

Comparative Efficacy of Exercise Training and Conventional Psychotherapies for Adult Depression: A Network Meta-Analysis

NICHOLAS HOOPER, MS¹; TESSA JOHNSON, MS²; MICHAEL SACHS, PHD³; ALEXIS SILVERIO, MPH³; LIN ZHU, PHD⁴; AISHA BHIMLA, MPH, PHD⁴; LOGAN TEAL, MSA⁵; STEPHANIE ROTH, MLIS⁶; CATILIN LAGROTTE, PSYD, MED⁷; JOYCE STRAVRAKIS, MS⁸; FRANK ARCANGELO, PHD⁹

¹Department of Medicine, Virginia Commonwealth University School of Medicine

²Department of Health and Rehabilitation Sciences, College of Public Health, Temple University

³Department of Kinesiology, College of Public Health, Temple University

⁴Center for Asian Health, Lewis Katz School of Medicine, Temple University

⁵Elevate Credit, Austin TX

⁶Ginsburgh Health Sciences Library, Temple University

⁷Behavioral Medicine, Cooper University

⁸Department of Education, Temple University

⁹Saratoga Psychological Associates, Saratoga Springs, New York

Correspondence: hoopernr@mymail.vcu.edu (Nicholas Hooper).

Objective An estimated 3.8% of the global population experiences depression, according to the [2019] WHO report. Evidence supports the efficacy of exercise training (EX) for depression; however, its comparative efficacy to conventional, evidence-supported psychotherapies remains understudied. Therefore, we conducted a network meta-analysis to compare the efficacy of exercise training (EX), behavioral activation therapy (BA), cognitive-behavioral therapy (CBT), and non-directive supportive therapy (NDST). **Methods** Our search was performed in seven relevant databases (inception to March 10, 2020) and targeted randomized trials comparing psychological interventions head-to-head and/or to a treatment as usual (TAU) or waitlist (WL) control for the treatment of adults (18 years or older) with depression. Included trials assessed depression using a validated psychometric tool. **Results** From 28,716 studies, 133 trials with 14,493 patients (mean age of 45.8 years; 71.9% female) were included. All treatment arms significantly outperformed TAU (standard mean difference [SMD] range, -0.49 to -0.95) and WL (SMD range, -0.80 to -1.26) controls. According to surface under the cumulative ranking (SUCRA) probabilities, BA was mostly likely to have the highest efficacy (1.6), followed by CBT (1.9), EX (2.8), and NDST (3.8). Effect size estimates between BA and CBT (SMD = -0.09, 95% CI [-0.50 to 0.31]), BA and EX (-0.22, [-0.68 to 0.24]), and CBT and EX (-0.12, [-0.42 to 0.17]) were very small, suggesting comparable treatment effects of BA, CBT, and EX. With individual comparisons of EX, BA, and CBT to NDST, we found small to moderate effect sizes (0.09 to 0.46), suggesting EX, BA, and CBT may equally outperform NDST. **Conclusions** Findings provide preliminary yet cautionary support for the clinical use of exercise training for adult depression. High study heterogeneity and lack of sound investigations of exercise must be considered. Continued research is needed to position exercise training as an evidence-based therapy.

Keywords: Exercise, Depression, Psychotherapy, Network Meta-Analysis, Physical Activity

Introduction

According to the World Health Organization, depression affects 3.8% of the global adult population and is a leading cause of global disability.¹⁻² Characterized by a depressed mood or a loss of interest or pleasure in daily activities, depression is often accompanied by problems with sleep, eating, energy, concentration, and self-worth.³ Considerable evidence demonstrates that exercise training (EX) reduces depressive symptoms,⁴⁻¹³ and some recent evidence-based guidelines support its use as a primary treatment for patients with mild to moderate depression.¹⁴ The National Institute for Health and Care Excellence (NICE), for example, recommends that patients with less severe presentations pursue a physical activity program as an initial treatment.⁸⁻⁹ For more severe presentations like major depressive disorder (MDD), studies demonstrate that adjunctive exercise training may improve clinical outcomes. EX combined with medication, for example, has produced higher remission rates than stand-alone medication treatment.¹⁵⁻¹⁶

Exercise training is an attractive therapy for depression for several reasons. First, exercise training (EX) is well-studied for its physical health benefits. Many patients with depression have health co-morbidities commonly associated with depression, including cardiovascular disease and diabetes mellitus.^{5-7,14} Exercise training programs may thus ease depressive symptoms directly and indirectly by resolving physical illnesses that might contribute to or worsen depression. Second, exercise is considered a “low-intensity therapy” because it can be pursued at a low cost, with less time investment from a specialized therapist, and with less client-therapist commitment¹⁷; therefore, it may be a more feasible treatment option for some patients compared to psychotherapy approaches.¹⁸ Indeed, many patients report practical barriers to psychotherapy, including concerns with the high cost of treatment,¹⁹ intense time commitment, and lack of access to qualified therapists. Patients may also encounter emotional and cultural barriers to psychotherapy.¹⁹⁻²⁰ Exercise training programs expect less disclosure of

personal and private information and are also imbued with less stigma. Thus, patients reluctant to pursue psychotherapy for such reasons may be more comfortable with an exercise-based approach. Finally, exercise training programs are well-tolerated by patients with a low risk of adverse side effects.²¹ Exercise may thus be an alternative approach for patients that respond poorly to medication. Indeed, up to 40% of patients report drug-related adverse effects.²²⁻²⁴ Due to drug-related side effects, patients increasingly prefer non-pharmacological approaches to treatment.²⁵

Though there is evidence for the antidepressant effects of stand-alone and adjunctive EX, some evidence suggests it remains underused as a treatment approach in clinical practice.²⁶ Indeed, EX is recommended less often for mental illnesses compared to physical illnesses despite growing evidence that EX eases the mental health burden.¹⁵ The lack of clinical implementation may reflect the lack of research on the comparative efficacy of exercise to other evidence-based psychotherapies for adult depression. Few randomized controlled trials have directly compared exercise to multiple established psychotherapeutic approaches. A network meta-analysis is a technique that can be used to gather evidence from both direct and indirect comparisons.²⁷ To date, no network meta-analysis has compared EX to multiple psychotherapies. The objective of this NMA was to compare the efficacy of EX and three evidence-supported behavioral therapies: cognitive-behavioral therapy (CBT), behavioral activation therapy (BA), and non-directive supportive therapy (NDST). CBT, a “gold standard” therapy, involves cognitive restructuring to correct maladaptive thinking, which is thought to contribute to behaviors that maintain or increase depression.²⁸ CBT often includes problem-solving strategies and skills training, behavioral activation, mindfulness and relaxation, exposure therapy, role-playing, and imagery²⁸ with evidence supporting its effective delivery in multiple formats (individual, group, in-person, book, computerized, and remote).²⁹ BA, widely used for depression, aims to reduce

depressive behaviors such as inactivity and avoidance through goal-setting, self-monitoring, problem-solving, and activity scheduling.^{30,31} Individuals receive positive reinforcement by engaging in activities that improve mood, thus mitigating depressive behaviors.³² Though these approaches share common features, they are

directed toward distinct goals: CBT resolves distorted cognitions³³, BA promotes behavioral activation³¹; and NDST increases social sharing and support³⁴. Evidence suggests that CBT, BA, and NDST elicit comparable treatment effects for individuals; therefore, we selected these therapies as comparators to EX.²⁵

Methods

Identification and Selection of Studies

The protocol for this network meta-analysis was registered at PROSPERO (CRD42018089067) and reported according to PRISMA guidelines (see Appendix 1).³⁵ A medical librarian conducted a detailed literature search (January 22, 2018, to March 10, 2020) in seven databases: PubMed (NLM); Embase (Elsevier); Scopus (Elsevier); Cochrane Central (Wiley); PsycInfo (EbscoHost); ClinicalTrials.gov; and PsychiatryOnline.org (see Appendix 2). Searches included a combination of controlled vocabulary and free text terms relevant to psychotherapy, exercise training, and depression with filters for human studies and randomized trials. Google Scholar was also searched to locate unpublished grey literature, ongoing studies, uncatalogued studies, and relevant dissertations. No language or publication date restrictions were imposed. After completing the search, two researchers independently screened studies for inclusion and exclusion using Rayyan QCRI software.³⁶ Full texts were retrieved if the title and abstract content were insufficient to determine inclusion. A third researcher resolved any disagreements.

Interventions were considered exercise training if they involved planned, structured, repetitive, and purposive exercise designed to improve or maintain physical fitness. Aerobic training, strength-focused training, and mixed training protocols (i.e., included both aerobic and strength-based training components) were included. Exercise protocols with contemplative components (e.g., yoga, tai chi, or qigong) were excluded. Contemplative techniques (e.g., mindfulness and/or meditation practices, breathwork, intention setting, loving-kindness,

and psychoeducation) often produce anti-depressant effects when practiced in isolation.⁷ Because this NMA sought to assess exercise-specific effects, we excluded mindful exercise programs. Prior work also indicates differential effects of non-mindful exercise compared to mindful exercise for depression³⁷; therefore, distinct mechanisms likely subserve the therapeutic action of non-mindful compared to mindful exercise programs. Randomized trials investigating mindful exercise programs also consistently suffer from significant methodological heterogeneity issues,³⁷ which are less common in randomized trials of non-mindful or pure exercise training protocols. In addition to exercise training, behavioral activation therapy, cognitive-behavioral therapy, and non-directive supportive therapy were included as treatment arms based on their distinct therapeutic approaches and widespread clinical use.³⁸⁻⁴⁰

Randomized trials comparing psychological interventions head-to-head and/or to a treatment as usual (TAU) or waitlist (WL) control were considered for inclusion. Trials included adult patients (18 years or older) with depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or a validated psychometric assessment for depression such as the Beck Depression Inventory (BDI)⁴¹ or the Hamilton Depression Rating Scale (HAMD).⁴² Trials including patients with or without somatic and/or non-psychotic mental illnesses were considered. No restrictions were imposed on the format or structure of psychological interventions (i.e., treatment duration, frequency, dose, setting

(internet or in-person), individual or group therapy) as some prior work indicates that treatments produce an anti-depressant effect regardless of format.²⁵ We excluded studies assessing patients with seasonal depressive

disorder, bipolar disorder, and/or psychotic disorders, studies assessing relapse prevention and maintenance treatment, and studies lacking English translation.

Data Analysis

Data Extraction Methods

An a priori data extraction form was adapted from the Cochrane Collaboration. From each study, the authors extracted: (1) general information (i.e., title, authorship, and publication date); (2) research design; (3) participant characteristics; (4) outcome measures; (5) statistical data; and (6) details

about the format and features of each intervention (i.e., type of intervention, frequency of sessions, intervention duration, session duration). Three researchers independently completed data extraction on included studies (see Appendix 3 for study characteristics).

Risk of Bias

Bias risk was judged using Cochrane's Risk of Bias Tool (RoB 2.0) for randomized trials and the CINeMA (Confidence in Network Meta-Analysis) web application.⁴³ Using the RoB 2.0 tool for randomized trials, two reviewers independently evaluated bias resulting from the randomization process; deviations from intended interventions missing outcome data; measurement of outcomes; and selection of the reported result.⁴⁴⁻⁴⁵ Bias risk for each criterion was judged as either low, some concerns, or high.⁴⁴⁻⁴⁵ The overall judgment for each domain of potential bias for each study was

then judged as low, high, or unclear. A third researcher resolved any disagreements. The certainty of the evidence for each outcome was then evaluated using the CINeMA approach—an approach based on the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) framework and used to evaluate within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence (see Appendix 4).⁴³ Using CINeMA, judgments were summarized into four confidence levels for each treatment effect: very low, low, moderate, or high.⁴³⁻⁴⁵

Network Meta-Analysis

The NMA was run through the program Stata version 15⁴⁶ using Stata routines as previously described by Chamimani and colleagues (see analysis codes in Appendices 5 and 6).⁴⁷ All within-group effect sizes were computed to run the NMA through Stata. The outcome measure was the standardized mean difference (SMD) statistic. A network plot was produced to illustrate the interventions and their respective evidence base with node size and line thickness corresponding to the number of patients randomized to each intervention and the number of studies between comparators,

respectively.⁴⁷ A contribution plot was also produced to inspect the influence of each direct piece of information on neighboring comparisons.⁴⁷ To evaluate the basic assumptions of an NMA, inconsistency and prediction interval plots were produced.⁴⁷ Inconsistency—understood as any discrepancy between direct and indirect effect estimates for the same comparison—threatens the validity of the results and the basic assumptions of an NMA. The inconsistency plot produces inconsistency factors (Ifs) for each closed loop (e.g., the loop of CBT-WL-BA).⁴⁷ Prediction

intervals (PrL) give the range within which the results of a future study might lie. Within the NMA framework, tests to assess multivariate heterogeneity have yet to be applied to NMAs.⁴⁸ Presenting summary effects with PrL facilitates the interpretation of the results even with heterogeneity but does not correct for high heterogeneity.⁴⁷ Lastly, surface under the cumulative ranking (SUCRA) probabilities were

produced to rank the treatments based on the outcome measure.⁴⁷ SUCRA curves express, as a percentage, the efficacy of every intervention relative to an imaginary intervention that always ranks best.⁴⁷ Therefore, larger SUCRA scores indicate a more effective intervention. As such, a higher SURCA score will correspond to a larger effect size and, thus, a treatment ranking closer to a first-place ranking.

Meta-Regression to Assess Moderators of Exercise Training Efficacy

To assess the effect of potential moderators on the efficacy of exercise training, we performed a meta-regression. Moderators included exercise type (i.e., aerobic, anaerobic, mixed), frequency (i.e., number of training sessions per week), intensity (i.e., low, moderate, vigorous), dose (i.e., minutes of exercise per training session), length of intervention (i.e., number of weeks), and severity of depression at baseline. Exercise intensity level for each study was determined based on the description of the intervention (e.g., low, moderate, or vigorous). If exercise intensity was unspecified, the type of physical activity or target heart rate determined intensity level. Using the American College of

Sports Medicine's guidelines⁴⁹, we defined an exercise intervention as moderate or vigorous if target heart rates were between 40-60% or 60-85% of maximum heart rate, respectively. If heart rate targets were unspecified and the intervention was described as walking (not brisk walking), the intervention was coded as low intensity. All anaerobic exercise studies were defined by how much weight individuals lifted (i.e., percentage of one's one repetition maximum). Baseline severity of depression was determined by interpreting the minimum cut-off score for inclusion in each study and comparing it to the scoring system for the depression scale implemented.

Results

Search Results and Study Characteristics

Of the 28,716 studies identified from the search, 133 randomized trials (14,493 patients) satisfied the inclusion and exclusion criteria (Figure 1; Appendix 9 for references of included studies). Detailed results and statistical code are available in Appendices 5, 6, 7.

The network plot, as shown in Figure 2, indicates that CBT, TAU, and WL were the most frequent comparators within the network. Most of the head-to-head trials compared an active treatment to either TAU or WL with most studies comparing CBT to TAU (n = 41) or CBT to WL (n = 40). Of the remaining treatment arms, most of the head-to-head trials were between CBT to NDST (n = 11) followed by BA to CBT (n = 7); EX to CBT (n = 5); BA to EX (n = 2); and BA and NDST (n = 1).

Overall, three arms lacked direct evidence: TAU and WL, NDST and EX, and NDST and WL. Most patients received CBT (n = 5,436) followed by EX (n = 1,665), BA (n = 778), and NDST (n = 508). More patients were assigned to TAU (n = 3,956) compared to WL (n = 2,150).

Across studies, most patients presented with mild to moderate depression. A diagnosis of unspecified depressive disorder was most common. Most of the patients were recruited from community samples or outpatient settings. Most of the participants were female (71.9%). The youngest average age of participants was 19.2 years,⁵⁰ and the oldest, 87.9 years.⁵¹ The average age of study participants was 45.8 years. Based on each study's reported average age of

participants, 23.3% of studies included predominately older adults (56 years and older), 53.4% middle-aged adults (36-55 years), and 23.3% younger adults (18-35 years). Most treatment lengths ranged from 8 to 12 weeks.

Across included studies, the average length of study duration was 12.2 weeks. The shortest duration of treatment was ten days,⁵² and the longest duration, 12 months (see Appendix 3).⁵¹

Figure 1. Flow Chart for the Inclusion of Studies

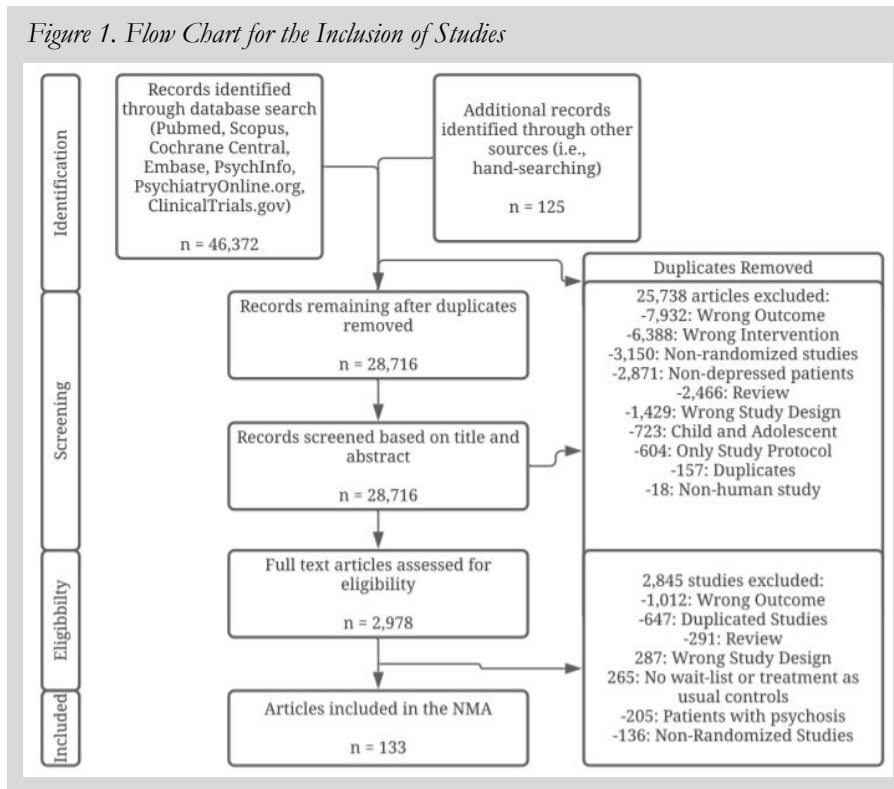
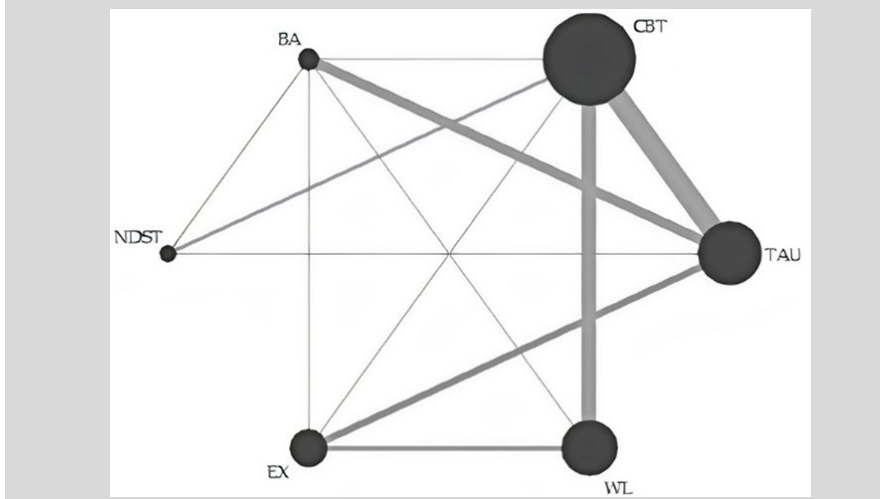


Figure 2. Network plot comparisons of exercise training (EX), behavioral activation therapy (BA), cognitive-behavioral therapy (CBT), non-directive supportive therapy (NDST), treatment as usual (TAU), and waitlist (WL). Nodes are weighted according to the number of patients randomly assigned to each of the four treatment interventions and two control conditions.



Exercise Training Study Characteristics

Of the 133 included studies, 36 studies (1,665 patients) implemented one or more exercise interventions. Based on the reported average age of participants, 41.7% of exercise studies included predominately older adults (56 years and older), 30.7% middle-aged adults (36-55 years), and 27.8% younger adults (18-35 years). Most studies (86.1%) included outpatient samples. Most studies (72.2%) included patients with a primary diagnosis of clinical depression or elevated symptoms of depression. The remaining studies included patients with clinical depression or elevated depression symptoms secondary to a brain-based disorder (e.g., stroke, multiple sclerosis, Parkinson's Disease, Alzheimer's Disease, or mild cognitive impairment), colorectal cancer, Sjogren's Syndrome, congestive heart failure, or polycystic ovarian syndrome. About half of the studies (55.6%) included patients with mild to moderate depression at baseline. Based on the 26 of 36 studies that provided sex characteristics, most participants ($n = 1093$) were female (73.6%). Most studies were conducted in North America (27.8%) and Europe (27.8%). Exercise interventions were most often supervised

(86.1%) by therapists, exercise specialists, or other trained professionals, delivered in a group format (55.6%), and conducted at a non-home-based location (66.7%). Exercise protocols were predominately aerobic; however, strength training (16.7%) and mixed protocols (19.4%) were also widely implemented. Aerobic interventions commonly featured walking, cycling, or running programs most often performed at a moderate intensity level (33.3%). The average duration of exercise training interventions was 11.6 weeks (ranging from 1.4 to 39.1 weeks). The average minimum dose (single bout) of exercise was 48.1 minutes (ranging from 20 to 60 minutes) with an average frequency of 3.2 exercise training sessions per week. All studies using anaerobic interventions implemented two or three training sessions per week. In contrast, only 65% of aerobic protocols implemented two to three training sessions per week; thus, aerobic training interventions had slightly higher variability in training frequency. In examining exercise intensity, most aerobic exercise interventions were of moderate intensity (45.5%), followed by low (31.8%) and vigorous intensity (22.7%).

Risk of Bias

Overall, most studies demonstrated a moderate to high risk of bias. Most of the direct evidence had a moderate risk of bias. Within-study bias most often resulted from a lack of blinding participants, researchers, and outcomes. Only one direct comparison—BA versus NDST—had an overall high risk of bias (see Figure 2).

According to CINeMA results, 3 of the 15 comparisons (20.0%) were rated with moderate confidence, 7 (46.7%) with low confidence, and 5 (33.3%) with very low confidence. Overall, each study showed a moderate risk for bias in each category.

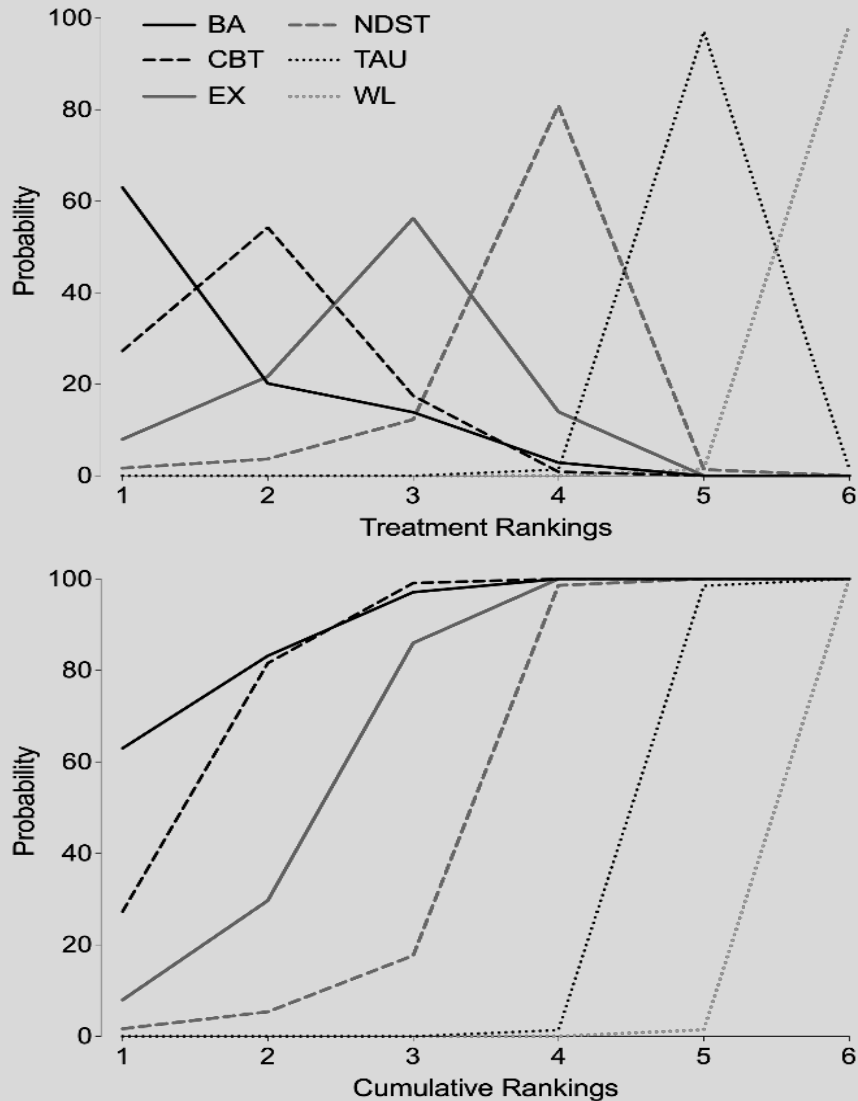
Network Meta-Analysis

SUCRA Treatment Rankings and Probabilities

Cumulative ranking plots for each of the treatment modalities, as shown in Figure 3, indicate the relative probability for each treatment arm to achieve a certain ranking. BA had a 97.1% chance of being ranked either first, second, or third. Of the treatments, BA had the

highest probability of being ranked first, at 63.0%. CBT had a 99.1% chance to rank in the top three treatments. Of the treatments, CBT had the highest probability of being ranked second, at 54.3%, and a 27.3% chance of being ranked first. EX, at 86.0%, had a slightly lower

Figure 3. Treatment and cumulative ranking plots for each intervention. This figure presents treatment (top) and cumulative (bottom) ranking plots formed using SUCRA. The treatment ranking plot shows the probability for each arm to receive a ranking of 1-6. The cumulative ranking plot show the cumulative probability of each arm.



BA = behavioral activation therapy; CBT = cognitive-behavioral therapy; EX = exercise training; NDST = non-directive support therapy; TAU = treatment as usual; and WL = waitlist.

chance of ranking in the top three treatments compared to BA and CBT and had the highest probability of being ranked third, at 56.3%, and a 21.7% likelihood of ranking second. Finally, NDST had the highest probability ranking fourth, at 80.9%, with only a 17.7% chance to rank in the top three. Finally, TAU had a 97.1%

chance of ranking second to last, and WL, a 98.5% chance of ranking last. Based on SUCRA values, BA (1.6) had the highest mean ranking, followed by CBT (1.9), EX (2.8), and NDST (3.8) (Table 1).

Table 1. SUCRA results, probability of each intervention being ranked 1st, and the average rank of each intervention when compared to each other.

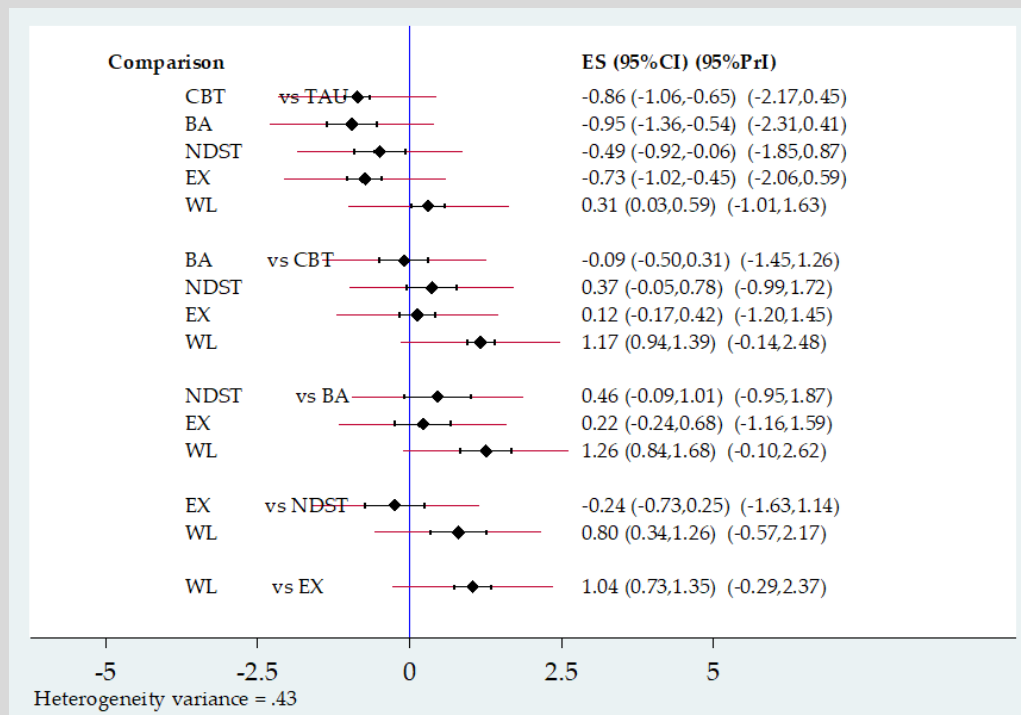
Treatment	SUCRA	Probability Ranked 1 st	Mean Rank
Behavioral Activation	88.7	63.0	1.6
Cognitive-behavioral Therapy	81.6	27.3	1.9
Exercise Training	64.7	8.0	2.8
Non-Directive Supportive Therapy	44.7	1.7	3.8
Treatment As Usual	20.0	00.0	5.0
Waitlist	00.3	00.0	6.0

Effect Size Estimates

All interventions were superior to TAU (SMD range, -0.49 to -0.95) and WL (SMD range, -0.80 to -1.26) control conditions (Figure 4). BA had the largest overall effect sizes compared to both WL (SMD = 1.26, 95% CI [0.84, 1.68]) and TAU (-0.95, [-1.36,-0.54]). EX also resulted in large effect sizes compared to both TAU (-0.73, [-1.02, -0.45]) and WL (1.04, [0.73, 1.35]) conditions. When comparing active treatment arms, EX resulted in a small effect

size compared to NDST (-0.24, [-0.73,0.25]). Finally, EX resulted in a small, less efficacious, effect size than both CBT (0.12, [-0.17,0.42]) and BA (0.22, [-0.24, 0.68]). Further analysis of effect measures can be found in the prediction interval plots (Figure 4). The contribution of direct and indirect statistics for each treatment arm can be found in the contribution plots (see Appendix 7).

Figure 4. Forest plots to present effect size estimates of comparisons. Prediction intervals (PrI) estimate where the outcomes of future RCTs may lie. Direct estimates are also presented. All outcomes are standardized mean difference with 95% confidence intervals (CI). The black line represents the current effect size 95% CI, while the red line represents the 95% prediction intervals. Heterogeneity variance = 0.43.



BA = behavioral activation therapy; CBT = cognitive-behavioral therapy; EX = exercise training; NDST = non-directive support therapy; TAU = treatment as usual; and WL = waitlist.

Heterogeneity

The inconsistency plot presents ten evidence loops within the network. When applying a common heterogeneity estimate to assess inconsistency, one of the ten loops showed statistically significant IF values suggesting some inconsistency between indirect

and direct estimates. However, when applying loop-specific heterogeneity estimates to assess inconsistency, none of the loops showed statistically significant IF values suggesting good agreement between indirect and direct estimates.

Exercise Training Meta-Regression

The moderator variables included in the meta-regression analysis yielded no significant effects

on the efficacy of exercise training (see Appendix 8).

Discussion

To our knowledge, this is the first network meta-analysis comparing the efficacy of exercise training to three conventional and common evidence-supported psychotherapies for adult depression. Based on comparative data from 133 randomized trials (14,493 patients), we present two findings: (1) as anticipated, exercise training, behavioral activation therapy, cognitive-behavioral therapy, and non-directive supportive therapy demonstrated greater efficacy for adult depression compared to two

inactive control conditions; and (2) exercise training demonstrated comparable efficacy to behavioral activation therapy, cognitive-behavioral therapy, and non-directive supportive therapy for adult depression. However, the methodological shortcomings of included trials hinder any conclusive statements of exercise training's evidence-based standing. Findings encourage more systematic investigation of exercise therapy for adult depression.

Differential Effects of Psychological Interventions

As anticipated, all treatment interventions were superior to control conditions. Of the four interventions, behavioral activation therapy was most likely to demonstrate the highest efficacy, followed by cognitive-behavioral therapy, exercise training, and non-directive supportive therapy. Though rankings suggest differential treatment effects, effect sizes between CBT and EX (0.12, [-0.17, 0.42]), EX and BA (0.22, [-0.24, 0.68]), and BA and CBT (-0.09, [-0.50, 0.31]) suggested no minimally important clinical differences (i.e., below the effect size cut-off of 0.24).⁵³ Thus, BA, CBT, and EX may produce comparable clinical treatment effects for adult depression. With individual comparisons of EX, BA, and CBT to NDST, effect sizes suggested minimally important clinical differences. Thus, EX, BA, and CBT may each produce a greater anti-

depressant effect compared to NDST. Overall, our effect size estimates converge with recent meta-analytic findings.⁵⁴⁻⁵⁷

Though our results indicate that EX, BA, and CBT have similar treatment effects, BA was most likely to have the highest efficacy compared to the other therapies. Though evidence for the efficacy of CBT for depression is most robust, multiple studies demonstrate superior efficacy of BA compared to CBT.⁵⁸⁻⁵⁹ In the 1990s, a component analysis of CBT found that the behavioral components worked as well as the entirety of the CBT intervention.⁵⁸ More recently, multiple RCTs have demonstrated that BA is comparable or superior to CBT.^{30,59} Such results indicate that there may be substantial value in using behavioral activation strategies (i.e., goal-setting, self-monitoring, activity scheduling, and reducing

avoidant behavior) for the treatment of depression.⁵⁹ These strategies are often incorporated into EX interventions.⁶⁰ Given the shared behavioral strategies used in BA and EX,

Exercise Training Features

Much to our surprise, our meta-regression analysis found no significant moderator effects. Strong evidence points to specific exercise training forms and formats that produce stronger anti-depressant effects.^{7,61} A recent cross-sectional study, for example, found that team sports produced the strongest anti-depressant effect followed by cycling, aerobic, and gym activities; therefore, social support may strengthen the anti-depressant effect of exercise training.⁷ Other evidence suggests that there may be important differences in response as a function of exercise type, frequency, and duration.⁷ For example, some evidence suggests an optimal effect with 45-minute bouts of exercise performed three to five times a week.⁷ The lack of moderator effects may stem from the considerable heterogeneity of included trials in this NMA. Some recent work, however, suggests that all exercise training formats reduce the burden of mental illness irrespective of training dose, type, and intensity.⁷ Because depression is commonly associated with reduced physical activity levels, sedentariness, and health issues consequent to inactivity,⁷ adults with depression may be particularly responsive to any structured exercise intervention. Current CDC guidelines recommend that adults perform at least 150 minutes per week of moderate-intensity activity.⁶² Most of the exercise interventions (61.1%) included in this NMA met the CDC's physical activity recommendations. Thus, when recommending exercise training as an alternative or adjunct treatment, clinicians might initially advise eligible patients to pursue any structured exercise program, provided the minimum physical activity requirements are met.

Given the inconsistent findings of moderator effects in the literature, additional systematic research is needed to parse the

BA and EX may share similar mechanisms of action and may be used in complementary ways, a speculation we discuss more below.

features of EX that may modulate its anti-depressant effect. This includes better characterizing high responders versus low non-responders. A patient's diagnosis, severity of depression, capacity for exercise, exercise history, motivational state, and other factors likely predict responsiveness to specific forms of exercise. For example, there is evidence that certain exercise training protocols may be more effective for certain types of patients, particularly those with chronic physical health problems.⁷ In addition, recent research suggests that comorbid anxiety may diminish the therapeutic effect of exercise for depression.⁶³ As such, it is important that further research examine the effect of exercise training formats, types of exercise, and co-morbidities on the therapeutic benefit of exercise training for depression. Assessing such factors will support the development of evidence-based guidelines for exercise training protocols for depression. As with other forms of therapy (e.g., BA), an individualized, patient-centered approach may optimize treatment.

Previous studies have examined the effectiveness of a combinational BA and EX approach.⁶⁰ In BA, the patient is guided to identify and practice activities perceived as pleasant.³¹ Exercise activities might be included to increase physical activity levels and improve health outcomes. It is well-established in the sport psychology literature that exercise adherence is stronger when the exerciser develops clear goals and is intrinsically motivated to partake in the exercise activity.⁶⁴ Thus, BA might provide a useful framework for promoting exercise in patients with depression whilst capitalizing on the benefits of both EX and BA. This combination approach might, in turn, produce a stronger anti-depressant effect for the patient. Future work might systematically explore the addition of exercise within a BA

framework. Similarly, CBT and EX may be stacked to augment the behavioral components of CBT. Exercise training interventions might

also borrow from behavioral activation principles to promote exercise adherence.

Limitations

Several limitations warrant mention. First, most studies suffered from methodological limitations, including small sample size, selective reporting of data and protocols, publication bias, and multiple outcome and time point measures. Second, this NMA excluded studies comparing pharmacology to exercise for depression. Many studies have compared exercise to pharmacology, but the objective of this study was to better assess the use of exercise compared to other behavioral, non-pharmacological approaches. Though anti-depressants are widely used in clinical practice, numerous studies report that patients increasingly prefer non-pharmacological treatments.^{25,65} Future research might conduct a more comprehensive NMA, comparing psychotherapy, psychopharmacology, and exercise training for depression.

Despite stringent inclusion and exclusion criteria, a large portion of the findings yielded heterogeneous outcomes. High heterogeneity may challenge the transitivity assumption. Given the heterogeneous outcomes and the questions regarding basic network meta-analytic assumptions, it is imperative to interpret the results of this analysis with caution.

As another confounding factor, this study did not control for depression severity, which may have affected the efficacy outcomes of each treatment modality. Most studies included patients with mild to moderate depression as scored with validated screening tools. The few studies that examined more severe forms of depression, such as major depression disorder (MDD), employed CBT. The use of CBT for MDD may be due to the overwhelming and long-standing support for CBT for depression.⁶⁶ At present, few studies have examined the efficacy of EX for MDD. Because amotivation is typically associated with MDD, individuals with MDD may lack the

necessary motivation to exercise.⁶¹ Future studies are needed to address this speculation. Future work will also benefit by controlling for the effect of depression severity.

Findings may also be limited by our use of a Frequentist in lieu of a Bayesian approach. Evidence suggests that differences in effect sizes can occur depending on which of these approaches is adopted.^{67,68} In a re-analysis of data from 14 NMAs, Sadeghirad and colleagues (2017) found differences in the magnitude of effect estimates.⁶⁷ However, similar to previous work,⁶⁸ the authors rarely found differences in the direction of treatment rankings. According to these findings, applying a Bayesian approach to this NMA may have produced slightly larger effect estimates, but the treatment rankings would have likely remained unchanged.

Use of treatment as usual and waitlist controls as comparators may have contributed to the study's moderate to high levels of bias and confounded treatment estimates. According to some findings, WL control conditions may produce a placebo effect.⁶⁹ Delayed treatment may implicitly discourage patients from seeking alternative treatments until the waitlist period has finished, which might cause disappointment and increased depression. As a result, this may drive spurious findings in favor of the active comparison. TAU also invites some concern as it is often an ill-defined and highly variable control condition across trials. TAU may depend, for example, on the clinical context of the research trial. It could consist of comprehensive clinical care or little to no care at all. It is possible, for example, that the structure of TAU is different when compared to CBT, a therapy more likely to be offered in clinical settings with good quality TAU than when it is compared to exercise, a therapy more likely to be offered in non-clinical settings without good quality TAU. To assess the differential effects of TAU and WL control conditions, we performed

two additional network analyses. The TAU network found that both BA and EX had an equal average ranking of 2.0, while CBT ranked 2.3. In contrast, the WL network found that BA ranked first (1.2), followed by CBT (2.0) and EX (3.3). Though TAU and WL may skew effect size estimates, previous NMAs heavily employ these control conditions.⁷⁰⁻⁷² Even so, the authors realize that claiming treatment interventions are effective because they outdo TAU and WL conditions is potentially flawed as TAU and WL conditions may be weak comparisons from which to arrive at such claims. Future investigations of psychological interventions for depression might consider using more clearly defined control conditions, active controls, and/or controlling for the quality of TAU.

Another important point to address is that the number of studies employing exercise training was comparatively less compared to CBT. The overwhelming evidence base of this NMA compared CBT to TAU or CBT to WL. In addition, most of the head-to-head trials included in the analysis compared an active treatment to either of these two control conditions. CBT for depression has been heavily researched for over 50 years; therefore, the

number of randomized trials examining CBT is expectedly greater than other interventions. Of the evidence base, however, 27% of our studies examined exercise as a treatment modality, which is the second highest for any treatment arm behind CBT. Although the evidence base included in this paper is less for exercise than for CBT, we are limited to the available evidence. In addition, there was a limited number of RCTs directly comparing EX to these established therapies. Due to the variability of depressive symptoms over time and the rate of spontaneous remission, it is important to have direct head-to-head RCTs comparing forms of therapy to draw stronger conclusions regarding therapeutic efficacy. Additional work evaluating the efficacy of exercise training for depression in larger samples is thus encouraged.

Finally, we limited our analysis to four psychological interventions, excluding both mindfulness-based exercise programs and psychopharmacology. Future work might consider including a more comprehensive set of treatments to make additional comparisons; however, such investigations must develop strict methodologies to ensure basic network meta-analysis assumptions are met.

Conclusions and Future Directions

According to findings from this network meta-analysis, exercise training may be a useful treatment option for adult depression with comparable effects to “gold standard” therapies.⁶⁶ However, there is insufficient evidence to recommend exercise training as a proven, evidence-based therapy to treat clinical depression in adults. There are very few methodologically sound RCTs that compare exercise to different non-pharmacologic treatments for adult depression. More research

is thus needed. Considering the limited evidence, clinicians might consider exercise training as an alternate or adjunct treatment for adults with mild to moderate depression. Most of the exercise interventions included in this NMA satisfied CDC physical activity guidelines for adult depression; thus, these guidelines might be recommended as part of treatment. Future research is needed to develop more well-defined exercise training guidelines.

Conflicts of Interest

None of the authors have any potential conflict of interests.

Funding Sources

L. Zhu's research is funded by Postdoctoral Fellowship, Award Number 18POST34030416 from American Heart Association (AHA), and TUFCCC/HC Regional Comprehensive Cancer Health

Disparity Partnership, Award Number U54 CA221704(5) from the National Cancer Institute of National Institutes of Health (NCI/NIH). The contents are solely the responsibility of the authors and do not necessarily represent the official views of the AHA or NCI/NIH.

Statement of Contributions

NH and MS had the idea for the paper. NH was the primary author. Other co-authors contributed specific sections: SR (literature search), AS (secondary reviewer and risk of bias assessment), TJ (manuscript preparation and data extraction), AB (data extraction), LT (data extraction), LZ (data analysis and coding), CL (tie breaker for inclusion), JS (tie breaker for inclusion), and FA (tie breaker for inclusion). All authors revised the draft report and approved the final version. TJ significantly contributed to the development of the manuscript.

References

1. CDC. National Center for Health Statistics: Depression. <https://www.cdc.gov/nchs/fastats/depression.htm>
2. World Health Organization. Depression: Fact sheet May 1 2021. <https://www.who.int/news-room/fact-sheets/detail/depression>.
3. American Psychiatric Association. (2013). Depressive Disorders. In Diagnostic and statistical manual of mental disorders (5th ed.). <https://doi.org/10.1176/appi.books.9780890425596.dsm05>
4. Correll CU, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* 2017; 16:163-180.
5. Vancampfort D, et al Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry* 2016;15:166-74.
6. Firth, J. et al. The Lancet Psychiatry Commission: A blueprint for protecting physical health in people with mental illness. *The Lancet Psychiatry* 2019; 6: 675-712/
7. Chekroud SR, et al. Association between physical exercise and mental health in 1.2 million individuals in the USA between 2011 and 2015: A cross-sectional study. *The Lancet Psychiatry* 2018;9: 739-746.
8. National Institute for Health and Care Excellence. Depression in adults: Recognition and management. April 2018. <https://www.nice.org.uk/guidance/cg90> (Jun 11 2019).
9. World Health Organization. Mental health: Physical activity. Jun 2012. https://www.who.int/mental_health/mhgap/evidence/resource/depression_q6.pdf?ua=1 (Jun 11 2019).
10. Schuch FB, Vancampfort D, Richards JA, Rosenbaum S, Ward PB, Stubbs B. Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. *J Psychiatr Res* 2016; 77: 42-51.
11. Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, McMurdo M, Mead GE. Exercise for depression. *Cochrane Database Syst Rev*. 2013 Sep 12;(9):CD004366. doi: 10.1002/14651858.CD004366.pub6.
12. Helgadóttir B, Forsell Y, Hallgren M, Möller J, Ekblom Ö. Long-term effects of exercise at different intensity levels on depression: A randomized controlled trial. *Prev Med*. 2017 Dec;105:37-46. doi: 10.1016/j.ypmed.2017.08.008.
13. Rethorst, C. D. (2019). Effects of exercise on depression and other mental disorders. In M. H. Anshel, S. J. Petruzzello, & E. E. Labbé (Eds.), *APA handbook of sport and exercise psychology*, Vol. 2. Exercise psychology (pp. 109–121). American Psychological Association. <https://doi.org/10.1037/0000124-006>
14. Stubbs B., et al. EPA guidance on physical activity as a treatment for severe mental illness: A meta-review of evidence and position statement from the European Psychiatric Association (EPA),

- supported by the International Organization of Physical Therapists in Mental Health (IOPTMH). *Eur Psychiatry* 2018; 54: 124-144.
15. Chekroud AM, Trugerman A. The opportunity for exercise to improve population mental health. *JAMA Psych* 2019. Published online Sep 4, doi: 10.1001/jamapsychiatry.2019.2282.
 16. Trivedi MH, Greer TL, Church TS, et al. Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. *J Clin Psychiatry* 2011; 72(5): 677-684.
 17. Bennett-Levy, J., Richards, D., Farrand, P., Griffiths, D. K., Klein, B., Proudfoot, J., & Ritterband, L. (2014). *Oxford Guide to low intensity CBT interventions*. OUP Oxford.
 18. Cochrane Collaboration Depression, Anxiety, and Neurosis Group. CCDAN Topic list: Intervention-psychological therapies. 2013. http://ccdan.cochrane.org/sites/ccdan.cochrane.org/files/uploads/CCDAN%20topics%20list_psychological%20therapies%20for%20website.pdf (Jun 11 2019).
 19. Chekroud AM, Foster D, Zheutlin AB, Gerhard DM, Roy B, Koutsouleris N, et al. Predicting Barriers to Treatment for Depression in a U.S. National Sample: A Cross-Sectional, Proof-of-Concept Study. *Psychiatr Serv*. 2018 Aug 1;69(8):927-934. doi: 10.1176/appi.ps.201800094
 20. Mohr DC, Hart SL, Howard I, Julian L, Vella L, Catledge C, et al. Barriers to psychotherapy among depressed and nondepressed primary care patients. *Ann Behav Med*. 2006 Dec;32(3):254-8. doi: 10.1207/s15324796abm3203_12
 21. Belvederi Murri M., Ekkekakis P, Magagnoli M, et al. Physical exercise in major depression: Reducing the mortality gap while improving clinical outcomes. *Frontiers in psychiatry* 2019; 9: 762. <https://doi.org/10.3389/fpsy.2018.00762>
 22. Cascade, E., Kalali, A. H., & Kennedy, S. H.. Real-World Data on SSRI Anti-depressant Side Effects. *Psychiatry (Edmont (Pa. : Township))* 2009; 6(2), 16–18.
 23. Hirsch M, Birnbaum RJ. Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects. *UpToDate* 2019.
 24. Gartlehner G, Thieda P, Hansen RA, et al. Comparative risk for harms of second-generation anti-depressants: A systematic review and meta-analysis. *Drug Saf* 2008; 31: 851-865.
 25. Cuijpers P, Quero S, Dowrick C, Arroll B. Psychological treatment of depression in primary care: Recent developments. *Curr Psychiatry Rep* 2019.
 26. Morres ID, Hatzigeorgiadis A, Stathi A et al. Aerobic exercise for adult patients with major depressive disorder in mental health services: A systematic review and meta-analysis. *Depress. Anxiety* 2018; 36(1):39-53.
 27. Petticrew M, Rehfuess E, Noyes J, et al. Synthesizing evidence on complex interventions: how meta-analytical, qualitative, and mixed-method approaches can contribute. *J Clin Epidemiol* 2013; Published online Aug 14. DOI: 10.1016/j.jclinepi.2013.06.005.
 28. Beck, J. S. (2011). *Cognitive behavior therapy: Basics and beyond*. New York, NY: Guilford Press
 29. Cuijpers P, Noma H, Karyotaki E, Cipriani A, Furukawa TA. Effectiveness and Acceptability of Cognitive Behavior Therapy Delivery Formats in Adults With Depression: A Network Meta-analysis. *JAMA Psychiatry*. 2019;76(7):700-707. doi: 10.1001/jamapsychiatry.2019.0268
 30. Soleimani, M., Mohammadkhani, P., Dolatshahi, B., Alizadeh, H., Overmann, K. A., & Coolidge, F. L. A Comparative Study of Group Behavioral Activation and Cognitive Therapy in Reducing Subsyndromal Anxiety and Depressive Symptoms. *Iran. J. Psychiatry* 2015; 10(2), 71–78.
 31. Dimidjian S, Barrera M Jr, Martell C, Muñoz RF, Lewinsohn PM. The origins and current status of behavioral activation treatments for depression. *Annu Rev Clin Psychol*. 2011;7:1-38. doi: 10.1146/annurev-clinpsy-032210-104535
 32. Hopko DR, Lejuez CW, Ruggiero KJ, Eifert GH. Contemporary behavioral activation treatments for depression: procedures, principles, and progress. *Clin Psychol Rev*. 2003;23(5):699-717. doi: 10.1016/s0272-7358(03)00070-9.

33. Hofmann, S. G., Asaani, A., Vonk, I. J. J., Sawyer, A. T. & Fang, A. The efficacy of cognitive-behavioral therapy: A review of meta-analyses. *Cognit Ther Res* 2012; 36(5), 427-440. doi: 10.1007/s10608-012-9476-1
34. Barth J, Munder T, Gerger H, et al. Comparative efficacy of seven psychotherapeutic interventions for patients with depression: A network meta-analysis. *PLoS Med* 2013; Published online May 28. DOI: 10.1371/journal.pmed.1001454.
35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
36. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan- A web and mobile app for systematic reviewers. *Syst Rev* 2016; 5: 210.
37. Tsang HW, Chan EP, Cheung WM. Effects of mindful and non-mindful exercises on people with depression: a systematic review. *Br J Clin Psychol*. 2008 Sep;47(Pt 3):303-22. doi: 10.1348/014466508X279260
38. Jobst A, Brakemeier EL, Buchheim A, et al. European Psychiatric Association Guidance on psychotherapy in chronic depression across Europe. *Eur Psychiatry* 2016; 33: 18-36.
39. Qaseem A, Berry MJ, Kansagara D. Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2016; 164: 350-359.
40. NICE. Depression in adults: Recognition and management clinical guidance. 2009. <https://www.nice.org.uk/guidance/cg90/chapter/Recommendations>
41. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4: 561-571.
42. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967; 6: 278-296.
43. Nikolakopoulou, A., Higgins, J., Papakonstantinou, T., Chaimani, A., Del Giovane, C., Egger, M., & Salanti, G. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS med* 2020, 17(4), e1003082. <https://doi.org/10.1371/journal.pmed.1003082>
44. National Collaborating Centre for Methods and Tools. Appraising the risk of bias in randomized trials using the Cochrane Risk of Bias Tool. 2016. <https://www.nccmt.ca/knowledge-repositories/search/280> (Jun 21 2019).
45. Page MJ, Shamsler L, Altman DG, et al. Epidemiology and reporting characteristics of systematic reviews of biomedical research: A cross-sectional study. *PLoS Med* 2016; Published online May 24. DOI: 10.1371/journal.pmed.1002028.
46. StataCorp. Stata Software. 2018. <https://www.stata.com/> (Jun 21 2019).
47. Chaimani A, Higgins JP, Mayrdis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013; Published online Oct 3. DOI: 10.1371/journal.pone.0076654.
48. Lin L. Use of Prediction Intervals in Network Meta-analysis. *JAMA Netw Open* 2019 Aug 2;2(8):e199735. doi: 10.1001/jamanetworkopen.2019.9735. PMID: 31433478; PMCID: PMC6707007.
49. Reibe D , Jonathan K , Liguori G , et al . ACSM's Guidelines for Exercise Testing and Prescription. 10th edn. Wolters Kluter, 2018.
50. McIndoo CC, File AA, Preddy T, Clark CG, Hopko DR. Mindfulness-based therapy and behavioral activation: A randomized controlled trial with depressed college students. *Behav Res Ther* 2016; 77; 118-128.
51. Williams CL, Tappen RM. Exercise training for depressed older adults with Alzheimer's disease. *Aging Ment Health* 2008; 12: 72-80.
52. Martin PR, Aiello R, Gilson K, Meadows G, Milgrom J, Reece J. Cognitive behavior therapy for comorbid migraine and/or tension-type headache and major depressive disorder: An exploratory randomized controlled trial. *Behav Res Ther* 2015; 73: 8-18.

53. Cuijpers P, Turner, EK, Koole SL, Dijke AV, Smit F. What is the threshold for a clinically relevant effect? The case of major depressive disorders. *Depress Anxiety* 2014; 00: 1-5.
54. Van Straten A, Geraedts A, Verdonck-de LI, Andersson G, Cuijpers P. Psychological treatment of depressive symptoms in patients with medical disorders: A meta-analysis. *J Psychosom Res* 2010; 69: 23-32.
55. Beltman MW, Voshaar RC, Speckens AE. Cognitive-behavioral therapy for depression in people with somatic disease: Meta-analysis of randomized controlled trials. *Br J Psychiatry* 2010; 197: 11-19.
56. Cuijpers P, Driessen E, Hollon SD, van Oppen P, Barth J, Andersson G. The efficacy of non-directive supportive therapy for adult depression: a meta-analysis. *Clin Psychol Rev* 2012;32(4):280-91. doi: 10.1016/j.cpr.2012.01.003.
57. Ekers D, Webster L, Van Straten A, Cuijpers P, Richards D, Gilbody S. Behavioural activation for depression; an update of meta-analysis of effectiveness and sub group analysis. *PLoS One* 2014;9(6):e100100. doi: 10.1371/journal.pone.0100100.
58. Jacobson, N. S., Dobson, K. S., Truax, P. A., Addis, M. E., Koerner, K., Gollan, J. K., et al. A component analysis of cognitive-behavioral treatment for depression. *J Consult Clin Psychol* 1996; 64, 295–304. <https://doi.org/10.1037/0022-006X.64.2.295>.
59. Dimidjian S, Hollon SD, Dobson KS, Schmaling KB, Kohlenberg RJ, Addis ME, et al. Randomized trial of behavioral activation, cognitive therapy, and anti-depressant medication in the acute treatment of adults with major depression. *J Consult Clin Psychol.* 2006;74(4):658-70. doi: 10.1037/0022-006X.74.4.658.
60. Lambert, JD., Greaves, CJ., Farrand, P., Price, L., Haase, AM., & Taylor, AH. (2018). Web-Based Intervention Using Behavioral Activation and Physical Activity for Adults With Depression (The eMotion Study): Pilot Randomized Controlled Trial. *J. Med. Internet Res.* 2018; 20(7), e10112. <https://doi.org/10.2196/10112>
61. Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB, Stubbs B. Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. *J Psychiatr Res.* 2016;77:42-51. doi: 10.1016/j.jpsychires.2016.02.023
62. How much physical activity do adults need? (2020, October 07). Retrieved February 05, 2021, from <https://www.cdc.gov/physicalactivity/basics/adults/index.htm>
63. Blumenthal JA, Babyak MA, Craighead WE, Davidson J, Hinderliter A, Hoffman B, et al. The role of comorbid anxiety in exercise and depression trials: Secondary analysis of the SMILE-II randomized clinical trial. *Depress Anxiety.* 2021;38(2):124-133. doi: 10.1002/da.23088.
64. Weinberg, Robert S, and Daniel Gould. *Foundations of Sport and Exercise Psychology.* Champaign, IL: Human Kinetics, 1995.
65. Hickie IB, Luscombe GM, Davenport TA, Burns JM, Highet NJ. Perspectives of young people on depression: awareness, experiences, attitudes and treatment preferences. *Early Interv Psychiatry.* 2007;1(4):333-9. doi: 10.1111/j.1751-7893.2007.00042.x.
66. David D, Cristea I, Hofmann SG. Why cognitive-behavioral therapy is the current gold standard for psychotherapy. *Front Psychiatry* 2018. Published online Jan 29, 2018. Doi: 10.3389/fpsy.2018.00004
67. Sadeghirad B, Brignardello-Petersen R, Johnston BC, Guyatt GH, Beyene J. Comparing bayesian and frequentist approaches for network meta-analysis: An empirical study. *Global Evidence Summit, Cape Town, South Africa.* 15 Sept 2017.
68. Hong H, Carlin, BP, Shamliyan TA, et al. Comparing Bayesian and frequentist approaches for multiple outcome mixed treatment comparisons. *Med Decis Making* 2013; 33: 702-714.
69. Furkawa TA, Noma H, Caldwell DM, et al. Waiting list may be a nocebo condition in psychotherapy trails: A contribution from network meta-analysis. *Acta Psychiatr Scand* 2014; 130: 181-192.

70. Cuijpers P, Noma H, Karyotakki E, Cipriani A, Furukawa TA. Effectiveness and acceptability of cognitive behavior therapy delivery formats in adults with depression: A network meta-analysis. *JAMA Psychiatry* 2019; 76: 700-707.
71. Lopez- Lopez JA, Davies SR, Caldwell DM, et al. The process and delivery of CBT for depression in adults: A systematic review and network meta-analysis. *Psychol Med* 2019; 49: 1937-1947.
72. Corbett MA, Rice SJ, Madurasinghe V, et al. Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: Network meta-analysis. *Osteoarthritis Cartilage* 2013; 21: 1290-1298.