

ActiveCBT for depression: Transforming treatment through exercise priming (CBT+ Trial)

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Protocol Revision History

Approval Date	Summary of Changes	Rationale
8/29/24	Site PI Change	The study PI took a new position at the University of Wisconsin-Madison. To finish the trial, Nathaniel Wade became the Site PI until study completion, with remote oversight from Jacob Meyer.
4/18/24	The consent was revised to detail that senior research team members (e.g., Research Scientist) would also have access to data on Lyssn.	This was necessary to allow senior research personnel to export the generated excel files from Lyssn to use in analyses
12/1/2023	The behavioral disturbance exclusionary criteria was revised to: <i>Exhibit behavioral disturbance (e.g., aggression, mild-moderate cognitive impairment) or relationships with study team members (i.e., clinical interviewers or therapists) that would significantly interfere with study participation, as assessed by clinical research personnel</i>	A participant reported relationships with both therapists and was exited from the study. This clause to the existing criterion was added to minimize this occurrence.

1. Background

Depression is a leading cause of disability worldwide, with 30% of US adults suffering from a major depressive episode in their lifetime and experiencing multiple episodes is common. While psychotherapy is a standard front-line treatment for depression, only half of patients respond to therapy, including cognitive behavioral therapy (CBT), and many relapse shortly thereafter. Taken together, the high prevalence and significant number of patients who do not respond to current treatments indicate that there is a critical need for novel approaches to improve MDD treatment success. Current therapy practice could be more effective, via augmenting non-pharmacological approaches, such as exercise, which is appealing to patients. Exercise has powerful acute psychobiological effects, including immediate improvements in psychological states and short-term enhancement of neuroplastic mechanisms. A combined approach sequencing moderate aerobic exercise immediately before treatment, however, needs to be tested in a larger trial to determine the potential for exercise priming to improve process mechanisms of CBT and eventual overall treatment success.

2. Study Objectives

This study was a 1:1 severity-stratified (mild, moderate-to-severe) parallel-group randomized controlled clinical trial of ActiveCBT (pre-therapy exercise) vs. CalmCBT (quiet rest pre-therapy) for the treatment of major depression with masked assessors and interventionists called the 'CBT+ Study.' The overall goals of this project are to examine the efficacy of exercise priming (i.e., intentional sequencing of aerobic exercise immediately prior to cognitive behavioral therapy ['ActiveCBT']) to treat depression. Specific aims were to 1) demonstrate the effects of exercise priming on mechanisms associated with therapy success (i.e., working alliance, behavioral activation), 2) examine how psychological (e.g., anhedonia) and neuroplastic (e.g., brain-derived neurotrophic factor) mechanisms relate to CBT mechanisms, and 3) determine the efficacy of exercise priming for treatment of depression.

3. Number of Participants

Forty individuals were enrolled in the study. Randomization of individuals occurred after all baseline measures are collected during the first CBT session. Individuals who withdraw were not replaced once randomized.

4. Inclusion and Exclusion Criteria

Participants included in the study were diagnosed with major depressive disorder and in a major depressive episode via the Structured Clinical Interview for Depression (SCID), had at least mild clinical symptoms of depression (Hamilton Rating Scale for Depression [HAMD] ≥ 8), aged 18–65, on a stable mental health medication or psychotherapy treatment regimen for at least eight weeks, willing to refrain from changing mental health treatment for the duration of the intervention, had not participated in structured CBT in the past 5 years, and reported they could safely participate in physical activity (via Physical Activity Readiness Questionnaire). Exclusion criteria were: body mass index ≥ 40 ; pose an imminent risk of harm to others or self-harm (Columbia Suicide Severity Rating Scale of 5); current substance use disorder; lifetime bipolar, mania, or psychosis; pregnant or planning to become pregnant during study enrollment; currently used tobacco or other nicotine products; or exhibited behavioral disturbance (e.g., aggression, mild-moderate cognitive impairment) that would significantly interfere with study participation, as assessed by clinical research personnel during intake.

5. Recruitment Methods

Participants were recruited via referral from university and community partners (i.e., student counseling services, on-campus medical clinic, therapist wait-lists, and surrounding clinics), mass emails, flyers, and contacts in large corporations in Ames, Iowa and surrounding communities.

6. Consent Process

Individuals interested in participating completed an online pre-screening survey to assess basic eligibility criteria. Eligibility criteria were subsequently verified via a phone screening survey. If potentially eligible after the online and phone screening process, individuals attended an Intake Visit at the Iowa State University Research Park, led by senior research personnel knowledgeable about all study procedures. Informed consent occurred in person at the beginning of the visit, and participants were asked to thoroughly read the informed consent document. The research team left the room to minimize influence and allow ample reading time. After, participants were given a verbal overview of the document, figures showing study visit flow, and images of the therapy space and assessment spaces, allowing additional opportunities for questions. After all questions were

answered, interested participants signed the informed consent document electronically on REDCap and enrolled in the study.

7. Procedures

Intake Visit

During the intake visit, participants completed the informed consent processes detailed above. Next, anthropometric assessments were taken. They then completed a Structured Clinical Interview for DSM-5 (SCID) by a trained Clinical Interviewer to screen for current MDD and assess for the presence of exclusionary psychological diagnoses. Only participants with MDD and no exclusionary psychological diagnoses were included in the study. The interviewer also completed the Hamilton Rating Scale for Depression (HAM-D) and Columbia Suicide Severity Rating Scale (C-SSRS) during this interview to assess depressive symptom severity and monitor risk of suicide. If participants expressed suicide ideation or plan, the interviewer collaboratively develop a safety plan for the participant to utilize during the week and to share with the participant's therapist during their first therapy session. After the clinical interview, eligible participants completed questionnaires (detailed in Table 1) via REDCap. Finally, participants were provided with instructions and asked to wear an activPAL accelerometer for 7 days (24 hours/day). They were provided with an activPAL log and asked to record all sleep time (e.g., time to sleep, wake time) and non-wear time. Participants scheduled their initial therapy session within the next week.

CBT+ Sessions

During the 8-week treatment period, participants arrived about 45 minutes prior to the start of their CBT session. Prior to blood draws (sessions 1, 4, and 8), participants were encouraged to not exercise and abstain from alcohol consumption 24-hour to the visit, and abstain from consuming caffeine or smoking nicotine products (e.g., tobacco, cigarettes, vaping) for at least 4 hours prior to the visit, as these activities and substances may influence blood biomarker levels. If participants did not comply with these lifestyle considerations, the session was still be completed but notes were recorded regarding the deviation.

During sessions 1 and 5, when participants arrive, they first returned the ActivPAL accelerometer and log. After, in session 1, participants were randomized to group. A randomization module on REDCap was used to implement the allocation sequence. The necessary allocation tables were generated by the study statistician and uploaded to the REDCap randomization module.

Next, in all sessions, participants completed questionnaires in REDCap, including Anhedonia, PHQ-9, BADS, and ATQ. Blood pressure and heart rate were then be collected. During sessions 1, 4, and 8, the SF-36, IPAQ (verbally), and GAD-7 were administered, and a blood sample was collected.

Following, individuals randomized to ActiveCBT completed 30 min of cycling on a recumbent stationary bicycle (Lode Corival Recumbent, Lode BV, Groningen, The Netherlands) at moderate intensity (rating of perceived exertion [RPE] of 13 on the 6–20 scale (Borg, 1998) while individuals in the CalmCBT condition sat quietly (RPE of 6). Standardized instructions for RPE were provided to all participants. All participants were asked to report their RPE and heart rate (Polar H10, Polar Electro Oy, Kempele, Finland) was recorded every minute for the first 3 min (ActiveCBT warm-up), at 5-min increments starting at minute 5, and then at every minute for the last 3 min starting at minute 27 (ActiveCBT cool-down). ActiveCBT participants were instructed to achieve a moderate intensity to coincide with the end of the 3-min warm-up and maintain that intensity by self-adjusting the workload until cool-down. Exercise workload (e.g., watts, cadence) was recorded at the same intervals for ActiveCBT participants.

Both the ActiveCBT and CalmCBT conditions were presented with equipoise, and each participant was aware that they may be randomly assigned to either condition. Each condition was described simply as a pre-therapy condition, and participants were informed that the study aimed to examine how these experiences might influence therapy. To provide a standardized experience across conditions, all participants watched 30 min of a standardized nature video.

All participants watched a standard 30-min segment from the nature documentary, Blue Planet II, Season 1 (Blue planet II, 2017). This was selected as it provided a neutral video stimulus, was available for the duration of the study, and a new segment could be used for all 8 study visits with episodes and start times in the protocol paper (Meyer et al., 2024).

Upon completion of the 30-minute video, all participants completed the Anhedonia and Video Survey on REDCap. During Sessions 1, 4, and 8, another blood sample will be taken at this time. Following, participants were escorted to meet with a trained therapist and begin their individual therapy within approximately 10 minutes after the end of the Active/Calm condition in a private therapy room.

Participants began a 50-min standardized therapy session with a trained mental health counselor, masked from group assignment. Each session had a theme and was standardized based upon the CBT manual developed by the South Central MIRECC (Cully and Teten, 2008). Additional content details are provided in the protocol paper. Each session was audio and video recorded using Lyssn (Lyssn, Seattle, WA), for ongoing supervision and fidelity checks. The Lyssn platform provides an algorithm-generated rating score for the Cognitive Therapy Rating Scale (CTRS (Young and Beck, 1980)) using an artificial intelligence-trained machine learning model based on the conversational content within each recorded session (e.g., (Imel et al., 2024)). Participants were instructed to not discuss their assigned pre-therapy condition/group assignment during therapy or clinical assessments with any incidental disclosure recorded.

Immediately following therapy, participants completed Anhedonia, WAI, and SEQ via REDCap. In sessions 1, 4, and 8, participants a third blood sample was collected. Additionally, after sessions 4 and 8, participants were asked to re-wear the activPAL accelerometer to return at their next visit (session 5 and Post-Intervention Visit, respectively).

Post Intervention Visit

Participants returned one week after their final therapy session for a Post-Intervention Visit. During this visit, a trained clinical interviewer assessed participants for MDD, symptom severity, and suicidality via the SCID, HAM-D, and C-SSRS, respectively. Additional final assessment measures included anthropometric assessments and REDCap questionnaires (detailed in Table 1).

20 and 52 Week Follow Up Visits

Participants returned for a 20- and 52- Week Follow Up Visit after the end of therapy to determine potential longer-term effects. At these timepoints, a trained clinical interviewer reassessed participants for MDD, symptom severity, and suicidality via the SCID, HAM-D, and C-SSRS, respectively. Additional final assessment measures included anthropometric assessments and REDCap questionnaires (detailed in Table 1).

Table 1. Time of Assessments

	Intake Visit	CBT+ Session 1	CBT+ Session 2	CBT+ Session 3	CBT+ Session 4	CBT+ Session 5	CBT+ Session 6	CBT+ Session 7	CBT+ Session 8	Post Intervention Visit	20 Week Visit	52 Week Visit
ENROLLMENT												
Informed Consent	X											
Eligibility Check	X											
Randomization		X										
INTERVENTION												
Active CBT		X	X	X	X	X	X	X	X			
Calm CBT		X	X	X	X	X	X	X	X			
Adverse Event Monitoring		X	X	X	X	X	X	X	X			
ASSESSMENTS												
Primary Outcomes												
WAI		X	X	X	X	X	X	X	X			
BADS	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Outcomes												
HAM-D	X									X	X	X
SCID	X									X	X	X
PHQ-9	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Other Outcomes												
Baseline Characteristics*	X											
Mental Health Treatment	X									X	X	X
Anthropometrics	X									X	X	X
IPAQ	X				X					X	X	X
SF36	X				X					X	X	X
GAD-7	X				X					X	X	X
ActivPAL*	X				X					X		
Blood Sample^		X			X				X			
Anhedonia^	X	X			X							
Video Survey		X	X	X	X	X	X	X	X			
ATQ	X	X	X	X	X	X	X	X	X	X	X	X
SEQ		X	X	X	X	X	X	X	X			
<i>Notes:</i> *Baseline Characteristics = Health History, DSM5 Level 1 Cross-Cutting Symptoms (DSM5), World Health Organization Disability Assessment Schedule (WHODAS), Adverse Childhood Events (ACE); Anthropometrics = height, weight, heart rate, blood pressure; *ActivPAL = issued at the visit and worn for 7 days before being returned; ^ = Measures taken 3 times (pre-Active/Calm condition, post-Active/Calm condition, and after therapy). <i>Acronyms:</i> WAI = Working Alliance Inventory; BADS = Behavioral Activation for Depression Scale; SCID = Structured Clinical Interview for DSM-5; HAM-D = Hamilton Depression rating scale; PHQ-9 = Patient Health Questionnaire 9-item scale; C-SSRS = Columbia Suicide Severity Rating Scale; IPAQ = International Physical Activity Questionnaire; SF36 = Short Form Health Survey; GAD-7 = Generalized Anxiety Disorder 7-item scale; ATQ = Automatic Thought Questionnaire; SEQ = Session Evaluation Questionnaire.												

8. Data Elements

Questionnaires

Questionnaires were administered electronically via REDCap. Time of administration of all questionnaires is detailed in Table 1.

Clinical Interviews

The participant met with a trained Clinical Interviewer who administered the Structured Clinical Interview for DSM-5 (SCID) to assess relative mental health outcomes. Interviewers were senior Counseling Psychology Ph.D. students or trained clinical interviewers with at least a bachelor's degree in psychology with structured training on diagnosis and assessment using the SCID and supervised by a licensed psychologist on the research team. All clinical interview components (including the SCID, HAM-D, and CSSRS) at each time point were audio and video recorded via Lyssn.

Lyssn Data

Lyssn is an artificial intelligence clinical training and supervision platform that uses gold-standard evaluation tools to assess and improve fidelity to evidence-based practices, including CBT. Therapy sessions and clinical interviews were recorded on Lyssn, and Lyssn used AI to code the conversation to provide session data regarding treatment fidelity (e.g., adherence to CBT principles, like 'agenda setting' or 'providing homework') and session effectiveness (e.g., collaboration score, empathy score). Lyssn is HIPAA, FERPA, and GDPR compliant.

Activity Assessment

Activity levels were measured via accelerometry (activPAL4, PAL Technologies Ltd., Scotland, UK). The activPAL is a small triaxial accelerometer that uses thigh position to classify physical activity as sedentary, upright or stepping. Participants were instructed to place the device on the midline of the thigh for 7 days (24 hours/day), removing only for water-based activities (e.g., swimming, bathing), and were given a log sheet and asked to record sleep time and when the monitor was on/off. Monitor data was processed and analyzed with activPAL propriety software (i.e., PALconnect, PALanalysis).

Anthropometric Assessments

Anthropometric assessments included height, weight, blood pressure and heart rate. A standard stadiometer and scale was used to assess height and weight, respectively. An Omeron blood pressure monitor was used to measure blood pressure and heart rate.

Blood sample

Blood samples were collected at the beginning (pre-exercise or pre-rest), mid-point (post-exercise or post-rest) and end (post-CBT) of each sessions 1, 4, and 8 (i.e., 3 needle sticks for each session) and stored to evaluate alternative mechanisms associated with or potentially underlying treatment responses. Serum samples (20 mL per timepoint) were collected and stored at -80°C for further processing.

9. Risks to Participants

Exercise Sessions: Exercise is generally very safe and tolerable. Most complications are minor and may include muscle soreness, joint pain, shortness of breath and feeling dizzy or fatigued. Very rarely a heart rhythm abnormality or heart attack may occur during exercise, requiring resuscitation and hospitalization. However, this is extremely uncommon even during maximal exertion. During each exercise session, participants were closely supervised by trained personnel, who monitored the perceived rating of exertion, heart rate, and workload frequently throughout the session. The exercise session was stopped if the participant reported dizziness or shortness of breath, and participants remained with the study team until all symptoms subsided. Senior research members were CPR certified, and a first aid kit and AED were available in the building.

Blood Draws: There was a small risk of fainting or dizziness during or after the blood draws. There was also a small risk of bruising or bleeding at the site of the needle (about 1 in 10 cases) and an extremely small risk (about 1 in 1000 cases) of infection. The total quantity of blood collected across all visits is much less than that taken during a single donation at the Red Cross Center or a blood drive. On rare

occasions, the needle could have damaged a nerve or the vein, causing the vein to become blocked. All of these risks were minimized by using trained phlebotomists to draw the blood and using sterile equipment in an area designed for the collection of blood samples.

Psychological Stress. There may have been limited psychological stress related to discussing mental health questions while completing questionnaires or during the CBT sessions. If any severe responses are encountered during any of the questionnaires, study personnel will respond by contacting appropriate emergency services. Mental health resources were also provided after the Intake Visit, and as needed throughout the study.

Social Risk. There may have been some social risk regarding the disclosure of mental health information. The main risks were harm to reputation, embarrassment, or stigmatization if participation in the study became known, however, given the study procedures, this risk was low. To minimize this risk, all participation was held on an individual basis to minimize contact with other participants. All CBT sessions were performed in closed rooms to minimize the chance that participation could be noticed by others.

Breach of confidentiality. Confidentiality was a central value of this study, as it is in any mental health treatment settings. However, there are situations in which participant confidentiality may need to be breached. These include contacting local authorities or other health service providers if the participant reveals (a) that a child is being abused or severely neglected, or (b) that the participant is an imminent threat to themselves (suicidality) or someone else. So, if study staff hear about current childhood abuse or severe neglect, that research team member, may be obligated to report it. If a report is made, this may be a breach of the participant's confidentiality. Language regarding this risk was transparent during the informed consent process. The informed consent document lists specific unique situations as required by law in which confidentiality may not be maintained.

10. Withdrawal of Participants

To ensure participant safety, the study team planned to pause study participation without a participant's consent and connect the participant with a higher-level of care in the following situations: 1) a participant was hospitalized overnight for suicidality, 2) a participant indicated high risk of suicide on the C-SSRS, 3) law enforcement was called and transports the participant to emergency services, or 4) a participant attempted suicide at any point during the study. If a mental health care provider indicated that continued participation in the study would be beneficial for the participant, they were allowed to continue in the trial if they provided verification of this recommendation from a licensed mental health professional. If not, the participant would have been withdrawn from the study.

11. Data Management and Confidentiality

Data was collected and stored on REDCap and backed up with secure cloud storage, with both platforms only accessible to authorized research personnel. Data from each study visit were electronically administered from REDCap (e.g., informed consent signature, questionnaires), manually entered to the platform (e.g., anthropometric assessments), or imported after the study visit (e.g., activPAL). Data were coded and the "key" linking identities to codes will be stored only in REDCap. Only those listed as key personnel will have access to the "key." Additionally, this study is funded by the National Institutes of Health and is covered by a Certificate of Confidentiality.

12. Study Analysis

See attached Statistical Analysis Plan.

13. References

Meyer, J. D., Kelly, S. J., Gidley, J. M., Lansing, J. E., Smith, S. L., Churchill, S. L., ... & Wade, N. G. (2024). Protocol for a randomized controlled trial: exercise-priming of CBT for depression (the CBT+ trial). *Trials*, 25(1), 663.

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