Alcohol Use Disorder (AUD)

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Specific Aims

Alcohol use disorder (AUD) affects over 28.3 million people in the U.S. and is linked to high morbidity and mortality rates. Chronic alcohol exposure disrupts intracellular signaling and synaptic structures, causing long-term changes in brain regions such as the basal ganglia, prefrontal cortex, and amygdala, which contribute to AUD-related behaviors. Treatments include pharmacological approaches, cognitive behavioral therapy, motivational enhancement, 12-step programs, and exercise. Aerobic and resistance training in particular increase brain-derived neurotrophic factor levels, supporting neurogenesis, memory, and learning. While exercise has been shown to reduce alcohol cravings and consumption in people with AUD, the specific neurobiological mechanisms remain unclear, limiting its therapeutic potential and highlighting the need for further research into how exercise may support recovery at the neurobiological level. Identifying these mechanisms is essential for developing personalized, exercise-based interventions that improve adherence and treatment outcomes in individuals with AUD.

To address the gap in understanding exercise's impact on neurobiology in AUD, we propose a 1-year longitudinal clinical study involving exercise, using functional near-infrared spectroscopy (fNIRS) headbands and clinical assessments such as the Penn Alcohol Craving Scale (PACS) and Obsessive-Compulsive Drinking Scale (OCDS). Our long-term goal is to develop personalized, exercise-based treatments that improve adherence, clinical outcomes, and quality of life by targeting exercise-induced neurobiological changes in patients with alcohol dependence. We hypothesize that exercise increases prefrontal cortex activity and changes biomarkers that correlate with reductions in alcohol cravings and consumption in individuals with AUD. This study will identify these neurobiological changes and determine optimal exercise duration, establishing a foundation for targeted, evidence-based exercise treatments that can be incorporated into clinical practice.

Aim 1: Identify neurobiological changes in the prefrontal cortex associated with exercise interventions in individuals with AUD. We will use fNIRS to monitor brain activity in key areas like the prefrontal cortex and conduct biomarker analysis to assess neurotransmitter levels before and after interventions.

Aim 2: Examine the impact of exercise interventions on alcohol cravings and consumption and their relationship to clinical assesments. We will correlate data from fNIRS biomarkers with self-reported measures (PACS, OSCD). Establishing this link will clarify how exercise mitigates cravings, supporting its role as a therapeutic intervention.

Aim 3: Determine optimal exercise protocols for maximizing therapeutic effects on neurobiological and clinical outcomes in AUD. We will compare different exercise regimens to identify the most significant benefits. This identification will facilitate personalized, effective exercise interventions for AUD, improving clinical outcomes and enhancing long-term recovery.

The groups will include: 1) 50 patients with AUD who receive standard care + an aerobic exercise intervention, 2) 50 patients with AUD who receive standard care, and 3) 50 patients with AUD who are not seeking treatment. This aim will provide foundational knowledge on how exercise affects alcohol cravings and consumption in AUD. This study is innovative in combining fNIRS, biomarker analysis, and clinical assessments to investigate the neurobiological effects of exercise in AUD, offering insights beyond behavioral outcomes. We expect to identify specific neurobiological changes tied to reduced cravings (Aim 1), clarify their link to clinical improvements (Aim 2), and determine optimal exercise protocols for therapeutic impact (Aim 3). By providing a foundation for personalized, exercise-based treatments, this research has the potential to enhance clinical outcomes and quality of life for individuals with AUD, positioning exercise as a targeted therapeutic intervention.

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RESEARCH STRATEGY

Background and Significance

Unhealthy alcohol consumption is the third leading preventable cause of death in the U.S., resulting in 178,000 deaths each year.[1] According to the 2023 National Survey on Drug Use and Health, over 28.9 million individuals aged 12 and older in the U.S. met the criteria for alcohol use disorder as defined by the DSM-5.[2] Neurobiological effects of alcohol on the brain include dysregulation of the reward system via dopamine and opioid deficits, increased brain stress system activity through corticotropin-releasing factor (CRF) and dynorphin, and disruptions in glutamatergic and GABAergic networks.[3] In addition, dysregulation of key prefrontal cortex (PFC) areas compromises executive control over motivation and goal-directed behavior, making it harder to resist drug-related cues.[4]

Current pharmacotherapy options include 3 drugs approved by the FDA for AUD treatment: naltrexone, acamprosate, and disulfiram.[5] For a person without insurance, the monthly cost of a supply of oral naltrexone can range from $25 to $108, with guidelines recommending 3 to 4 months of treatment.[6] In addition, patients on oral naltrexone must have a monthly visit with a healthcare provider to monitor their status. This can place a significant burden on low-income and uninsured patients leading to increased stress and putting the patient at risk of relapse. Behavioral interventions include cognitive behavioral therapy. Patients meet 1-on-1 with a counselor for 6 to 20 weeks. Sessions can range from $100 to $250 per hour, an additional barrier to receiving treatment for low-income and uninsured patients.

While pharmacological and behavioral interventions are valuable, their limitations call for accessible and cost-effective alternatives, such as exercise-based interventions. In general, physical activity has been shown to regulate neurotransmission and promote neuroplasticity, potentially through increased expression of brain-derived neurotrophic factor (BDNF), insulin-growth-factor-1 (IGF-1), and improved cerebral circulation.[7] Although exercise has shown a decrease in alcohol cravings and consumption in people with AUD, the mechanism is still unclear, and the precise neurobiological mechanisms underlying these effects remain poorly understood. This lack of clarity hinders the development of targeted, evidence-based exercise interventions for clinical use. We hypothesize that exercise increases prefrontal cortex activity and changes biomarkers that correlate with reductions in alcohol cravings and consumption in individuals with AUD.

Innovation

Currently, studies have measured alcohol consumption, AUD severity, and AUD symptoms such as cravings.[8–10] A recent study identified plasma levels of 12-HETE, 15-HETE as potential biomarkers for predicting alcohol cravings in individuals with AUD.[11] The proposed study will integrate functional near-infrared spectroscopy (fNIRS) headbands and biomarker assessments to investigate the neurobiological changes induced by exercise in patients with AUD. To our knowledge, no study has yet identified the specific neurobiological mechanisms induced by exercise-based interventions for AUD. By elucidating these mechanisms, this study will establish a foundation for targeted, evidence-based exercise treatments, with potential scalability for underserved populations through affordable and adaptable approaches, and address stigma-related barriers to accessing treatment. By integrating real-time PFC activity monitoring with biomarker analysis, our study uniquely bridges physiological and subjective measures, offering a multidimensional view of exercise's therapeutic impact.

Approach

This investigation will use a longitudinal clinical design to investigate the neurobiological effects of exercise as a therapeutic inter-

vention for AUD. Although exercise has shown promise in reducing alcohol cravings and consumption in individuals with AUD, the specific neurobiological mechanisms underlying these effects remain unclear. The proposed experiments are independent yet complementary, with each aim contributing to a comprehensive understanding of how exercise influences brain function and alcohol-related behaviors.

Aim 1 will use fNIRS to monitor brain activity in the PFC, a region known to be impaired in chronic alcohol use, before, during, and after exercise interventions and biomarker analyses (12-HETE, 15-HETE, BDNF, IGF-1) to characterize the physiological impact of exercise interventions.[12]

In Aim 2, we will examine the impact of exercise interventions on alcohol cravings and consumption and their relationship to clinical assessments and will incorporate fNIRS and biomarker data to explore how these neurobiological markers predict or mediate clinical outcomes.

Aim 3 will investigate the optimal exercise protocols by comparing different regimens– moderate intensity vs high-intensity aerobic exercise–to determine which provides the most significant neurobiological and clinical improvements. Comparing moderate- and high-intensity exercise regimens will help identify optimal protocols by evaluating adherence rates and their feasibility for clinical implementation.

General Methods

This study will be a 1-year longitudinal clinical trial with three groups of patients diagnosed with AUD, who meet DSM-5 criteria for AUD, are aged 18–65 years, and are actively pursuing sobriety. The study will employ both neurobiological and clinical assessments, including fNIRS and biomarker analysis. Group 1 will include 50 patients with AUD who will receive standard care + aerobic exercise intervention. Group 2 will include 50 patients with AUD receiving only standard care. Group 3 will include 50 patients with AUD who are not seeking treatment. This investigation will exclude patients who have significant neurological or cardiovascular disease, ongoing substance use other than alcohol or use medications that interfere with lipid metabolism or neurobiological assessments.

Aim 1: Identify neurobiological changes in the PFC associated with exercise interventions in individuals with AUD.

Rationale: Individuals with AUD experience dysregulation of the PFC, a region involved in executive function, motivation, and goal-directed behavior.[4] Chronic alcohol use impairs PFC activity, contributing to the difficulty in resisting alcohol-related cues and maintaining sobriety. Exercise has been shown to increase PFC activity, potentially improving cognitive control and reducing cravings.[12] By utilizing fNIRS, a non-invasive method for measuring real-time brain oxygenation, we can monitor PFC activity during exercise interventions and examine how these changes relate to neurobiological biomarkers.

Procedure: 50 participants diagnosed with AUD who meet DSM-5 criteria for the disorder and are aged 18–65 years will be assessed at baseline for their PFC activity using fNIRS. Participants will be seated comfortably, and the fNIRS device will be applied to the forehead to monitor oxygenated and deoxygenated hemoglobin levels as an indicator of brain activity. A blood draw will be administered at the beginning of the study to collect baseline biomarkers and will serve as a baseline for physiological measures. Participants will undergo a moderate-intensity aerobic exercise intervention (treadmill walking at 60-70% heart rate maximum) for 30-40 minutes and we will ensure that the intensity is consistent across participants. During exercise, the participants will monitor PFC activity continuously using fNIRS headband. After the session, participants will measure PFC activity immediately and at 15-minute intervals up to 45 minutes after the session. After weeks 6 and 12 of the exercise intervention, we will reassess biomarkers to examine any lasting effects of the exercise on biomarkers.

Data Analysis: For the fNIRS analysis, we will use standard fNIRS processing techniques to measure oxygenated hemoglobin and deoxygenated hemoglobin levels in the PFC. We will analyze changes in these levels during baseline, during exercise, and post-exercise. We will apply statistical tests such as paired t-tests and repeated measures ANOVA to compare PFC activity across time points (baseline, during, and post-exercise). For biomarker analysis, we will perform a comparison of biomarker levels before and after exercise using paired t-tests or ANOVA to detect significant changes in biomarker concentrations. Lastly, we will correlate changes in biomarkers with changes in PFC activity to examine potential associations between neurobiological changes and PFC activation.

Expected Results: We expect to see an increase in PFC activity during and immediately after the exercise intervention. Specifically, oxygenated hemoglobin levels should increase as a sign of enhanced brain oxygenation. Biomarkers such as BDNF and IGF-1 are expected to show an increase post-exercise, suggesting exercise-induced neuroplasticity and neuroprotection. We anticipate that increases in PFC activity will be positively correlated with changes in biomarkers, indicating that exercise-induced neurobiological changes may mediate improvements in PFC function.

Potential Pitfalls and Alternative Approaches: Participants may struggle to maintain the prescribed exercise intensity or duration, leading to variability in PFC activity changes. An alternative approach could be to use wearable fitness trackers to monitor adherence to exercise intensity and duration. If needed, include exercise coaches or online video tutorials to support participants. Additionally, changes in PFC activity and biomarkers may only be transient and not persist after exercise cessation. Alternatives, we could incorporate a longer follow-up period (e.g. 6 months) to assess whether neurobiological changes persist over time or implement an exercise maintenance phase to evaluate long-term effects.

Aim 2: Examine the impact of exercise interventions on alcohol cravings and consumption and their relationship to clinical assessments.

Rationale: AUD is characterized by intense alcohol cravings and compulsive drinking, which are major contributors to relapse. While exercise has been shown to reduce alcohol cravings and consumption in some studies, the underlying mechanisms are not yet fully understood. Exercise may alter the neurobiological pathways associated with craving and reward systems, leading to reduced cravings and consumption.[9,10] This aim seeks to assess how exercise interventions influence alcohol cravings and consumption in individuals with AUD, to identify a potential therapeutic approach to improve outcomes and reduce relapse risk.

Procedure: Participants will be randomized into three groups: Group 1) 50 participants with AUD who will receive standard care (pharmacotherapy, counseling) + aerobic exercise intervention (moderate-intensity exercise, 30–40 minutes, three times per week). Group 2) 50 participants with AUD who will receive standard care only (pharmacotherapy, counseling). Group 3) 50 participants with AUD who are not seeking treatment. Group 3 will serve as a baseline for comparing the effectiveness of the exercise intervention and standard care. At the start of the study, participants will complete self-reported measures of alcohol cravings (PACS, OCDS). These scales will assess the intensity and frequency of alcohol cravings and the compulsive nature of drinking. After 6 and 12 weeks of exercise, participants will complete the same alcohol craving scales (PACS, OCDS). Aim 1 procedures for fNIRS and biomarker assessments will be followed to monitor the relationship between neurobiological changes and clinical outcomes.

Data analysis: Using repeated measures ANOVA, we will compare changes in cravings and consumption over time within and between groups. We will also examine how changes in PFC activity and biomarkers correlate with these clinical outcomes. The analysis will explore whether neurobiological changes mediate the improvements in alcohol-related behaviors, particularly in the exercise intervention group.

Expected Results: We expect that the exercise group (Group 1) will show the most significant reductions in cravings and consumption, with positive correlations between PFC activity, biomarkers, and clinical improvements. The standard care group (Group 2) will likely exhibit moderate improvements, while the no-treatment group (Group 3) will show minimal to no changes in cravings or consump-

tion. At the 12-week follow-up, the exercise group is expected to retain these improvements, suggesting that exercise may have lasting effects on both neurobiological markers and alcohol-related behaviors.

Potential Pitfalls and Alternative Approaches: Some participants in Group 1 may struggle to adhere to the exercise regimen, leading to variability in the intervention's effectiveness. This could affect the consistency of the results, particularly in terms of changes in cravings and consumption. To improve adherence, we could provide additional support such as regular check-ins, motivation sessions, or exercise coaches to ensure participants remain consistent in their exercise efforts. Alternatively, using wearable devices to monitor and encourage exercise intensity could help maintain protocol adherence.

Aim 3: Determine optimal exercise protocols for maximizing therapeutic effects on neurobiological and clinical outcomes in AUD.

Rationale: While exercise has shown promise in alleviating alcohol cravings and improving neurobiological function in individuals with AUD, the optimal exercise protocol remains unclear. Different exercise intensities and durations may lead to distinct neurobiological changes, and it is crucial to identify the protocol that provides the greatest therapeutic benefits.[8] Understanding the ideal exercise regimen for improving cognitive control and reducing alcohol consumption could help integrate exercise-based treatments into clinical practice, especially for underserved populations. This aim will compare various exercise protocols to identify the most effective approach for improving both brain function and alcohol-related behaviors.

Procedure: Group 1) 50 participants will engage in a moderate-intensity aerobic exercise regimen (60-70% of heart rate maximum) for 30-40 minutes per session, three times per week. Group 2) 50 participants will engage in a high-intensity aerobic exercise regimen (80-90% of heart rate maximum) for 30-40 minutes per session, three times per week. Group 3) 50 participants will receive standard care (no exercise intervention). The participants will undergo baseline assessments, as described in Aim 2. Exercise sessions will be administered over a 12-week period, and participants will be reassessed at the end of the intervention. The study will track adherence to the exercise regimen using wearable devices and monitor PFC activity and biomarkers at baseline, post-intervention, and 6 weeks after exercise initiation.

Data Analysis: The primary analysis will compare changes in PFC activity, biomarker levels, and alcohol cravings across the three groups using ANOVA. We will analyze changes in oxygenated hemoglobin and deoxygenated hemoglobin levels measured by fNIRS during and post-exercise. Additionally, we will assess changes in alcohol consumption and cravings using self-reported scales and examine how these clinical outcomes correlate with changes in neurobiological markers. Post-hoc comparisons will be conducted between the two exercise regimens (moderate vs. high-intensity) to determine which exercise protocol leads to the most significant improvements in brain function and alcohol-related behaviors.

Expected Results: We anticipate that both moderate- and high-intensity exercise regimens will lead to increased PFC activity, as indicated by higher oxygenated hemoglobin levels during and after exercise. We expect that the high-intensity exercise group will show more significant improvements in neurobiological markers like BDNF and IGF-1, reflecting greater neuroplasticity. Additionally, we expect both exercise regimens to lead to reductions in alcohol cravings and consumption, with a more pronounced effect in the high-intensity group. The standard care group is expected to show minimal changes in PFC activity, biomarkers, and alcohol-related behaviors. Ultimately, this aim will identify which exercise protocol maximizes neurobiological improvements and clinical benefits for individuals with AUD.

Potential Pitfalls and Alternative Approaches: Some participants may find it difficult to adhere to the prescribed intensity or duration, especially in the high-intensity group. If adherence is low, we could provide additional support through regular check-ins with exercise coaches or modify the intensity to accommodate individual needs. In addition, high-intensity exercise may result in higher dropout rates, particularly in participants who are less accustomed to regular physical activity. We can implement a progressive exercise protocol to help participants build up to the prescribed intensity gradually. Additionally, provide personalized support, such as fitness coaches to improve engagement and adherence.

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