Official Study Title: **Enhancing Exercise and Psychotherapy to Treat Pain and Addiction in Adults with an Opioid Use Disorder (OUD): A Randomized Trial**
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CASE WESTERN RESERVE UNIVERSITY EST. 1826

INFORMED CONSENT DOCUMENT

Enhancing Exercise and Psychotherapy to Treat Pain and Addiction in Adults with an Opioid Use Disorder (OUD) in Residential Drug Treatment

This research study is being conducted by researchers at Case Western Reserve University and University of Colorado at Denver.

KEY INFORMATION

Purpose

The purpose of this study is to determine the feasibility of integrating exercise and psychotherapy that is specifically targeted at helping to reduce and manage pain into existing residential drug treatment programs. In addition to understanding feasibility, we are interested in seeing if this exercise and targeted psychotherapy program for pain improves outcomes such as drug cravings, fitness, body composition, pain, depression, anxiety and sleep. There have been a few prior studies which suggest that exercise may improve these outcomes in adults with substance use disorders (SUDs) but more studies are needed to better understand response to exercise and psychotherapy with self-regulation and biofeedback in adults with opioid use disorders (OUDs) and pain.

Procedures and Duration

Summary of Procedures: If you agree to participate in this research, we would ask you to do the following things:

1) complete an exercise screening questionnaire, which will take approximately 5 minutes;
2) if deemed eligible, participate in an exercise "fitness" test on a stationary bike that will take approximately 1 hour;
3) complete a set of body compositions tests (weight, waist/hip circumference, body fat) that will take approximately 15 minutes;
4) complete a pain test ("Cold Pressor Task") that will take approximately 15 minutes; and,
5) complete a set of paper-based questionnaires on your own that will take a total of approximately 1-2 hours to complete.

Participants who complete all of the baseline testing described above will be randomized to receive one of the possible combinations, which may include the following: 1) exercise only; 2) psychotherapy for pain only; 3) both exercise and psychotherapy for pain; or, 4) neither exercise or psychotherapy for pain and only the treatment you would normally receive as part of the normal treatment center program, which we call treatment as usual or "TAU". A computer program will be used to randomly determine which group/treatments you will receive. You will not be able to choose which group you are assigned to.

Participants who are randomized to receive the exercise program will be asked to cycle on a stationary bike for approximately 30 minutes to 1 hour per session, 3 days per week, for the duration of their residential drug treatment center program (~8 weeks/60 days). Participants who receive the exercise program may be randomized to a standard or a special bike that mechanically assists you to pedal a little bit faster than you pedal voluntarily on your own (called an "assisted" bike). The exercise sessions will be conducted at your residential drug treatment center. Patients randomized to the psychotherapy for pain program will be asked to attend individual or group (depending on the number of participants enrolled) sessions of approximately 1 hour, one day per week, for the duration of their drug treatment center program (~8 weeks/60 days).

At the end of the program, we will ask you to complete all of the tests mentioned above again to see if/how things may have changed.

Reasons You Might Choose to Volunteer For This Study

You may or may not benefit directly from taking part in this study. Your participation in this study will help us to understand the feasibility of integrating exercise and psychotherapy targeted at reducing and better managing pain into existing programs for patients with an OUD at residential drug treatment centers. These programs may also help improve your overall health and quality of life and would help us design future larger studies in drug treatment programs at other locations. Please see the Detailed Consent section below for a complete description of the anticipated benefits.

Reasons You Might Choose Not to Volunteer For This Study

There could be some minor emotional discomfort or anxiety when answering sensitive questions on the questionnaires. You could also experience minor emotional discomfort when discussing sensitive issues with the therapists during the psychotherapy sessions. However, you can elect to not to provide a response to any question you do not wish to answer. Please see the Detailed Consent section below for a complete description of the foreseeable risks and discomforts.

Voluntary Participation:

If you decide to participate in the research, it should be because you want to volunteer. There is no penalty or loss of benefits for not participating or for discontinuing your participation at any time.

DETAILED CONSENT

You were selected as a possible participant because you have been diagnosed with an opioid use disorder (OUD) and have reported some form of pain and you are enrolled in a collaborating residential drug treatment center. The staff of that the residential treatment center to which you are enrolled thought you might be interested in this study and recommend that we speak with you about the study. We hope to recruit about 198 people to volunteer for this research. Please read this form and ask any questions that you may have before agreeing to participate.

Procedures

The following provides additional details about each one of the tasks we will ask you to complete as part of the study as mentioned above.

1. Screening: If you agree to participate in the study, you will be asked to complete exercise screening where you will be asked questions devised by the American Heart Association and American College of Sports

Medicine about your medical history as it relates to your heart. If you are identified to be "at risk" for exercise, you may not be able to participate in the research study. If it is determined that you are able to exercise by these questions, we will then ask you more detailed questions related to your general health and to participate in the exercise testing (described in more detail in Item 2 below).

2. Exercise, Body Composition and Pain Testing: During the exercise test you will pedal on a stationary bike while your heart rate, blood pressure and breathing are monitored. Your heart rate will be monitored with a heart monitoring device / electrode (small circular sticky patches) system worn under your clothes and your breathing may be monitored with a specially designed mask. An example of the type of equipment that may be used during the exercise test is shown in Figure 1. However, the actual equipment used during the testing may vary by site and the special mask may not be used. As the exercise test progresses, the pedaling will become more difficult. We will ask you how you are feeling and to rate your level of perceived exertion using a chart called the Rating of Perceived Exertion (RPE) chart throughout the test. You will be asked to continue to pedal until you feel very tired and until you decide that you cannot continue. After you finish the exercise test, you will be asked to remain to rest with us for approximately 10 to 15 minutes. During this recover period, your heart rate and blood pressure will be monitored. The actual exercise test will only take about 15 minutes but we will ask you to plan on the test taking about 1 hour to include time for the set up and recovery period observation. If the exercise testing reveals a potential abnormality in your heart, you may not be allowed to participate in the research study at this time. If we find a potential abnormality, we will recommend that you follow up with a physician to examine your heart further. If no abnormalities are detected during the exercise testing, you will be eligible to be randomized into one of the groups/treatment programs as discussed above.

We will ask you to participate in body composition testing, which will involve measuring your height, weight, waist and hip circumference and a test using a bioimpedance meter, which will measure the amount of your fat mass and lean mass. The body composition will take about 10 to 15 minutes to complete.

We will also ask you to participate in a pain test ("Cold Pressor Task") whereby you will place your non-dominant hand in a cold water bath and you report when you first feel pain. You will remove your hand when the pain becomes intolerable to you but no more than a maximum of 5 minutes. If you have Raynaud's or other condition that makes you extremely sensitive to cold temperatures you do not have to complete the Cold Pressor Task. The Cold Pressor Task will be completed after the exercise testing so if we find a contraindication to exercise during the exercise testing we will not proceed with the Cold Processor Task.

You will be asked to complete the exercise, body composition and pain task testing two times – once at the start of the study (baseline) and once after you have completed the intervention program.

3. Exercise Sessions: If you are randomized to either exercise group (the standard or "assisted" bike), you will be asked to perform exercise on a stationary bicycle for about 30 minutes to 1 hour in each session, 3 days per week for the duration of your residential drug treatment (~8 weeks/60 days). You will need to be in comfortable clothes such as shorts and a t-shirt and athletic shoes (e.g., tennis, walking or running shoes) to perform the exercise. The exercise sessions will be conducted at your residential drug treatment center. Each session will consist of a 5-minute warm-up (easy pedaling on the stationary bicycle) followed by 20 to 40 minutes of exercising at a higher rate, which will be progressive and based upon your fitness level determined from the "fitness" testing. The exercise intensity, which is determined, in part, by how fast and how hard (resistance) you pedal as well as your age and fitness level, will be determined by your target heart rate zone. We aim to have you exercise in your target heart rate zone during the 20 to 40 minutes of the exercise session. You will then

proceed with a 5-minute cool down period where you will pedal easily. You will be asked to wear a heart rate monitor (see Figure 2 for an example) so that we can measure you heart rate throughout the exercise session.

4. Psychotherapy for Pain Sessions: If you are randomized to the psychotherapy for pain sessions, you will be asked to participate in individual or group therapy sessions in a program called I-STOP (Self-regulation Treatment for Opioid addiction and Pain). You will be asked to attend approximately 1 hour sessions once per week for the duration of your treatment center program (~8 weeks/60 days). Ideally, the sessions will be held in small groups of about 6 to 10 patients; however, if no other participants are enrolled simultaneously in this program while you are enrolled, then your sessions may be completed individually. The sessions will be led by a trained therapist. The I-STOP program focuses on trying to make permanent lifestyle changes to reduce and better manage pain by helping patients to make small, progressive improvements through self-regulation, self-monitoring, reasonable goal setting, biofeedback using Biodots™ (stickers that affix to the hand to measure temperature; see Figure 3) and other techniques which will be taught during the I-STOP sessions. If you are randomized to the standard program offered at the treatment center, you will not receive the I-STOP sessions.

5. Questionnaires: Quality of Life, Exercise, Eating and Sleep Habits and Drug Use History: You will be asked to complete questions regarding your quality of life, exercise, dietary and sleep behaviors using standardized questionnaires. In addition, you will be asked to complete standardized questionnaires related to your drug and other substance use history. The paper-based questionnaires, which you will complete on your own, will take a total of approximately 1 to 2 hours to complete. We will give you an envelope containing the packet of questionnaires that you can place the completed versions in and provide the packet back to the study staff/ investigators. You will be asked to complete these questionnaires at the start of the study ("baseline") and after you have completed the intervention program (end of treatment or "EOT"). For baseline, we ask that you provide the packet to study staff no later than the day of the first day of exercise or psychotherapy.

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers as soon as possible.

Foreseeable Risks and Discomforts

All treatments and procedures may involve some level of risk to you, whether foreseeable or not.

There are no known risks, harms or discomforts associated with this study beyond those encountered in normal daily life. Some of the activities we will ask you to complete might make you feel uncomfortable. You may refuse to answer any of the questions, take a break, or stop your participation in this study at any time. The possible risks and/or discomforts associated with the procedures described in this study include a minor risk of emotional distress or anxiety when answering questions when completing the questionnaires and/or in the psychotherapy for pain sessions. However, you can elect to not provide a response to any question that you do not wish to answer. You may ask to not participate in discussions in the therapy session if the issue upsets you.

The intensity of the exercise may be slightly uncomfortable at times but you will be allowed to rest at any time during the sessions, if needed. You may experience minor muscle aches if you have not participated in exercise for a while but we will use a progressive program individualized to you with about 48 hours or more of recovery time between exercise sessions. There is a minimal risk of a cardiovascular event during exercise and exercise testing including shortness of breath, changes in blood pressure, abnormal heart rhythm and, in very rare instances, a heart attack. These risks are similar to the risks you would have if you were exercising on your own such as going for a jog in the park. Research staff supervising the exercise sessions will be trained in Basic or Advanced Life Support including emergency resuscitation and other life saving techniques.

The stationary bicycle you will be exercising on is very stable but there is a chance that you could stumble or

fall getting on or off the bike resulting in a muscle or ligament strain. To minimize your risk of injury getting on and off the bike, the exercise trainer will help you get on and off the bike. You may find the heart rate monitor and mask a little uncomfortable; however, the devices are small, lightweight, and the straps are adjustable to make the devices as comfortable and easy to wear as possible. The Cold Pressor Task, which requires placing one hand in cold water, will induce a small amount of pain intentionally; however, you have full control of how long you leave your hand in the cold water bath. We will end the task after 5 minutes if you do not remove your hand by then.

COVID-19 Related Risks: There is a potential for increasing the spread of COVID-19 with exercise due to an increase in the droplets and/or aerosols that could be released during exercise. To minimize these risks, we will ask you to do the following:

1) complete a short survey of questions about your health prior to starting each exercise session ("daily health attestation");
2) have your temperature taken prior to starting each exercise session;
3) to wear a mask while exercising if tolerable and you feel comfortable doing so; and,
4) to sanitize and/or wash your hands before and after each exercise session.

The exercise trainer/exercise supervisor will wear a mask and clean/sanitize the exercise equipment and other high touch surfaces in the room before and after each exercise session. He/she will also be asked to sanitize and/or wash their hands before and after each exercise session.

Anticipated Benefits

You may or may not directly benefit from participation in this study.

If you participate regularly in the exercise program, your level of cardiorespiratory fitness may increase and you may improve your lean mass while decreasing your body fat. If you adhere to the exercise program and participate regularly in the I-STOP psychotherapy program, you may experience a potential reduction in your pain in general, in pain flares and in drug cravings; however, we cannot be sure what the exact benefits are at this point since there is very little known about the effects of exercise and psychotherapy in adults with an OUD and pain. It is possible that patients may not directly benefit from participating in the study; however, your participation will help us improve our understanding of whether exercise and/or psychotherapy for pain improves outcomes such as drug cravings, fitness, body composition, sleep, depression, anxiety and overall quality of life.

Compensation

There will be no costs to you for study participation.

You will receive the following compensation/reimbursement: 1) a $50 gift card for completing the baseline testing and questionnaire packet; and, 2) a $50 gift card for completing the end of treatment (EOT) program testing and questionnaire packet. The gift card(s) will be provided to you after you complete all of the required testing and return the packet of questionnaires to study staff at each time point (i.e., at baseline and EOT). We will also provide a certificate of completion to participants who complete 80% or more of the program sessions.

If you withdraw from the study before completing the testing and questionnaires at baseline or at the end of treatment, you will not receive the $50 gift card for the baseline or end of treatment event, respectively.

Alternative(s) to Participation

You have the option to not participate in the research study. If you do not participate in the research study, you will still receive the standard treatment offered at the treatment center to which you are enrolled.

Voluntary Nature of the Study

Your participation is voluntary. If you choose not to participate, it will not affect your current or future relations with the University or the residential drug treatment center to which you are enrolled. There is no penalty or loss of benefits for not participating or for discontinuing your participation.
You are free to withdraw from this study at any time. If you decide to withdraw from this study you should notify the research team immediately. The research team may also end your participation in this study if you do not follow instructions, miss scheduled visits, or if your safety or welfare are at risk. Any data collected before the time of withdrawal may be used by the study researchers.

Privacy of Protected Health Information (PHI)

The Health Insurance Portability & Accountability Act (HIPAA) is a Federal law that helps to protect the privacy of your health information and to whom this information may be shared within and outside of Case Western Reserve University and the University of Colorado at Denver. This Authorization form is specifically for a research study entitled "Enhancing Exercise and Psychotherapy to Treat Pain and Addiction in Adults with an Opioid Use Disorder (OUD) in Residential Drug Treatment" and will tell you what health information (called Protected Health Information or PHI) will be collected for this research study, who will see your PHI and in what ways they can use the information. In order for the Principal/Responsible Investigators, Drs. Nora L. Nock and Amy Wachholtz, and the research study staff to collect and use your PHI, you must sign this authorization form. You will receive a copy of this signed Authorization for your records. If you do not sign this form, you may not join this study. Your decision to allow the use and disclosure of your PHI is voluntary and will have no impact on your treatment the collaborating drug treatment center where you are enrolled. By signing this form, you are allowing the researchers for this study to use and disclose your PHI in the manner described below.

Generally, the Principal Investigator and study staff at Case Western Reserve University and the University of Colorado at Denver and the residential drug treatment center which you are enrolled who are working on this research project will know that you are in a research study and they will see and use your PHI. The researchers working on this study will collect the following PHI about you: name, address, phone number, email address, age, date of birth, medical record number and relevant behavioral and medical information (e.g., diagnosis date of OUD, chronic pain). This PHI will be used to confirm your eligibility for this research and to aid in communicating with you. Your access to your PHI may be limited during the study to protect the study results.

Your PHI may also be shared with the following groups/persons associated with this research study or involved in the review of research: the sponsor (National Institutes of Health); other medical staff from the collaborating residential treatment center; Government representatives or Federal agencies, when required by law.
Your permission to use and disclose your PHI does not expire. However, you have the right to change your mind at any time and revoke your authorization. If you revoke your authorization, the researchers will continue to use the information that they previously collected, but they will not collect any additional information. Also, if you revoke your authorization you may no longer be able to participate in the research study. To revoke your permission, you must do so in writing by sending a letter to: Dr. Nora L. Nock 10900 Euclid Avenue, WG-57, Cleveland, OH 44106; If you have a complaint or concerns about the privacy of your health information, you may also write to the University's Director of Privacy Management, Lisa Palazzo at lisa.palazzo@case.edu or 216-368-4286 or to the Federal Department of Health and Human Services (DHHS) at DHHS Regional Manager, Office for Civil Rights, US Department of Health and Human Services, 233 N. Michigan Ave., Suite 240, Chicago, IL 60601.

The researchers and staff agree to protect your health information by using and disclosing it only as permitted by you in this Authorization and as directed by state and Federal law. Case Western Reserve University and University of Colorado at Denver are committed to protecting your confidentiality. Please understand that once

your PHI has been disclosed to anyone outside of, Case Western Reserve University and University of Colorado at Denver, there is a risk that your PHI may no longer be protected.

I authorize all of my behavioral health information including substance use disorder information to be shared with researchers at Case Western Reserve University and University of Colorado at Denver for the study "Enhancing Exercise and Psychotherapy to Treat Pain and Addiction in Adults with an Opioid Use Disorder (OUD) in Residential Drug Treatment" that includes information covering my most recent treatment episode.

Confidentiality

The records of this research will be kept confidential. Any time information is collected, there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

In any reports published, we will not include any information that will make it possible to identify a participant. Research records will be kept in a locked file and access will be limited to the researchers, the University review board responsible for protecting human participants, regulatory agencies and the sponsor (National Institutes of Health). If someone on the research team tests positive for COVID-19 and has been in contact with you, we may be required to reveal your name to the local public health agency as part of contact tracing. The treatment center directors and staff may know that you are participating in the research study; however, the treatment center directors and staff will not have access to the information that you provide to us for this research study.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality (CC) from the National Institutes of Health. This CC adds special protection for the research information about you. The CC will protect the investigators from being forced, even under a court order or subpoena, to release information that could identify you. We may release identifying information in some circumstances, however. One example is if you agree that we can give out research information with your name on it. Other examples may include, disclosing medical information in cases of medical necessity related to your care, or taking steps (including notifying authorities) to protect you or someone else from serious harm, including child abuse or neglect, or disclosing auditing information required by the agency or entity funding the research. In addition, we may use certain information in future research as permitted by law.

Subject Identifiable Data

All information that identifies you will be removed and replaced with a code. A list linking the code and your identifiable information will be kept separate from the research data. These identifiers are needed to refer back to occasionally to verify the correct attributes have been matched to the responses being evaluated.

Data Storage

Research data will be maintained in a secure location at CWRU and at University of Colorado at Denver. Only authorized study staff/researchers will have access to the research data. Research data will be stored electronically in password protected and/or encrypted files.

Data Retention

The researchers intend to keep the research data:

- For approximately 5 years after completion of the study as required by the sponsor (National Institutes of Health, NIH).

Your identifiable information, which is being collected for this research, may have the identifiers removed and be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

Research Related Injury

If you suffer a research related injury and/or illness as a result of being in the study, you should seek medical care as applicable; however, neither the Sponsor (National Institutes of Health) or Case Western Reserve University has funding to pay for your care/treatment for the injury or illness. There are no plans for Case Western Reserve University or the Sponsor or to provide other forms of compensation (such as lost wages or other indirect losses) to you for research related injuries or illnesses. You are not waiving any legal rights by signing this form including the right to seek compensation for an injury. To help avoid injury, it is very important that you follow all study directions.

Contacts and Questions

The researchers conducting this study are Drs. Nora L. Nock and Amy Wachholtz. You may ask any questions you have now. If you have other questions, concerns or complaints about the study, you may contact them at:

Dr. Nora L. Nock
10900 Euclid Avenue, WG-57
Cleveland, OH 44106
(216) 368-5653

Dr. Amy Wachholtz
Campus Box 173, PO Box 173364
Denver, CO 80217
(303) 315-7051

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: (1) questions, concerns or complaints regarding this study, (2) research participant rights, (3) research-related injuries, or (4) other human subjects issues, please contact Case Western Reserve University's Institutional Review Board at (216) 368-4514 or write: Case Western Reserve University; Institutional Review Board; 10900 Euclid Ave.; Cleveland, OH 44106-7230.

You will be given a copy of this form for your records.

Statement of Consent

Your signature below certifies the following:

- You are at least 18 years of age.
- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

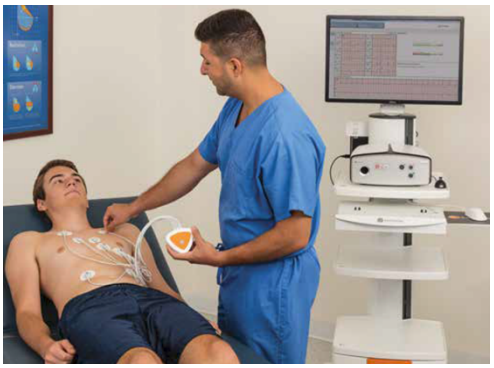
_____
Printed Name of Participant

_____ Date: _____
Signature of Participant:

_____
Printed Name of Person Obtaining Consent

_____ Date: _____
Signature of Person Obtaining Consent

Figure 1. Example of Equipment that May Be Used During Exercise Testing



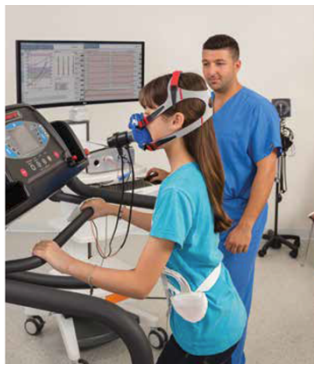


Figure 2. Example of a Heart Rate Monitor to be Worn Around the Chest During Exercise Sessions

Figure 3. Example of the "Biodots" to be Used in the I-STOP Psychotherapy Program