Protocol Summary and SAP

Behavioral Strategies to Reduce Stress Reactivity in Opioid Use Disorder (1 R21 DA046937-01)
NCT03616379

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Medical Monitor: N/A, no medical monitor is required for this behavioral study

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A. Summary of Protocol

A.1. Study Design Overview

The overarching aim of the proposed study is to test cognitive-behavioral strategies for reducing stress reactivity in adults with opioid use disorder. The goals of the proposed project include (1) to engage a putative target mechanism (stress reactivity), and (2) to test the degree to which engaging the mechanism is associated with a short-term behavior change (distress tolerance). We will investigate two putative mechanisms identified by the Science of Behavior Change (SOBC) Program: stress reactivity and self-regulation, leveraging validated measures from the SOBC Research Network Measures Repository. Specifically, we propose to (1) test the effect of two affect regulation strategies on stress reactivity relative to a control condition, and (2) test the effect of these strategies on behavioral tolerance of a stressor as an indicator of short-term behavior change. We will also investigate whether deficits in self-regulation reduce the ability to successfully engage stress reactivity using these affect regulation strategies.

We will recruit men and women with opioid use disorder for a single study corresponding to our study aims. Participants will be randomly assigned to a group: Intentional Affect Regulation, Incidental Affect Regulation, or Psychoeducational Control. Participants will receive a brief (20 minute) training in the affect regulation strategy (or control), followed by a stressor during which the participant will apply this strategy. We will measure stress reactivity, defined as affective (self-report of negative affect), peripheral physiological (cortisol and galvanic skin response), and opioid craving responses to laboratory stress induction. These measures will be collected prior to and following the stress induction. In Aim 1 (*Determine the impact of intentional and incidental affect regulation strategies on reactivity to a stressor*), we will compare groups with respect to stress reactivity. In Aim 2 (*Determine the association between intentional and incidental affect regulation strategies and behavioral distress tolerance)*, we will examine the association between randomized condition and a short-term behavioral outcome, distress tolerance during a stressor. In our secondary aim (*Quantify the impact of self-regulatory deficits on the efficacy of affect regulation strategies*), we will investigate individual differences in self-regulation as a potential predictor of response to behavioral strategies.

A.2. Primary and Secondary Outcome Measures

The primary outcome measure for Aim 1 is self-reported negative affect on the Positive and Negative Affectivity Schedule. Secondary outcomes include: self-reported opioid craving (Opioid Craving Scale), salivary cortisol, and skin conductance response.

The primary outcome for Aim 2 is behavioral distress tolerance, measured using the Computerized Mirror Tracing Persistence Task (time to discontinuation of the task).

A.3. Inclusion/Exclusion Criteria

Inclusion criteria include (1) age 18 years or older, (2) primary diagnosis of opioid use disorder, and (3) ability to read and provide informed consent. Exclusion criteria include (1) major psychiatric or medical condition that would interfere with the ability to complete study procedures (e.g., acute psychosis), (2) current opioid withdrawal (defined as a score ≥4 on the Clinical Opiate Withdrawal Scale; Wesson & Ling, 2003), (3) presence of another current substance use disorder at a severity that requires acute treatment (e.g., alcohol detoxification), (4) endocrine disease or current steroid prescription, or (5) opioid-positive urine drug screen or breath alcohol test on the day of enrollment (not including prescribed medications).

A.4. Power Calculation and Sample Size
We conducted a statistical power analysis to estimate the minimum effect size for the primary outcomes that we would be able to detect with 80% power at a significance level of alpha = 0.05. For this study, we aim to recruit a total of 120 participants. A study of 120 subjects (40 randomized to each group) will have power of at least 80% to detect a difference between means in the magnitude of an effect size of $f = 0.29$ for Aims 1 and 2. For Aim 3, in which self-regulation is added to the ANCOVA model, we would have a statistical power of .80 to detect an effect of $f = 0.31$. Thus, for the main study hypotheses, the study is more than adequately powered to detect a moderate effect size or larger.

B. Trial Management
B.1. Participating Enrolling Clinics
McLean Hospital is the performance site for the proposed study. All participant enrollment and data collection will occur in Dr. McHugh's Lab in the Division of Alcohol and Drug Abuse at McLean Hospital.

B.2. Projected Timeline
Months 1-2: hire study staff, pilot tasks; Months 3-21: recruit and enroll participants; Months 22-24: conduct data analysis and manuscript preparation. Data entry and quality assurance will be conducted throughout the study.

B.3. Target Population Distribution
The proposed study includes men and women from all ethnic backgrounds. Subjects age 18 years and older will be included in this study. We will not include children under the age of 18. The representation of opioid use disorder in the Alcohol and Drug Abuse Treatment Program (ADATP) at McLean Hospital consists of a majority of male patients (approximately 73%). Because the inclusion of both men and women is needed in this study to ensure that the study aims are addressed in both genders, we plan to over-sample women to obtain an approximately equal representation of men and women in the proposed study. We will maintain recruitment efforts to keep a nearly equal gender mix.

Previous research with this population from the ADATP has consisted of approximately 88% White and 8% Hispanic subjects, roughly consistent with the national data on opioid use disorder prevalence (79% White, 14% Hispanic). Nonetheless, we will continue to increase our efforts to include minority subjects, by publicizing the study in areas in and around Boston with higher minority representation. According to 2008 census figures, 86% of the Massachusetts population was White, 7% Black/African-American, and 7% other minority.

C. Data Management and Analysis
C.1. Data Acquisition and Transmission
Data collected for the proposed study will include: interviewer-administered measures, self-report instruments, computerized behavioral task measures, and peripheral physiological data (salivary cortisol, galvanic skin response). Interviewer-administered and self-report data will be collected using Research Electronic Data Capture (REDCap). Computerized behavioral task data will be collected on an encrypted computer stored in a locked research office. Biological specimens (saliva) will be collect in Dr. McHugh's Lab and stored in a locked freezer in a locked laboratory. These specimens will then be transported by research staff to the external lab for the quantification of cortisol. Specimens will be transported with only unique study code and will not be transported with identifying information.

C.2. Data Entry Methods

Participant data will be directly entered by the participant into REDCap. Any data entry (e.g., medical record data extraction) conducted by a study staff member will be entered directly into the study database and will be double-entered (i.e., entered on 2 separate occasions, and checked for discrepancies) to protect against potential transcription error.

C.3. Data Analysis Plan

First, descriptive statistics and exploratory graphical techniques will be used to assess the presence of skewness and/or outliers in the data. The quantitative data will be appropriately transformed if necessary. Randomized groups will be compared with respect to baseline demographic and clinical variables using t-tests and chi-square tests; if significant group differences are identified in any variables known to be highly predictive of outcome, these variables will be adjusted for via their inclusion as covariates.

Aim 1. The hypothesis that the intentional and incidental affect regulation manipulations will be associated with lower reactivity to stress relative to a comparison condition will be tested using a series of analyses of covariance (ANCOVA) of post-baseline (stress-reactive) outcomes (negative affect, craving, and cortisol/galvanic skin response) in a model with both the randomized groups and baseline values of these markers as covariates. A formal test of the main hypothesis of interest corresponds to the test of the randomized group effect in the ANCOVA model (i.e., a test of whether the magnitude of adjusted change in stress markers is different among the three randomized groups). Aim 2. The hypothesis that intentional and incidental affect regulation manipulations will be associated with greater behavioral tolerance of a stressor will be tested using an ANOVA with distress tolerance (i.e., time to discontinuation of the task) as the dependent variable. The test of the main hypothesis of interest corresponds to the test of the randomized group effect in the ANOVA model. Contrasts of interest (for Aims 1 and 2) include the comparison between each affect regulation condition and the control. In exploratory analyses, we will investigate the contrast between the two affect regulation conditions, and whether stress reactivity mediates the effect of group in Aim 2. Secondary Aim. We will investigate whether differences in baseline (pre-manipulation) self-regulatory deficits are associated with stress reactivity. The self-regulation measures will be added to the ANCOVA and the tests of interest include the main and interaction (group by self-regulation) effects.

D. Quality Assurance

D.1. Procedures to Ensure Data Validity and Integrity

The study research methodology was developed to ensure validity of the data in several ways. First, measures for use in the study were selected carefully with regard to their established psychometric properties. We also considered balancing the need for a multidimensional assessment of outcome that is intensive enough to yield valid, meaningful data with the need to remain sensitive to the fact that an overly taxing assessment battery can cause fatigue, diminished reliability of responses, and potential dropout.

Data will be collected using a secure, Health Insurance Portability and Accountability Act (HIPAA) compliant web-based system, which will allow for real-time monitoring of data completeness and accuracy along with audit trails to facilitate ongoing data monitoring throughout the trial. REDCap (Research Electronic Data Capture) is a free, secure, HIPAA compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. The system offers easy data management with audit trails, reports for monitoring and querying participant records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

Participants will be fully informed about confidentiality protections (including the Certificate of Confidentiality) and will be informed that their responses to any questions will not impact their treatment at McLean Hospital. These procedures were designed to maximize participant willingness to disclose accurate information.

Finally, all study staff will be trained in research methods and the importance of ensuring data validity. In Dr. McHugh's Lab meeting, responsible conduct of research topics (e.g., data management, research misconduct), are covered on a monthly basis with lab staff. Dr. McHugh will monitor data on an ongoing basis, including bi-monthly downloads of the REDCap database to ensure data completeness.

D.2. Procedures to Guarantee Accuracy and Completeness of Data

In addition to the procedures described above, several procedures will be implemented to ensure accuracy and completeness of data. First, in the REDCap database we will use restricted ranges (i.e., rejecting any data point out of the potential range) and forced responses to all questions. This will ensure that we have complete data, with the exception of a participant choosing to discontinue a study prior to completion. Participants will still have the option to decline to answer any question through the availability of a decline to answer checkbox for each question. Second, research assistants or other staff implementing study procedures will be instructed to check the completeness of all data prior to a participant leaving the clinic, consistent with prior studies in Dr. McHugh's Lab. Finally, the dataset will be careful screened prior to data analysis for out-of-range values and to ensure that any missing data (i.e., declined questions) are labeled accurately and accounted for appropriately in all data analysis.

E. Regulatory Issues

The proposed research will be reviewed and approved by the Partners HealthCare IRB (which covers all Partners HealthCare hospitals, including McLean Hospital). In addition, the PI will have responsibility for continuous monitoring of the data and safety of subjects in the study. Data and safety monitoring will take place continuously throughout the study's duration. We will report adverse events and all serious adverse events that occur during the course of the trial to the Partners HealthCare IRB. At the time of annual, continuing review, we will provide the Partners HealthCare IRB with a summary of any unexpected and related adverse events, as well as any other unanticipated problems that occurred since the last continuing review.

E.1. Reporting Serious Adverse Events (SAEs)

We will also follow the Partners HealthCare IRB policies for expedited reporting of unexpected adverse events and serious adverse events. We will report to the IRB any non-serious, unexpected adverse events that are related or possibly related to a subject's participation in the research that occur while a subject is enrolled in the study. These events will be reported within 5 working days or 7 calendar days of our knowledge of the event by phone, fax, or e-mail to the Senior IRB Administrator at McLean Hospital. In addition, we will provide the IRB with a full written report using the Research Reportable Event Form within 10 working days following initial IRB notification. We will also report to the IRB serious adverse events that occur while a subject is enrolled in the study within 24 hours of our knowledge of the event by phone, fax, or e-mail to the Senior IRB Administrator. We will make a full written report to the IRB regarding the event within 10 working days of initial IRB notification. SAEs will be reported to NIDA within 72 hours.

E.2. Reporting of IRB Actions to NIDA

We will report any major protocol changes, changes in the study risk-benefit ratio, and action taken by the Partners Healthcare IRB related to these topics promptly to NIDA. SAEs will be reported to NIDA within 72 hours.

E.3. Report of Changes or Amendments to the Protocol
Any minor changes or amendments to the protocol (e.g., addition of a new study staff member, addition of a new recruitment flyer) will be reviewed by the Partners Healthcare IRB. Any major changes or amendments (e.g., substantive changes to the study manipulations or outcome measures) will be submitted to both the Partners Healthcare IRB and NIDA for review.

E.4. Trial Stopping Rules
The PI, in collaboration with Co-Investigators will closely evaluate changes in the risk-benefit ratio (e.g., adverse events) on an ongoing basis and will report any changes in the risk-benefit ratio to the IRB. In this low-risk behavioral study we do not anticipate that the risk-benefit ratio will change during the trial. Investigators have extensive experience with the population of interest and with the use of proposed methods and measures. Nonetheless, if unanticipated changes in the risk-benefit ratio are detected, investigators will work closely with the IRB and NIDA to determine whether the risk-benefit ratio remains acceptable. This is not a treatment trial, and thus efficacy monitoring is not applicable to this proposal.

E.5. Disclosure of Conflict of Interest
All investigators involved in the design and conduct of the proposed study are required to disclose any conflicts of interest at several time points: (1) submission of the proposal, (2) just-in-time requests, and (3) on an annual basis. Any conflicts of interest that could have impact on the scientific integrity of the proposal will be reported to NIDA. Conflicts will also be reported in any presentations or papers resulting from the proposed study.

F. Trial Safety
F.1. Potential Risks and Benefits for Participants
As in any study involving assessment of psychiatric symptoms, there is some risk of discomfort from discussing emotional topics (e.g., symptoms of substance use, negative affect). However, we anticipate that this discomfort will be transient. In addition, the laboratory stress induction is designed to elicit mild to moderate, transient distress. Our prior work has demonstrated that this stress induction is safe in this population, consistent with evidence suggesting that the implementation of stress reactivity procedures in research studies is not associated with increased risk for relapse following participation. Nonetheless, subjects will be closely monitored for evidence of excessive or enduring distress following these procedures and precautions to protect against this risk will be taken.

Another potential risk is the possibility that subjects may experience dangerous or suicidal behavior. We do not anticipate that our study procedures will increase this particular risk. If a subject becomes very upset, is intoxicated, or is suicidal during the study, he or she will be seen by one of the study clinical staff. An assessment will be conducted, and the appropriate clinical recommendation will be made; this could involve treatment either at McLean Hospital or elsewhere.

Another potential risk is a breach of confidentiality. However, as with the other risks mentioned above, we will take precautions to protect against this risk (see below).

F.2. Collection and Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs)
We will also follow the Partners HealthCare IRB policies for expedited reporting of unexpected adverse events and serious adverse events. We will report to the IRB any non-serious, unexpected adverse events that are related or possibly related to a subject's participation in the

research that occur while a subject is enrolled in the study. These events will be reported within 5 working days or 7 calendar days of our knowledge of the event by phone, fax, or e-mail to the Senior IRB Administrator at McLean Hospital. In addition, we will provide the IRB with a full written report using the Research Reportable Event Form within 10 working days following initial IRB notification. We will also report to the IRB serious adverse events that occur while a subject is enrolled in the study within 24 hours of our knowledge of the event by phone, fax, or e-mail to the Senior IRB Administrator. We will make a full written report to the IRB regarding the event within 10 working days of initial IRB notification. SAEs will be reported to NIDA within 72 hours. A case report form for the monitoring and reporting of AEs and SAEs is provided by the Partners Healthcare IRB.

F.3. Management of SAEs and Other Study Risks

The PI will monitor study risks on an ongoing basis using the procedures described above for identifying, documenting and reporting AEs, SAEs and other risks. In addition the following procedures will be used to protect against study risks.

Subjects will be fully informed about potential risks during the Informed Consent process. All study personnel will be trained in the appropriate care of human subjects, and will have completed a Collaborative Institutional Training Initiative (CITI) Basic Biomedical, Basic Social and Behavioral, or Good Clinical Practice course, or the National Cancer Institute (NCI) Human Participants Protections Education for Research Teams course and research assistants will be closely supervised by the study PI.

Should participants experience distress associated with assessment procedures or the stress induction that exceed a moderate intensity or transient duration, the PI will be contacted and appropriate clinical assessment will be conducted to determine the need for intervention. Consistent with our previous studies conducted in the ADATP, we have an established procedure for communicating any distress elevations to the PI. If intervention is indicated, the PI and study staff will facilitate either provision of intervention on-site or arrangement of an appropriate referral. Dr. McHugh (PI) is a trained clinical psychologist and licensed health service provider in the Commonwealth of Massachusetts, and Dr. Weiss (Co-Investigator) is a licensed addiction psychiatrist.

Individuals will be excluded from participating in the study if they exhibit acutely dangerous behavior at the time of screening. This helps protect against the risk of enrolling subjects who would pose a greater likelihood of experiencing acute dangerous behavior. Consistent with our previous studies conducted in the ADATP, we have an established mechanism for communicating with subjects' attending psychiatrist, should emergencies arise.

To protect against the loss of confidentiality, we will keep all study data locked in a separate file, coded by a unique study code number (with names and other personal identifying information stored separately). Only research staff who need access to personal identifying information for research purposes will have access to information linking the code to the participant's identification. This information will be stored in a separate locked file and will be destroyed upon completion of the study to minimize the risk of linking identifying information to research data. Electronically stored data will be de-identified with use of the study code number and will be stored in a password-protected file on a password-protected computer located in a locked office in accordance with all local institutional policies. In addition, the consent form will clearly inform subjects of the limits of confidentiality, including the circumstances in which confidentiality may be breached, such as in cases of suspected child abuse or neglect, suspected abuse of a disabled person or an elderly person, and dangerousness to self or others.

In the event that subjects experience discomfort when completing the study procedures, they will be free to refuse answering any questions that make them uncomfortable, to discontinue an assessment session at any time, or, if they wish, to withdraw from the study.

G. Trial Efficacy
This is not a treatment trial, and thus efficacy monitoring is not applicable to the proposed study.

H. DSM Plan Administration
H.1. Responsibility for Data and Safety Monitoring
The overall framework for data and safety monitoring for this project includes oversight on two levels. First, the proposed research will be reviewed and approved by the Partners HealthCare IRB. Second, the PI will have responsibility for continuous monitoring of the data and safety of subjects in the study. The PI will also consult with the investigator team on any specific issues that arise in the course of the study regarding the data as well as the safety of subjects. Further consultation will be obtained if necessary from the McLean Hospital Office of Research Administration.

H.2. Frequency of Data and Safety Monitoring
Continuous, close monitoring of safety issues by the PI will take place throughout the study's duration. Adverse events, serious adverse events, and protocol violations will be monitored on an ongoing basis. In addition, quarterly thorough quality assurance reviews will be conducted and documented in the regulatory binder. These reviews include: informed consent forms, data completeness, study procedural and tracking forms (e.g., tracking of screened and enrolled participants), and study regulatory binders (e.g., ensuring all IRB documentation has been filed and all amendments recorded). Finally, data will be monitoring both on an ongoing basis (i.e., research staff will confirm completeness of all forms prior to the participant leaving the lab), as well as regular (at least weekly) downloading of the REDCap data, and monthly review with the PI. In the event that a problem is identified, the frequency of monitoring will increase and a remediation plan developed.

H.3 Content of Data and Safety Monitoring Report
A Data and Safety Monitoring Report will be submitted to NIDA annually. This report will include the following elements: a brief description of the trial, baseline sociodemographic characteristics, retention and disposition of study participants, quality assurance issues, regulatory issues, adverse events, and serious adverse events.

I. DSM Board Plan
This project is not a multi-site clinical trial or a Phase III clinical trial, and is associated with minimal risk. Therefore, it is our opinion that a formal Data and Safety Monitoring Board (DSMB) is not needed, and that the safety monitoring plan described above is adequate.