2016) and low-intensity aerobics (Murri et al., 2015). Most studies assessed adults in general; only two studies investigated older adults (Mather et al., 2002; Murri et al., 2015).

Of special interest are the studies using exercise placebo groups as a control group, in which improvements were observed in the aerobic exercise as compared to stretching (Knubben et al., 2007; Legrand and Neff, 2016), and the Murri et al. (2015) study that showed the greatest improvement in high-intensity aerobics, followed by low intensity aerobics, followed by antidepressants only. The Chalder et al. (2012) study only gave guidance about exercise but did not provide an exercise program.

Conclusion: All studies but one (Chalder et al., 2012) informed that patients using exercise as an adjunctive treatment for depression showed a significant depressive improvement after the exercise period, and/or that the proportion of patients with a clinical response was larger for the exercise group than the control.

Meta-Analyses or Systematic Reviews
Table 2 presents a map of RCTs comparing exercise to antidepressants in the meta-analyses or systematic reviews.

Almost all reviews examining exercise vs. other treatments of depression, including antidepressants, support the use
### TABLE 1 | Randomized controlled trials (RCTs) comparing exercise to antidepressants in the treatment of depression.

| Study | Participants | Treatment groups | Exercise | Duration | Conclusion |
|-------|--------------|------------------|----------|----------|------------|
| Blumenthal et al., 1999 | MDD Older adults | 1. Group exercise 2. Antidepressants 3. Combined | Three times/week  Walking or jogging | 4 months | Exercise and antidepressants equally effective |
| Blumenthal et al., 2007 | MDD Adults | 1. Group exercise 2. Home-based exercise 3. Antidepressants 4. Placebo pills | Three times/week  Walking or jogging | 4 months | Participants in either exercise or antidepressants groups tended to show greater improvement in comparison with placebo participants |
| Hoffman et al., 2011 (follow-up of Blumenthal et al., 2007) | MDD Adults | 1. Group exercise 2. Home-based exercise 3. Antidepressants 4. Placebo pills | Three times/week  Walking or jogging | 1 year follow-up | No differences between treatment groups. Those who reported regular exercise following the intervention - the least likely to be depressed at follow-up |
| Brenes et al., 2007 | Minor depression Older adults | 1. Group exercise 2. Antidepressants 3. Usual care (discussions on health status) | Three times/week  Aerobic and resistance | 4 months | Both antidepressants and exercise led to improvements as compared to the usual care. Individuals in the exercise condition also improved in physical functioning |

### Exercise combined with antidepressants vs. antidepressants only (combination comparisons)

| Study | Participants | Treatment groups | Exercise | Duration | Conclusion |
|-------|--------------|------------------|----------|----------|------------|
| Knubben et al., 2007 | MDD Adults, inpatients | 1. Aerobic exercise + antidepressants 2. Low-intensity + antidepressants | 1. Individually treadmill walking 2. Individually stretching and relaxation | 10 days Every day | Aerobic exercise as add-on therapy significantly improved depression. The proportion of patients with a clinical response was larger for the aerobic exercise group |
| Pilu et al., 2007 | MDD Treatment-resistant women | 1. Physiological strengthening + antidepressants 2. Antidepressants | Group cardio-fitness machines – aerobics and strengthening Two times/week | 8 months | Exercise group showed a significant depression improvement |
| Mota-Pereira et al., 2011 | MDD Treatment-resistant adults | 1. Aerobic exercise + antidepressants 2. Antidepressants only | Home-based, five times/week (1 day/week supervised) | 12 weeks | In exercise group, 21% showed response and 26% remission. None in control showed response or remission |
| Schuch et al., 2011 | MDD Adults inpatients | 1. Aerobic exercise + antidepressants 2. Antidepressants only | Stationary bike, or treadmill or an elliptic, on individual basis, Three times/week | Through-out hospitalization | At 2 weeks, – both groups achieved improvements in depressive symptoms and quality of life, but difference favorable to exercise group at discharge. |
| Chalder et al., 2012 | MDD Adults | 1. Facilitated physical activity + usual care (58% antidepressants) 2. Usual care (56% antidepressants) | Three face to face sessions and 10 telephone calls with a trained physical activity facilitator | 8 months. | Facilitated physical activity did not improve depression or reduce use of antidepressants compared with usual care alone, after 4, 8, and 12 months |
| Schuch et al., 2015 | MDD Adults inpatients | 1. Aerobic exercise + antidepressants 2. Antidepressants only | Treadmill or bike or transport machine, on individual basis, Three times/week | Through-out hospitalization | Exercise group improved significantly more than control group on depressive symptoms and quality of life, as noticed at the second week of hospitalization and at discharge |
| Carneiro et al., 2015 | MDD Adult women | 1. Aerobic exercise + antidepressants 2. Antidepressants only | Traditional games, natural circuit workouts with resistance bands, jump ropes, fitness balls, brisk walking, and dancing, Three times/week | 4 months | Exercise group decreased in depression, anxiety and in stress and improved in physical functioning as compared to the control group |

(Continued)
of exercise in the treatment of depression, at least as an add-on therapy. Earlier reviews, which included only a few RCTs, were more careful in actually recommending exercise. For example, one review stated that “it is reasonable to recommend exercise...” (Mead et al., 2009, p. 14). Another review pointed out that “… exercise may be as effective as psychological or pharmacological treatments...” (Cooney et al., 2013, p. 35). Later reviews were more conclusive, claiming “a strong effectiveness of exercise combined with antidepressants” (Mura et al., 2014, p. 503); “Overall, our results provide robust evidence that exercise can be considered an evidence-based treatment for the management of depression.” (Schuch et al., 2016b, p. 47); and “Physical exercise is an effective intervention for depression. It also could be a viable adjunct treatment in combination with antidepressants” (Kvam et al., 2016, p. 67).

On the other hand, the two recent reviews from 2016 assessing antidepressants vs. other treatments of depression, including exercise, did not recommend exercise for the treatment of depression (Garlechner et al., 2016; Qaseem et al., 2016). However, when comparing exercise to antidepressants, these reviews examined mainly the Blumenthal et al. (1999, 2007) studies, excluding other RCTs comparing exercise to antidepressants that were included in other recent reviews.

**DISCUSSION**

Exercise vs. pharmacologic treatment of depression in the clinical practice guideline of the American College of Physicians – is it evidence-based?

It appears that the reviews examining pharmacologic vs. non-pharmacologic treatments of depression as a basis for clinical practice guidelines examined limited evidence on exercise vs. antidepressants, and thus disregarded exercise as a viable choice for treating depression as a stand-alone treatment or as an add-on therapy. This position is contrary to the reviews examining exercise vs. other treatments for depression, including antidepressants, which generally recommend exercise as a stand-alone and/or as adjunctive treatment for depression. The evidence is even greater when considering two additional recent well-designed RCTs not included in any of the reviews (possibly because they were published later than the RCTs mentioned in the reviews) which pointed out the effect of exercise as a complement to antidepressant medication (Carneiro et al., 2015; Legrand and Neff, 2016) (Table 1). Furthermore, while the underlying biological mechanisms mediating between exercise and reduced depressive symptoms are not entirely clear, it is apparent that exercise induces both acute and chronic responses, particularly in hormones, neurotrophines, and inflammation biomarkers, and that there is an association between hippocampus neurogenesis as a result of exercise and depressive symptoms’ improvement (Schuch et al., 2016a).

| Study | Participants | Treatment groups | Exercise | Duration | Conclusion |
|-------|--------------|------------------|----------|----------|------------|
| Kerling et al., 2015 | MDD Adults inpatients | 1. Aerobic exercise + CBT + antidepressants (only 77% antidepressants) 2. Usual care – CBT + antidepressants (only 75% antidepressants) | Bicycle ergometer followed by personal preference for cross trainer, stepper, arm ergometry, treadmill, recumbent, or a rowing ergometry Three times/week | 6 weeks | Decline in depressive symptoms in both groups. Significantly more in exercise group classified as responders - at least 50% reduction in depression. Exercise group improved in physiological measures |
| Muri et al., 2015 | MDD Older adults | 1. High-intensity aerobic exercise + antidepressants 2. Low-intensity aerobic exercise+ antidepressants 3. Antidepressants only | 1. High-intensity, progressive, mainly bicycles 2. Low-intensity, non-progressive mainly bicycles. Three times/week | 24 weeks | Remission occurred in 81% of high-intensity 73% of low-intensity 45% of antidepressants only |
| Legrand and Neff, 2016 | MDD Adult inpatients | 1. Aerobic exercise + antidepressants 2. Placebo exercise + antidepressants 3. Antidepressants only | 1. Walking or running mostly on individual basis 2. Stretching | 10 days upon hospitalization, Every day | Both aerobic and stretching improved. A larger effect size in aerobic exercise. No change in depressive symptoms in control group |
| Mather et al., 2002 | Minor depression, Older adults poorly responsive to depressive symptoms | 1. Exercise + antidepressants 2. Health education + antidepressants | Endurance, strength and stretching Two times/week | 10 weeks | Significant higher proportion - 55% – of exercise group than control – 33% experienced a greater than 30% decline in depression |
| Reviews                                      | Reviews comparing the effect size of exercise vs. antidepressants in a specific sub-analysis | Reviews assessing a general effect size of exercise | Conclusion                                                                 |
|---------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------|-----------------------------------------------------------------------------|
| Rethorst et al., 2009                       | RCTs included in monotherapy comparison                                                    | All RCTs comparing exercise to other treatments including antidepressants |
| Meta-analysis of exercise vs. other         | 2 unpublished papers, 1 irrelevant                                                           |                                                   | A significant overall effect size of exercise.                               |
| treatments                                   |                                                                                             |                                                   | **No difference between effect sizes of exercise vs. antidepressants**, but  |
|                                             |                                                                                             |                                                   | insufficient suitable studies. Supports the use of exercise in the treatment  |
|                                             |                                                                                             |                                                   | of major depression.                                                        |
|                                             |                                                                                             |                                                   | Generally, exercise reduced depression.                                     |
|                                             |                                                                                             |                                                   | **No difference between effect sizes of exercise vs. antidepressants.**      |
| Mead et al., 2009                           | RCTs included in combination comparison                                                     | Blumenthal et al., 1999, 2007                    | The general effect of exercise on depression is short-term. Little          |
| Cochrane review of exercise vs. other        |                                                                                             |                                                   | evidence of a long term beneficial effect.                                  |
| treatments                                   |                                                                                             |                                                   | High quality trials, with long term follow-up, are required.                |
|                                             |                                                                                             |                                                   | **A large (general) effect size of exercise** (walking) on depression        |
| Krogh et al., 2011                          | RCTs together in mono and combination                                                       | Mather et al., 2002; Blumenthal et al., 2007     | **No difference between exercise and antidepressants.** Exercise may be as  |
| Meta-analysis and systematic review of       |                                                                                             |                                                   | effective as antidepressants, but small number of trials and participants.  |
| exercise vs. other treatments                |                                                                                             |                                                   | **Exercise is an efficient alternative treatment for depression** **(general  |
|                                             |                                                                                             |                                                   | effect size)**, specifically in old age and for mild depression. Based on   |
|                                             |                                                                                             |                                                   | Blumenthal et al. (1999, 2007) studies, aerobic training is as effective as  |
|                                             |                                                                                             |                                                   | antidepressants **General effect size:** For mild to moderate depression –  |
|                                             |                                                                                             |                                                   | exercise comparable to antidepressants, for severe depression – exercise     |
|                                             |                                                                                             |                                                   | valuable as complementary therapy **A strong effectiveness of exercise** **  |
|                                             |                                                                                             |                                                   | combined with antidepressants**, but the majority of studies suffered from   |
|                                             |                                                                                             |                                                   | methodological weaknesses.                                                  |
| Robertson et al., 2012                      | RCTs together in combo                                                                    | Knubben et al., 2007; Mota-Pereira et al., 2011 |                                                                             |
| Meta-analysis and systematic review of       |                                                                                             |                                                   | **A large and significant effect size of exercise, larger for MDD, for aerobic  |
| exercise vs. other treatments                |                                                                                             |                                                   | exercise, and for supervised formats.** Criticized previous meta-analyses for  |
|                                             |                                                                                             |                                                   | underestimating benefits of exercise due to publication bias. Not right to    |
|                                             |                                                                                             |                                                   | calculate exercise-drugs as exercise may potentially overlap with potential  |
|                                             |                                                                                             |                                                   | mechanisms of drugs.                                                        |
| Cooney et al., 2013                         | RCTs included in combination comparison                                                     | Blumenthal et al., 1999, 2007                    | (Continued)                                                                 |
| Cochrane review of exercise vs. other        |                                                                                             |                                                   |                                                                            |
| treatments                                   |                                                                                             |                                                   |                                                                            |
|                                             |                                                                                             |                                                   |                                                                            |
| Silveira et al., 2013                        | RCTs included in combination comparison                                                     | Blumenthal et al., 1999, 2007                    |                                                                            |
| Meta-analysis and systematic review of       |                                                                                             |                                                   |                                                                            |
| exercise vs. other treatments                |                                                                                             |                                                   |                                                                            |
|                                             |                                                                                             |                                                   |                                                                            |
| Knappen et al., 2015                        | RCTs included in combination comparison                                                     | Blumenthal et al., 2007; Knubben et al., 2007    |                                                                            |
| (review of reviews of exercise vs. other     |                                                                                             |                                                   |                                                                            |
| treatments)                                  |                                                                                             |                                                   |                                                                            |
|                                             |                                                                                             |                                                   |                                                                            |
| Mura et al., 2014                           | RCTs included in combination comparison                                                     | Blumenthal et al., 1999, 2007                    |                                                                            |
| Meta-analysis and systematic review          |                                                                                             |                                                   |                                                                            |
| (some non-RCTs included)                     |                                                                                             |                                                   |                                                                            |
|                                             |                                                                                             |                                                   |                                                                            |
| Schuch et al., 2016b                        | RCTs included in combination comparison                                                     | Blumenthal et al., 2007; Brenes et al., 2007;    |                                                                            |
| Meta-analysis of exercise vs. other treatments |                                                                                             | Pili et al., 2007; Mota-Pereira et al., 2011;    |                                                                            |
|                                             |                                                                                             | Kerling et al., 2015; Schuch et al., 2015         |                                                                            |

(Continued)
TABLE 2 | Continued

| Reviews | Reviews comparing the effect size of exercise vs. antidepressants in a specific sub-analysis | Reviews assessing a general effect size of exercise | Conclusion |
|---------|-------------------------------------------------------------------------------------------------|-------------------------------------------------|------------|
|         | RCTs included in monotherapy comparison | RCTs included in combination comparison | RCTs together in mono and combination | All RCTs comparing exercise to other treatments including antidepressants |
| Kvam et al., 2016 | Meta-analysis of exercise vs. other treatments | Blumenthal et al., 1999, 2007; Pilu et al., 2007; Mota-Pereira et al., 2011; Schuch et al., 2011 | |  |
| Qaseem et al., 2016 | Systematic review of all treatments | Blumenthal et al., 2007; Hoffman et al., 2008 (irrelevant as not assessing depression) | Blumenthal et al., 1999 |  |
| Gartlehner et al., 2016 | Systematic review of all treatments | Blumenthal et al., 2007 | Blumenthal et al., 1999; Murri et al., 2015 |  |

**Monotherapy:** Exercise efficient as drugs. 
**Combination:** Moderate effect size trending toward significance. 
Exercise can be recommended as a stand-alone treatment and as an adjunct to antidepressant medication.

**Exercise vs. antidepressants:** No difference in remission in both mono and combination therapy. However, exercise not recommended as a treatment of depression. 
Low quality evidence.

**Exercise vs. antidepressants:** No difference in monotherapy, improvement in combination therapy. However, exercise not recommended as a treatment of depression. 
Low to moderate quality evidence.

2017), which may cause cardiovascular diseases and metabolic syndrome (Gardner-Sood et al., 2015). Thus, exercise contributes to the physical health in addition to mental health. It is also worth mentioning the adverse effects commonly associated with drugs, including constipation, diarrhea, dizziness, headache, insomnia, nausea, adverse sexual events, and somnolence (Qaseem et al., 2016), which may further support the use of exercise as a viable alternative or adjunctive pharmacotherapy.

It is unclear why exercise was disregarded as a viable choice for treating depression in the clinical practice guidelines recommended in the two recent reviews (Gartlehner et al., 2016; Qaseem et al., 2016). Is there a reluctance among academics and health care practitioners to view exercise as medicine? Do they caution that there is no strong evidence to suggest that modifiable lifestyle factors as opposed to pharmacological treatment can alter biological mechanisms in similar pathways or similar dynamics to biochemical interventions?

Interestingly, this argument was raised by Nagamatsu et al. (2014) regarding the effect of exercise on the brain and cognition in old age. These authors made the case that despite the large and consistent pool of evidence generated over the past five decades linking exercise to improved cognitive functions in older adults, skepticism remains and health practitioners continue to hinder the adoption of exercise as a legitimate medical strategy for the prevention of cognitive decline.

Future directions of research should include dose-response interventions to determine the precise dose of exercise required to maximize the benefits for depression. In addition, more studies are needed to inquire the underlying molecular and cellular mechanisms mediating between exercise and depression. Furthermore, another important issue for assessing the benefits of exercise for depression is its effectiveness as opposed to efficacy (Beedie et al., 2016). While efficacy refers to the ability of exercise to achieve the desired effect under well controlled circumstances, effectiveness refers to the ability of exercise to affect depression in real life situations. Therefore, longitudinal observational studies exploring the benefits of exercise in depression are needed, which assess adherence issues as well as economic and professional matters.

**AUTHOR CONTRIBUTIONS**

The author confirms being the sole contributor of this work and approved it for publication.
REFERENCES

Adamson, B. C., Yang, Y., and Motl, R. W. (2016). Association between compliance with physical activity guidelines, sedentary behavior and depressive symptoms. *Prev. Med.* 91, 152–157. doi: 10.1016/j.ypmed.2016.08.020

Agency for Healthcare Research and Quality [AHRQ] (2016). Effective Health Care Program. Rockville, MD: Agency for Healthcare Research and Quality.

Almody, M., Ingle, L., and Sandercorn, G. R. (2016). Effects of exercise-based cardiac rehabilitation on cardiorespiratory fitness: a meta-analysis of UK studies. *Int. J. Cardiol.* 221, 644–651. doi: 10.1016/j.ijcard.2016.06.101

Ambrose, K. R., and Golightly, Y. M. (2015). Physical exercise as non-pharmacological treatment of chronic pain: why and when. *Best Pract. Res. Clin. Rheumatol.* 29, 120–130. doi: 10.1016/j.berh.2015.04.022

Beedie, C., Mann, S., Jimenez, A., Kennedy, L., Lane, A. M., Domone, S., et al. (2016). Death by effectiveness: exercise as medicine caught in the efficacy trap! *Br. J. Sports Med.* 50, 323–324. doi: 10.1136/bjsports-2014-094389

Blumenthal, J. A., Babyak, M. A., Doraiaiswamy, P. M., Watkins, L., Hoffman, B. M., Barbour, K. A., et al. (2007). Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom. Med.* 69, 587–596. doi: 10.1097/PSY.0b013e318148c19a

Blumenthal, J. A., Babyak, M. A., Moore, K. A., Craighead, W. E., Herman, S., Khatri, P., et al. (1999). Effects of exercise training on older patients with major depression. *Arch. Intern. Med.* 159, 2349–2356. doi: 10.1001/archinte.159.19.2349

Blumenthal, J. A., Babyak, M. A., O’Connor, C., Ketyesian, S., Landberg, J., Howlett, J., et al. (2012). Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-ACTION randomized trial. *JAMA* 308, 465–474. doi: 10.1001/jama.2012.8720

Brenes, G. A., Williamson, J. D., Messier, S. P., Rejeski, W. J., Pahor, M., Ip, E., et al. (2007). Treatment of minor depression in older adults: a pilot study comparing sertraline and exercise. *Aging Ment. Health* 11, 61–68. doi: 10.1080/13607860700736372

Brezun, J., and Daszuta, A. (2000). Serotonin may stimulate granule cell proliferation in adult hippocampus, as observed in rats grafted with foetal raphe neurons. *Eur. J. Neurosci.* 12, 391–396. doi: 10.1046/j.1460-9566.2000.00092.x

Buman, M. P., and King, A. C. (2010). Exercise as a treatment to enhance sleep. *Am. J. Lifestyle Med.* 4, 500–514. doi: 10.1177/1559827610375532

Carneiro, L. S., Fonseca, A. M., Vieira-Coelho, M. A., Mota, M. P., Ambrose, K. R., and Golightly, Y. M. (2015). Physical exercise as non-pharmacological treatment of chronic pain: why and when. *Best Pract. Res. Clin. Rheumatol.* 29, 120–130. doi: 10.1016/j.berh.2015.04.022

Duman, R., Heninger, G., and Nestler, E. A. (1997). Molecular and cellular theory of depression. *Arch. Gen. Psychiatry* 54, 597–606. doi: 10.1001/archpsyc.1997.0183019015002

Dumas, M. C., and Loprinzi, P. D. (2016). Effects of a sedentary behavior-inducing randomized controlled intervention on depression and mood profile in active young adults. *Mayo Clin. Proc.* 91, 984–998. doi: 10.1016/j.mayocp.2016.03.021

Eklund, U., Steene-Johannessen, J., Brown, W. J., Fagerland, M. W., Owen, N., Powell, K. E., et al. (2016). Does physical activity attenuate, or even eliminate, the detrimental effect of sitting time with respect to mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet* 388, 1302–1310. doi: 10.1016/S0140-6736(16)30370-1

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., et al. (2011). Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. U.S.A.* 108, 3017–3022. doi: 10.1073/pnas.1015950108

Ernst, C., Olson, A. K., Pinel, J. P., Lam, R. W., and Christie, B. R. (2006). Antidepressant effects of exercise: evidence for an adult-neurogenesis hypothesis? *J. Psychiatry Neurosci.* 31, 84–92.

Firth, J., Carney, R., Elliott, R., French, P., Parker, S., McIntyre, R., et al. (2016). Exercise as an intervention for first-episode psychosis: a feasibility study. *Early Interv. Psychiatry* doi: 10.1111/eip.12329 [Epub ahead of print].

Firth, J., Cotter, J., Elliott, R., French, P., and Yung, A. (2015). A systematic review and meta-analysis of exercise interventions in schizophrenia patients. *Psychol. Med.* 45, 1343–1361. doi: 10.1017/S0033291714003110

Gardner-Sood, P., Lally, J., Smith, S., Atakan, Z., Ismail, K., Greenwood, K. E., et al. (2015). Cardiovascular risk factors and metabolic syndrome in people with established psychotic illnesses: baseline data from the IMPACT randomized controlled trial. *Psychol. Med.* 45, 2619–2629. doi: 10.1017/s0033291715000562

Garthleber, G., Gaynes, B. N., Forneris, C., Amick, H. R., Asher, G. N., Morgan, L. C., et al. (2016). Comparative benefits and harms of antidepressant, psychological, complementary, and exercise treatments for major depression: an evidence report for a Clinical Practice Guideline from the American College of Physicians. *Ann. Intern. Med.* 164, 331–341. doi: 10.7326/M15-1813

Hallgren, M., Herring, M. P., Owen, N., Dunstian, D., Ekblom, O, Helgadottir, B., et al. (2016). Exercise, physical activity, and sedentary behavior in the treatment of depression: broadening the scientific perspectives and clinical opportunities. *Front. Psychiatry* 7:56. doi: 10.3389/fpsyt.2016.00036

Hallgren, M., Vancampfort, D., Giesen, E. S., Lundin, A., and Stubbs, B. (2017). Exercise as treatment for alcohol use disorders: systematic review and meta-analysis. *Br. J. Sports Med.* doi: 10.1136/bjsports-2016-096814 [Epub ahead of print].

Hoffman, B. M., Babyak, M. A., Craighead, W. E., Sherwood, A., Doraiaiswamy, P. M., Coons, M. J., et al. (2011). Exercise and pharmacotherapy in patients with major depression: one-year follow-up of the SMILE study. *Psychosom. Med.* 73, 127–133. doi: 10.1097/PSY.0b013e318234933a5

Hoffman, B. M., Blumenthal, J. A., Babyak, M. A., Smith, P. J. R., Rogers, S. D., Doraiaiswamy, P. M., et al. (2008). Exercise fails to improve neurocognition in depressed middle-aged and older adults. *Med. Sci. Sports Exerc.* 40, 1344–1352. doi: 10.1249/MSS.0b013e318168b777

Josefsen, T., Lindwall, M., and Archer, T. (2014). Physical exercise intervention in depressive disorders: meta-analysis and systematic review. *Scand. J. Med. Sci. Sport* 24, 259–272. doi: 10.1111/smss.12050

Kandola, A., Hendrikse, J., Lucassen, P. J. J., and Yucel, M. (2016). Aerobic exercise as a tool to improve hippocampal plasticity and function in humans: practical implications for mental health treatment. *Front. Hum. Neurosci.* 10:373. doi: 10.3389/fnhum.2016.00373

Kerling, A., Tegtbur, U., Gützlaff, E., Kück, M., Borchert, L., Ates, Z., et al. (2015). Exercise as an intervention for first-episode psychosis: a feasibility study. *Front. Psychiatry* 6:207. doi: 10.3389/fpsyt.2015.00206

Knapp, J., Vancampfort, D., Morien, Y., and Marchal, Y. (2015). Exercise therapy improves both mental and physical health in patients with major depression. *Disabil. Rehabil.* 37, 1490–1495. doi: 10.3109/09638288.2014.972579

Krubben, B., Reischies, F. M., Adli, M., Schlattmann, P., Bauer, M., and Dimeo, F. (2007). A randomized controlled study on the effects of a short-term endurance
training programme in patients, with major depression. Br. J. Sports Med. 41, 29–33. doi: 10.1136/bjsm.2006.030130

Krogh, J., NORDENTOFT, M., STERNE, J. A., and LAWLOR, D. A. (2011). The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials. J. Clin. Psychiatry 72, 529–538. doi: 10.4088/JCP.09M1538

KVAM, S., KLEPPE, C. L., NORDHUS, I. H., and Hovland, A. (2016). Exercise as a treatment for depression: a meta-analysis. J. Affect. Disord. 157, 67–86. doi: 10.1016/j.jad.2016.03.063

LEGRAND, F. D., and NEFF, E. M. (2016). Efficacy of exercise as an adjunct treatment for clinically depressed inpatients during the initial stages of antidepressant pharmacotherapy: an open randomized controlled trial. J. Affect. Disord. 191, 139–144. doi: 10.1016/j.jad.2015.11.047

LIN, K. Y., FRAWLEY, H. C., DENEHY, L., FEIL, D., and Granger, C. L. (2016). Exercise interventions for patients with gynaecological cancer: a systematic review and meta-analysis. Physiotherapy 102, 309–319. doi: 10.1016/j.physio.2016.02.006

LIU, M., WU, L., and YAO, S. (2016). Dose-response association of screen time-based sedentary behaviour in children and adolescents and depression: a meta-analysis of observational studies. Br. J. Sports Med. 50, 1252–1258. doi: 10.1136/bjsports-2015-095084

Martiny, K., REFGAARD, E., LUND, V., LUNDE, M., SORENSEN, L., THOUGAARD, B., et al. (2012). A 9-week randomized trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depressive disorder patients treated with duloxetine. J. Clin. Psychiatry 73, 1234–1242. doi: 10.4088/JCP.11m07625

Mather, A. S., Rodriguez, C., Guthrie, M. F., McHARG, A. M., Reid, I. C., and 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. doi: 10.1192/bjp.180.5.41

MEAD, G. E., MORLEY, W., Campbell, P., Greig, C. A., McMURDO, M., and LAWLOR, D. A. (2009). Exercise for depression. Cochrane Database Syst. Rev. CD004366. doi: 10.1002/14651858.CD004366.pub4

Mendez-David, I., Hen, R., Gardier, A. M., and David, D. J. (2013). Adult hippocampal neurogenesis: an actor in the antidepressant-like action. Ann. Pharm. Fr. 71, 143–149. doi: 10.1016/j.pharma.2013.02.006

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

Mura, G., Moro, M. F., Patten, S. B., and Carta, M. G. (2014). Exercise as an add-on strategy for the treatment of major depressive disorder: a systematic review. CNS Spectr. 19, 496–508. doi: 10.1016/S1092859213000953

MURRI, M. B., AMORE, M., Menchetti, M., Toni, G., Neviani, F., Cerri, M., et al. (2012). Exercise interventions for patients with gynaecological cancer: a systematic review and meta-analysis. Physiotherapy 102, 309–319. doi: 10.1016/j.physio.2016.02.006

MATHUR, A. S., GURHAR, L., Denehy, L., and PEREZ DE LA CHAFA, A. (2016). Exercise as a treatment for depression: a meta-analysis. J. Affect. Disord. 191, 139–144. doi: 10.1016/j.jad.2016.03.063

ZHAI, L., ZHANG, Y., and Zhang, D. (2015). Sedentary behaviour and the risk of depression: a meta-analysis. PLoS ONE 10, e0131545

WHO (2016). Available at: http://www.who.int/mediacentre/factsheets/fs369/en/

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Netz. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.