Study: # 7193 entitled NEUROCOGNITIVE MECHANISMS OF DISULFIRAM TREATMENT OF ALCOHOL USE DISORDER

PI: Nasir Naqvi, MD, PhD

NCT# NCT02735577

Study Protocol Date: January 26, 2016

New York State Psychiatric Institute

Institutional Review Board

January 26, 2016

To: Dr. Nasir Naqvi

From: Dr. Edward Nunes, Co-Chairman
Dr. Laurence Greenhill, Co-Chairman

Subject: Approval Notice

Your protocol # **7193** entitled: **NEUROCOGNITIVE MECHANISMS OF DISULFIRAM TREATMENT OF ALCOHOL USE DISORDER** Protocol version date 01/26/2016 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **January 26, 2016 to December 20, 2016.** (Reviewed at the Full Board meeting on December 21, 2015.)

Consent requirements:
☐ Not applicable:
☐ 45CFR46.116 (d) waiver of consent for the telephone interview
√ Signature by the person(s) obtaining consent is required to document the consent process
☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: √ No ☐ Yes

Field Monitoring Requirements: √ Routine ☐Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

Cc: CU Business Office (internal acct: Gertsner Jr. Scholar Award); CUMC IRB

Encl: CF, consent quiz, MRI findings letters, patient instructions

EN/LG/alw

Signed copy on file at IRB

Protocol Title:
Neurocognitive Mechanisms of Disulfiram Treatment of Alcohol Use Disorder

Version Date:
01/26/2016

Protocol Number:
7193

First Approval:
01/26/2016

Clinic:
Substance Treatment And Research Services (STARS)

Expiration Date:
12/20/2016

Principal Investigator:
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Co-Investigator(s):
Frances Levin, MD
John Mariani, MD

Research Chief:
Herbert Kleber, MD

Cover Sheet

Choose from the following that is applicable to your study
I am submitting a new protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Substance Abuse
Within the division/department, what Center or group are you affiliated with, if any?
STARS

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
None

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Medication Trial
✓ MRI

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50
✓ Substance Users

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account
Louis V. Gerstner, Jr., Scholar Award (internal Columbia University Medical Center Award)
Is the project externally funded or is external funding planned?
No

Study Location

Indicate if the research is/will be conducted at any of the following

✓ NYSPI

This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research
The overall goal of this project is to combine functional brain imaging and clinical methods in order to examine how treatment with disulfiram (DIS) alters neural activity related to alcohol-seeking motivation in patients with alcohol use disorder (AUD). DIS is an established, effective, FDA-approved medication for AUD that causes a highly aversive visceral reaction if alcohol is consumed while it is being taken. The mere awareness of the risk or threat the DIS-alcohol reaction deters alcohol use, i.e. it is not necessary to drink

alcohol while taking DIS to change behavior. By uncovering the neural mechanisms underlying this risk/threat-based psychological effect, it will be possible to integrate DIS with biologically based treatments targeted at these neural mechanisms, with the goal of improving the efficacy of DIS. Furthermore, the results will shed light on the general neural mechanisms by which awareness of risks of substance use impacts addictive motivation. This is a core process in a number of behavioral treatments for substance use disorders, such as Motivational Interviewing and Contingency Management, as well as in behavior change in non-treatment settings.

Background, Significance and Rationale

Background, Significance and Rationale

Disulfiram (DIS) is one of the oldest, most effective, and most commonly used treatments for alcohol use disorder (AUD)(1). DIS is a medication that causes a highly aversive visceral reaction if alcohol is consumed while it is being taken (the DIS-alcohol reaction). Most patients who take DIS do not sample alcohol while taking it (2) indicating that the experience of the DIS-alcohol reaction is not necessary for behavior change, but instead that the mere expectancy or threat of this aversive reaction, i.e. subjective risk, is sufficient to induce behavior change. Here, we are interested in examining the neural underpinnings of this risk-based behavior change mechanism.

The fact that some patients do drink during DIS treatment despite the subjective risk of the DIS-alcohol reaction suggests a limitation of efficacy rooted in a failure of risk-based decision processes. There is a large body of evidence that AUD and other addictive disorders are associated with deficits in risk-based decision making and its neural substrates(3, 4). By understanding the neural mechanisms that mediate behavior change (and the failure of behavior change) during DIS treatment, it may be possible to improve the efficacy of DIS and other treatments that depend upon an awareness of risks by identifying targets for biologically-based augmentation therapies can be combined with such therapies. Such risk-based therapies include DIS, as well as behavioral treatments such as Motivational Interviewing and Contingency Management. Furthermore, reduction in alcohol use as a result of a shift in subjective risk is likely to play an important role in behavior change outside of treatment.

Previous work by the PI(5) and others(6) has provided circumstantial evidence that excitatory inputs from the insula and the ventromedial prefrontal cortex (VMPFC) into the ventral striatum (VS) drive a specific “goal-directed” form of drug and alcohol seeking that is engaged when there is a high level of subjective risk. The PI has also shown that cue-induced alcohol craving can be reduced by thinking about risks of alcohol use(7). In cigarette smokers, this risk-based form of cognitive regulation of craving is mediated by negative functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and the VS(8). Furthermore, effective AUD treatments consistently down-modulate cue-induced activity in the VS(9), suggesting an important role for this region in therapeutic behavior change.

Based upon this prior work, we propose that DIS treatment - specifically, the mere belief that drinking will cause the DIS-alcohol reaction - changes behavior by promoting a goal-directed mode of cue-induced alcohol seeking. In this mode, the output of the VS is governed by a balance between (1) excitatory inputs from the insula and the VMPFC that together represent the incentive value of alcohol, and (2) inhibitory inputs from the DLPFC that down-modulate VS output according to the perceived unpleasantness and likelihood of the DIS-alcohol reaction. The resulting VS output determines the magnitude of cue-induced craving during DIS treatment, and predicts the likelihood of relapse during DIS treatment.

The goal of this project is to provide pilot data supporting this model by combining clinical DIS treatment with fMRI experiments that probe the neural correlates of alcohol-seeking motivation. The results will represent the first evidence in treatment-seeking AUD patients of a highly novel and clinically relevant model of alcohol seeking motivation and behavior change under specific behavioral contexts that involve high subjective risk and conflict. Because this is a pilot study, it lacks control groups to address certain important confounds. For example, a control group that receives no treatment while still receiving the general supportive elements of the study would control for factors such as the motivation to enter treatment, the effects of general supportive elements, and the mere passage of time; a control group that receives a placebo instead of DIS would control for potential direct CNS effects of DIS, such as effects on dopamine beta hydroxylase. If the pilot study provides a positive signal for the involvement of the proposed circuitry in the mechanism of behavior change during DIS treatment, this will substantiate subsequent, larger, R01-funded studies that will include non-treatment and placebo control groups. The results will also provide specific anatomical targets for future clinical studies that aim to increase the efficacy of DIS and other risk-based behavior interventions by combining them with biological treatments, such as repetitive transcranial magnetic stimulation (rTMS).

An important secondary goal of this study is to examine the neural mechanisms underlying adherence to DIS treatment. There is evidence that adherence to DIS treatment is a major limiter of its effectiveness (10). Thus, by identifying neural markers that predict adherence during ongoing DIS treatment, as well as markers that predict the decision to continue DIS treatment when there is an option to stop, it may be possible to identify patients who are likely to benefit the most from DIS treatment. Furthermore, these neural markers may also serve as anatomical targets for biological treatments that can be combined with DIS to improve adherence.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

We plan to complete data collection in 25 treatment-seeking AUD patients. Following a brief inpatient lead-in phase to facilitate abstinence, the patients will undergo a pre-DIS fMRI scan using a passive alcohol cue-reactivity paradigm, with high-calorie food cues serving as control stimuli. They will then receive 10 days of outpatient open-label DIS treatment that includes taking DIS 500 mg every other day, with supervised dosing. They will then undergo a post-DIS fMRI scan using the same cue-reactivity task used in the pre-DIS scan. They will then be followed for 30 days while receiving open-label DIS 250 mg daily, with weekly medical management visits that will include monitoring of alcohol use and medication adherence, and administering a supervised dose of DIS 250 mg. During both phases, patients will be repeatedly informed of the risk of the DIS-alcohol reaction.

Aim 1: Measuring the effects of DIS treatment on cue-elicited neural activity: We predict that, from the pre- to the post-DIS fMRI scans, there will be: increased cue-induced activity in the insula, VMPFC and DLPFC; increased cue-induced insula-VS positive functional connectivity; increased cue-induced VMPFC-VS positive connectivity; increased cue-induced DLPFC-VS negative functional connectivity; reduced cue-induced activity in the VS; reduced cue-induced craving; and a stronger relationship between cue-induced VS activity and cue-induced craving. These effects of DIS treatment will be specific to alcohol cues. Furthermore, we predict that the effects of DIS treatment on insula-VS and VMPFC-VS functional

connectivity will be mediated by self-report measures of alcohol incentive salience at the post-DIS scan; and that the effects of DIS treatment on DLPFC-VS negative functional connectivity will be mediated by self-report measures of the perceived likelihood and unpleasantness of the DIS-alcohol reaction at the post-DIS scan.

Aim 2: Using the effects of DIS treatment on cue-elicited neural activity to predict relapse: We predict that individual differences in cue-induced VS activity in the post-DIS fMRI scan will predict relapse during a subsequent 30 days of DIS treatment, after controlling for cue-induced VS activity during the pre-DIS scan. Here, relapse will defined as any alcohol use during the 30-day DIS treatment period.

Secondary Aims: (1) We will identify regions across the whole brain in which the effects of 10-day DIS treatment on cue-induced neural activity predict adherence during 30-day DIS treatment. (2) We will identify regions across the whole brain in which the effects of 10-day treatment on cue-induced neural activity predict the decision to continue DIS treatment beyond 30-days. (3) We will acquire baseline measures of AUD severity, alcohol saliency, motivation for change, impulsivity, self-regulation and tolerance for risk, and will examine how these variables moderate the effects of DIS on cue-induced neural activity. (4) If a significant number (>1/3) of patients sample alcohol during the 10-day DIS treatment and thus experience the DIS alcohol reaction, we will perform a subgroup analysis comparing how the neural effects of DIS treatment in such patients differ from patients who do not sample DIS during the 10-day treatment. This will allow us to determine whether the neural effects of actually experiencing the DIS-alcohol reaction are different from the effects of mere expectation of the DIS-alcohol reaction.

Description of Subject Population

Sample #1

Specify subject population
Patients with Alcohol Use Disorder
Number of completers required to accomplish study aims
25
Projected number of subjects who will be enrolled to obtain required number of completers
40
Age range of subject population
21-60

Gender, Racial and Ethnic Breakdown
Forty adults with a primary DSM-V diagnosis of Alcohol Use Disorder will be enrolled. It is anticipated that 18 of them will be women, based upon our recruitment for similar studies. Approximately 10 participants will be Hispanic; 3 will be Asian; 12 will be Black or African American. This profile is broadly representative of the racial demographics of New York City.
Description of subject population
The subject population will be right-handed men and women with a primary DSM-V diagnosis of Alcohol Use Disorder. These will be adults, ages 21-60, who are currently drinking at least 5/4 standard drinks per day for men/women on at least 4 days/week on average during the previous 28 days.

Recruitment Procedures

Describe settings where recruitment will occur
Participants will be recruited using previously successful methods for substance use disorder treatment trials at conducted at the Substance Treatment and Research Service (STARS). Recruitment and screening of potential participants at STARS is covered by an umbrella recruitment and screening protocol, #6582R: Evaluation of Potential Substance Abuse Research Participants (PI: John J. Mariani, MD). Recruitment through this umbrella protocol occurs in the local community, as well as from local outpatient clinics and emergency rooms. Clinical trials at STARS have historically drawn a broad sample of patients from the greater New York City metropolitan area. These recruitment procedures are already being utilized to recruit the population under study (treatment-seeking, currently drinking alcohol-dependent patients) for other active protocols at STARS. No modification of this umbrella protocol is required for the current study.
How and by whom will subjects be approached and/or recruited?
As per protocol #6582R, a standardized telephone interview is initially conducted and prospective patients who meet screening eligibility criteria are scheduled for the first screening visit.
How will the study be advertised/publicized?
As per protocol #6582R, a combination of radio, print, cable television and Internet advertising will be directed at prospective patients in the New York City metropolitan area who have been experiencing problems related to alcohol use and are seeking treatment. The advertisements that will be used in this study have already been IRB approved as part of protocol #6582R, which includes subway, radio and television advertisement text and graphics. Outreach to other clinical sites and individual clinicians will be accomplished by targeted mailings, phone solicitations of clinic directors, and the use of clinically oriented e-mail newsgroups and other Internet resources.
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
The recruitment and screening process is covered by a separate general recruitment and screening IRB protocol utilized for all research at STARS (Protocol # 6582R: EVALUATION OF POTENTIAL SUBSTANCE ABUSE RESEARCH PARTICIPANTS). This is not a separate research study, but nevertheless is a separate IRB protocol with its own consent, etc. This umbrella recruitment and screening protocol is already being utilized to recruit the population under study for the current protocol (i.e.

treatment-seeking, currently drinking AUD patients). Therefore, no modification of that umbrella protocol is required, other than indicating therein that the present protocol is one of the studies in which recruited participants may be enrolled.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Alcohol Use Disorder Patients
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criterion	Method of Ascertainment
1. Between the ages of 21-60	Self-report; photo ID
2. Right-handed	Self-report
3. Capable of giving informed consent and complying with study procedures	Psychiatric interview
4. Reports drinking a minimum of 5 standard drinks for men or 4 standard drinks for women on at least 4 days per week on average over the past 28 days	Self-report; TLFB
5. Meets DSM-V criteria for current Alcohol Use Disorder	MINI; Psychiatric interview
6. Seeking treatment for Alcohol Use Disorder	Self-report
7. Agree to not seek additional treatment, apart from Alcoholics Anonymous	Self-report
8. Willing to attempt to abstain from alcohol completely for the duration of the study	Self-report
9. Willing to be hospitalized on a research unit for a minimum of 4 days	Self-report

Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion Criterion	**Method of Ascertainment**
1. Risk of severe alcohol withdrawal (e.g. history of seizures or delirium tremens)	Psychiatric interview
2. Current Moderate or Severe Substance Use Disorder, other than Alcohol, Nicotine or Caffeine Use Disorders	MINI, psychiatric interview
3. Lifetime history of Bipolar Disorder, Schizophrenia or Schizoaffective Disorder	MINI, psychiatric interview
4. Any current psychiatric disorder, other than Alcohol Use Disorder, that, in the judgment of the investigator, will require treatment that will interfere with study participation.	MINI; psychiatric interview
5. Current severe depression (HAM-D >24) or anxiety (HAM-A >24)	HAMD; HAMA; psychiatric interview
6. Significant suicide or violence risk	MINI; psychiatric interview
7. Currently taking any psychotropic medications	Self-report; medical history
8. Legally mandated to participate in treatment	Self-report
9. History of prior treatment with disulfiram	Self-report
10. Sufficiently socially unstable as to preclude participation (e.g. homeless)	Self-report
11. Contraindications to disulfiram treatment (liver disease, kidney disease, cardiac disease, seizure disorder, hypothyroidism, diabetes mellitus, pregnancy or lactation, allergy to disulfiram or thiuran derivatives)	Medical history; physical exam; blood test; EKG
12. Neurological or medical conditions that would interfere with MRI scanning (e.g. history of stroke, seizure, brain tumor, brain infection, traumatic brain injury, multiple sclerosis, dementia, metal device in body, pregnancy, claustrophobia, color blindness, severe hearing impairment, weight>300 lbs., wheelchair-bound)	Medical history; psychiatric interview; physical examination
13. Currently taking medications containing alcohol, metronidazole, isoniazid, paraldehyde, phenytoin, warfarin, or theophylline.	Self-report; medical history
14. Significant alcohol withdrawal (CIWA>8) at screening, after confirming a blood alcohol level of zero.	CIWA-Ar; Breathalyzer

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No

Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
5474R
Describe Study Consent Procedures

Potential participants will contact the study via a designated telephone number posted in recruitment materials. After providing verbal informed consent, the initial phone screen will be performed by a member of the research staff of STARS. This will ascertain if demographic criteria, treatment-seeking status, quantity of alcohol, handedness, and any current psychotropic medications. Based on the results of this screen, participants will be invited to STARS for an in-person screening.

Participants will arrive at the STARS clinic for the initial screening appointment at which time they will be provided with a copy of the consent form for the general screening procedures at STARS (protocol #6582R: Evaluation of Potential Substance Abuse Research Participants, PI John Mariani). After reading the consent form, each participant will meet with a screener who has been authorized to obtain consent for the general screening. The screener will guide the participant through the informed consent process, which includes a review of the consent form and answering questions related to the form and screening process. Subsequent to completion of these tasks the participant and screener both sign the consent form.
Participants will then proceed with the screening process.

Participants identified by the screeners as possibly eligible for treatment will be evaluated by the psychotherapist using the MINI diagnostic interview. Participants who are thus far deemed eligible will provide blood and urine samples, and will undergo Breathalyzer testing and EKG. The psychiatrist will then perform a psychiatric evaluation, physical examination and CIWA-Ar, and will review the results of blood tests, EKG, urine toxicology and Breathalyzer, all for final determination of eligibility. This includes a determination of whether the participant is intoxicated or in alcohol withdrawal, since these may affect their competence for providing informed consent for the study. Those who meet criteria for the current study will be offered participation in this study. Those who are not eligible will be assisted in finding treatment programs in the community.

Once the participant is deemed eligible for the study using the umbrella screening protocol, the specific consent procedures for the study will occur. Each participant will receive an explanation
of the study protocol, its risks, potential benefits, and alternative treatment by a study staff member. The participant will complete a quiz to ascertain their understanding of the study risks and benefits. A physician

will speak with the participant about the study and answer any questions that s/he may have. This includes informing the participant about the risks and benefits, as well as discussions of alternative treatments. Following this discussion, the physician will review with the participant their understanding of risk/benefits/alternatives, including review of the consent quiz. The physician and the participant will then both sign the consent document.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form
✓ Information Sheet

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Bisaga, Adam, MD
Brezing, Christina
Dakwar, Elias, MD
Evans, Elizabeth, MD
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, MD
Naqvi, Nasir, MD
Williams, Arthur
Type in the name(s) not found in the above list

Robin Williams, MD

Study Procedures

Describe the procedures required for this study
Personnel:
Nasir Naqvi, M.D., Ph.D.
John Mariani, M.D.
Frances R. Levin, M.D.
Robin Williams, MD
Sean Luo, MD
Adam Bisaga, M.D.
Elias Dakwar, MD
Elizabeth Evans, MD
Christina Brezing, MD
Elizabeth LeQuesne, MD
Peter Van Roessel, MD, PhD
Olivia Joly, MD

Kenneth Carpenter, PhD
Amy Mahony, MA
Daniel Brooks, MA
Kaitlyn Mishlen, MA
Elisa Liemsider, CSW
Payal Pandya, MA
Marcia Loughran, NP

Principal Investigator: Dr. Nasir Naqvi, MD, PhD, is an Assistant Professor of Clinical Psychiatry at Columbia University and a Clinical Physician at RFMH/New York State Psychiatric Institute. He is a board certified psychiatrist with subspecialty training in addiction psychiatry. Dr. Naqvi completed a NIDA-funded T-32 substance abuse research fellowship at Columbia University/New York State Psychiatric Institute in 2011 and is currently the recipient of a NIAAA K23 award and a Louis V. Gerstner, Jr., Scholar Award through CUMC. As a resident, fellow and now as a junior faculty, Dr. Naqvi has had extensive clinical experience treating alcohol use disorders using disulfiram and other pharmacotherapies, and has had mentored experience in conducting substance use disorder clinical trials for addiction pharmacotherapies. Dr. Naqvi also has prior experience working as an inpatient psychiatrist taking care of patients requiring alcohol detoxification. As PI, Dr. Naqvi will be responsible for coordination of all study procedures, such as supervision of research assistants and safety monitoring. Dr. Naqvi will also serve as a research psychiatrist for the study, along with other STARS research psychiatrists. Additionally, Dr. Naqvi (or another STARS outpatient psychiatrist when Dr. Naqvi is not available) will assess all patients in person on the day after admission, following the 24-hour monitoring period, to aid in the ruling our our treatment of alcohol withdrawal. Dr. Naqvi or a covering STARS outpatient psychiatrist also be available at all times by telephone to be consulted by the 5-S attending physicians, and to see patients on the unit as the clinical situation dictates.

Co-Investigator: Dr. Frances Levin, MD, is a Professor of Psychiatry at Columbia University. She is a board-certified psychiatrist with subspecialty training in addiction psychiatry. She is the senior physician conducting clinical trials at the STARS clinic, and is involved in mentoring of junior faculty who are conducting pharmacotherapy trials. Dr. Levin has extensive experience in the design and implementation of clinical trials of pharmacotherapies for substance use disorders, including alcohol use disorders. Dr. Levin will serve in a mentoring role for Dr. Naqvi, supervising him on the design and execution of the clinical aspects of this protocol. Additionally, Dr. Levin will ensure that Dr. Naqvi has full access to the resources and personnel at STARS. Dr. Levin will also serve as one of the study physicians for this protocol.

Co-Investigator: Dr. John Mariani is an Associate Professor of Clinical Psychiatry at Columbia University and a Research Psychiatrist II at the New York State Psychiatric Institute. He is a board certified psychiatrist with subspecialty certification in addiction psychiatry. Dr. Mariani completed a NIDA-funded T-32 substance abuse research fellowship at Columbia University/New York State Psychiatric Institute in 2005 and is currently the recipient of multiple R01 awards for addiction pharmacotherapy trials. As the Director of the Substance Treatment and Research Service (STARS) of Columbia University/New York State Psychiatric Institute, Dr. Mariani oversees the overall operations of STARS. Dr. Mariani has extensive experience in conducting and managing substance use disorder pharmacotherapy clinical trials, including a recent pharmacotherapy trial examining the efficacy of gabapentin in the treatment of Alcohol Use Disorder. He is also the PI on the umbrella screening protocol for the recruitment of study participants at

STARS (Protocol # 6582R: EVALUATION OF POTENTIAL SUBSTANCE ABUSE RESEARCH PARTICIPANTS).

Psychotherapists (CSW, MA, PhD): The psychotherapists (Kenneth Carpenter, PhD, Amy Mahony, MA, Elisa Liemsider, CSW, Kaitlyn Mishlen, MA, Payal Pandya, MA) have a doctorate in clinical psychology, a master's degree in psychology, or a master's degree in social work. The psychotherapists are responsible for conducting screening assessments to evaluate for substance use and psychiatric disorders, and to determine initial eligibility, preceding examination by a psychiatrist for medical evaluation and completion of screening.

STARS Outpatient Psychiatrist (MD): The research psychiatrists at STARS (Drs. Naqvi, Levin, Mariani, Bisaga, Evans, Luo, Dakwar, Brezing and Williams) are all either board-eligible/board-certified addiction psychiatrists, or are current fellows in the addiction psychiatry fellowship who have completed a general psychiatry residency, and who are under supervision of Drs. Mariani and Levin. The STARS research psychiatrist will perform psychiatric and medical evaluations, to assess the patients' eligibility for study entry, including confirming the diagnostic impression made by the psychologist based on the MINI, determining the presence of co-morbid psychiatric disorders that are likely to require treatment during the study, as well as determining the presence of intoxication, alcohol withdrawal, severe anxiety or depression, suicidal or homicidal ideation, cognitive impairment, or any medical contraindications to study participation. After individuals are determined to be eligible for the study based on all eligibility criteria, the research psychiatrist will describe the study to the patient and obtain informed consent after s/he has answered all questions related to the study procedures. All research psychiatrists who are responsible for enrolling participants will 1) review the medical chart, 2) evaluate the patient in person, and 3) sign the eligibility checklist. Once participants are enrolled, the psychiatrists will perform the medication management procedures. This includes monitoring for disulfiram adverse effects, recent alcohol use, medication adherence, and psychiatric symptoms, including psychosis, suicidality and homicidality. Additionally, the STARS psychiatrists will play a role in covering for Dr. Naqvi when he is not available for consultation on patients admitted to 5-S.

Attending Inpatient Psychiatrist (MD): The attending psychiatrists on the inpatient unit on 5-S (Drs. LeQuesne, Van-Roessell and Jolly) will have primary responsibility for admitting and treating patients during the inpatient lead-in phase when patients will initiate abstinence from alcohol and be detoxified as needed. This will include psychiatric and medical evaluation as per usual 5-S protocol for inpatient admissions for treatment-seeking research participants, with specific focus on the presence alcohol intoxication and/or withdrawal. During the admission, they will monitor patients for the emergence of alcohol withdrawal syndrome, and initiate detoxification medications as needed through consultation with Dr. Naqvi. They will continually evaluate patients' capacity to consent for participation in this study. They will also prescribe the first dose of DIS that is to be given after the pre-DIS MRI scan, and will explain disulfiram effects prior to discharge, including warning about the risks of alcohol use after starting DIS.

Outpatient Research Nurse (RN or NP): The research nurse (Marcia Loughran, NP) will meet with patients at the screening to obtain vital signs, monitor side effects, collect urine samples, and perform screening medical and physical examinations when these are not performed by the psychiatrist (only psychiatrists will perform screening psychiatric evaluations, which include evaluations for alcohol intoxication and

withdrawal). Additionally, the research nurse will meet with patients on the first STARS clinic visit in order to assess for adverse effects of DIS, and to instruct patients about the DIS-alcohol reaction.

Inpatient Nurse (RN or NP): The inpatient nurse (TBD) will perform usual nursing duties on 5S. This includes the routine monitoring of safety and vital signs; the dispensing of medications; and administering milieu therapy. Additionally, the inpatient nurses will have primary responsibility for administering the Clinical Institute Withdrawal Assessment-Alcohol (revised) (CIWA-Ar), which is a standardized clinical instrument for the assessment of alcohol withdrawal. All of the inpatient nurses will attend an in-service given by Dr. Naqvi on the administration of the CIWA-Ar, as well as on recognizing signs and symptoms of complicated withdrawal (e.g. agitation, delirium, severe autonomic instability) and Ativan toxicity (e.g. ataxia, stupor, respiratory suppression).

Research Assistant (BA or BS): The research assistant (TBD), working closely with Dr. Naqvi, will manage data collection and help coordinate clinical and fMRI scanning operations. The research assistant will also conduct screening telephone interviews and will be involved in participant recruitment. They will attend the fMRI scanning sessions and assist with preparing participants for these sessions, such as obtaining ratings and practice behavioral tasks, administering rating scales for alcohol withdrawal, collecting vital signs, urine samples, blood samples and breath alcohol samples. They will undergo the MRI training course at NYSPI that is designed for research assistants, which includes safety training. Research assistants who are approved staff members for other research protocols operating at STARS will provide cross-coverage for this study when necessary.

Screening and Consent Procedures:
This study will utilize the umbrella recruitment screening procedures utilized for all research studies at STARS, which has its own IRB protocol (# 6582: EVALUATION OF POTENTIAL SUBSTANCE ABUSE RESEARCH PARTICIPANTS), and includes advertisements (attached) and screening procedures for potential research participants with alcohol use disorder. Participants will be initially screened by phone following a verbal consent. Based upon the results of the phone screening, participants will be invited to an in-person screening visit at the Substance Treatment and Research Service (STARS) outpatient clinic at 3 Columbus Circle in Manhattan. At the in-person screening visit, participants will provide informed consent for the umbrella screening process. Participants who provide this consent will then be administered relevant eligibility measures.

As per Protocol # 6582R, a psychotherapist will administer the MINI International Neuropsychiatric Instrument (MINI), to diagnose Alcohol Use Disorder as a well as to rule out exclusionary psychiatric disorders. An RA will measure vital signs, including height, weight, temperature, pulse, blood pressure, will obtain blood and urine samples, EKG, Breathalyzer, the 30-day Timeline Followback and will administer the Montreal Cognitive Assessment (MOCA) to document the level of cognitive functioning. **Approximately 10cc (2 tablespoons) of blood will be drawn, and the primary purpose of blood sampling is to rule out medical contraindications to disulfiram treatment (e.g. liver disease, diabetes, thyroid disease).** Patients who who have a positive BAL (>0.05) will be asked to return on another day after having abstained until the time of screening. Patients who thus far meet study eligibility criteria will then be assessed by a psychiatrist, who will perform a psychiatric history and mental status examination. This includes an assessment for current alcohol withdrawal using the Clinical Institute Withdrawal Assessment-Alcohol (revised) (CIWA-Ar). The psychiatrist will also complete the Hamilton Depression

Inventory (HAM-D), to quantify the level of depressive symptoms; the Hamilton Anxiety Inventory (HAM-A) to quantify the level of anxiety symptoms; and the Clinical Global Impression Scale - Severity (CGI-S) to quantify the current level of overall psychiatric symptoms and functioning. Either the psychiatrist or nurse practitioner will then complete a medical history and a physical examination. It will be the assessment of the psychiatrist, who will review the results of all of the screening procedures with the psychologists and research assistants, that will provide the final determination for inclusion in the study. In cases where study inclusion in uncertain, the patient will be discussed at the weekly STARS clinical meeting with the PI and co-PI's.

If participants are eligible for the study, they will provide specific informed consent for the study. The psychiatrist will perform the consent procedures. Participants will be instructed to abstain from alcohol for the consent procedure, and the breathalyzer will be checked again at consent. If the BAL > 0.05, then the consent will be rescheduled. The screening and consent procedures may be broken up over several days, depending upon participation schedule and availability of clinic staff for the various procedures. All participants will receive $50 for completing the screening procedures, whether they qualify for the study or not.

Inpatient Lead-In Phase

All patients will be voluntarily hospitalized on the 5-S research unit at NYSPI for 4-6 days. This inpatient admission serves to safely initiate abstinence by restricting patients' access to alcohol and monitoring for alcohol withdrawal and detoxification as needed (the exclusion criteria are specifically designed to exclude patients who will require detoxification, but we are nevertheless including procedures to detect alcohol withdrawal and detoxify patients if necessary).

The admission will begin with an evaluation by the admitting psychiatrist that will include an assessment of current alcohol intoxication and/or withdrawal and recent alcohol use, including Breathlyzer testing and CIWA-Ar, as well as recent psychiatric symptoms, suicidality, homicidality and any current medical problems. Patients will sign the usual legal paperwork for voluntary psychiatric admission.

The current standard of care for alcohol detoxification is to utilize a symptom-triggered approach to detect and treat alcohol withdrawal with sedative-hypnotic medication (we will use Ativan), followed by a taper of Ativan according to a standard schedule. During the first 24 hours of the admission, the CIWA-Ar, which includes measurements of vital signs, will be assessed by a nurse every 4 hours while patients are awake (patients who are asleep are unlikely to be in alcohol withdrawal). Any CIWA-Ar score greater than 8 (indicative of mild alcohol withdrawal) will result in administration of lorazepam (Ativan) 1 mg. Thus, a patient may receive up to 6 mg of Ativan in the first 24 hours of admission based upon this schedule alone. If patients do not show signs or symptoms of alcohol withdrawal (CIWA-Ar>8) for 24 hours, they have a very low risk of withdrawal at any later time point. Nevertheless, to provide an extra layer of caution, patients who do not show evidence of alcohol withdrawal during the initial 24-hour monitoring period will continue to be monitored with the CIWA-Ar every 8 hours for another 24 hours.

Dr. Naqvi (the PI) or a covering addiction psychiatrist will assess the patients in person following the 24-hour initial monitoring period and, based upon this assessment, will confirm the presence or absence of alcohol withdrawal; advise the 5-S attending on the need to change Ativan dosing; assess for Ativan toxicity; and to determine whether the patient requires a higher level of care, i.e. medically supervised

detoxification. For patients in whom the Ativan dosing in the first 24 hours was adequate, Dr. Naqvi will advise the 5S attending on an Ativan taper schedule. The taper will involve a reduction of approximately 25% per day of the total daily dose of Ativan, given in divided (TID) doses. A set of sample taper schedules is attached. For patients who require detoxification, MRI scanning will occur at least 12 hours after the last Ativan dose, to minimize the effects of Ativan on MRI measures. This may result in a slightly longer length of stay, compared to patients not requiring detoxification, depending on the quantity of Ativan administered. For example, a patient requiring a total of 6 mg of Ativan in the first 24 hours will have a total length of stay of 6 days, instead of 4.

Patients who receive Ativan in the initial 24-hour monitoring period will continue to have the CIWA-Ar with vital signs assessed every 4 hours for an additional 24 hours, followed by every 8 hours until the Ativan taper is completed. The 5-S attending or doctor on call will be contacted by the nurse for the following parameters: CIWA-Ar > 11 at any time; CIWA > 8 after receiving a total of 6 mg Ativan over 24 hours; confusion; hallucinations; agitation; SBP <90 or >190; DBP<40 or >100; pulse<50 or >110; a change in heart rate or blood pressure that reaches 20 points above baseline at admission; respiration<10/minute; ataxia; stupor; airway compromise. The physician will assess the patient in person to determine the need for a change in Ativan dosing or the need to transfer to a higher level of medical care. Dr. Naqvi or a covering addiction psychiatrist will be available by telephone at all times to advise the 5-S attending or doctor on call on management of these complications. Patients who experience any of these complications will be seen the following day by Dr. Naqvi or a covering addiction psychiatrist, who will provide recommendations for ongoing management and continue to see the patient thereafter as the clinical situation dictates. Patients deemed by the 5S physician or DOC as requiring a higher level of care (e.g. medically supervised detoxification) will be managed as per usual 5S protocol for patients with urgent medical issues, i.e. consultation with the Milstein Hospital Medicine service for potential transfer.

All patients will be given thiamine 100 mg daily, folic acid 1 mg daily and a multivitamin table daily, to address nutritional deficiencies that can accompany AUD. Additionally, patients will be provided the following as-needed medications: Benadryl (diphenhydramine) 50 mg at bedtime for insomnia; Tylenol (acetaminophen) 650 mg every 6 hours for pain and headache; Maalox (magnesium/aluminum hydroxide) 30 cc once daily for gastrointestinal distress; and Compazine (prochlorperazine) 10 mg every 6 hours for nausea.

All patients will participate in the milieu therapeutic activities (e.g. recreation groups), and will be subject to the same rules and restrictions of all other voluntary patients on the unit. Patients will also complete a number of self-report assessments, administered by the RA, on the first or second day of admission (see Assessment Instruments).

On the day of discharge, patients will undergo the pre-DIS MRI scanning session. Once this scan is complete, the patients will return to the unit, where they will receive the first dose of DIS 500 mg, followed by instruction by the inpatient psychiatrist about DIS-alcohol reaction (see below for details). Following this, they will be discharged, with a follow-up appointment to attend the STARS clinic 2 days later. Prior to discharge, patients will be given a card (attached) that instructs them on the consequences of consuming alcohol while taking DIS, a list of common products that contain alcohol and are to be avoided (e.g. cough syrups, hand sanitizers), as well as a telephone number to reach the STARS on-call MD in the even of any problems or concerns.

10-Day DIS Treatment:
The 10-day treatment period will involve supervised dosing of DIS 500 mg every other day, administered by either a physician or a nurse. Two days after discharge from the inpatient unit, patients will attend the STARS clinic for the first of 4 clinic visits that will occur every other day to facilitate observed dosing of DIS to ensure full therapeutic effects for the post-DIS MRI scan. The STARS clinic is located at 3 Columbus Circle in midtown Manhattan.

Each clinic visit will include the following procedures: an RA will measure vital signs; perform breath alcohol and urine ethyl glucoronide (EtG) testing; obtain self-reports of alcohol use since the previous clinic visit; a physician or a nurse will administer a single dose of disulfiram 500 mg and instruct about the DIS-alcohol reaction, and review for any alcohol use and any adverse effects of disulfiram. At the third clinic visit, a physician will assess for psychiatric symptoms, including administering the HAM-A, HAM-D and CGI; and perform a Treatment Services Review. On the 4th clinic visit (after 10 days of taking DIS 500 mg every other day) patients will complete a number of self-report measures (OCDS, RCQ, AASE). **A blood sample (10cc, or 2 tablespoons) will be obtained for liver functions and CBC on the 4th visit, to determine the presence of any effects of disulfiram on liver function and blood cell counts.** After completing the clinic procedures on the 4th clinic visit, patients will be escorted in a taxi to the MRI facility located at NYSPI for the post-DIS MRI scan. They will then return to the STARS clinic 2 days later to begin the 30-day DIS treatment period.

30-Day DIS Treatment:
After completing the post-DIS MRI scan, patients will be followed for 30 days while continuing DIS treatment. In this phase, they will attend the STARS clinic weekly, for a total of 4 visits. The first weekly visit will occur 2 days after the post-DIS MRI scan. The procedures at each visit will include the following: the RA will measure vital signs; perform Breathalyzer and urine EtG testing; administer TLFB self-report of alcohol use over the previous 7 days; obtain self-report of DIS adherence; and count pills remaining from the previous week. A physician will meet with the patient to monitor for adverse effects of DIS; inquire about alcohol use since the last visit; assess for the presence of depression, psychosis and suicidal ideation; administer the CGI and the TSR; give a single dose of disulfiram 250 mg; dispense a 6-day supply of DIS 250 mg tablets to be taken once daily until the next clinic visit; and instruct about the DIS-alcohol reaction.

Instruction About the DIS-Alcohol Reaction:
DIS 250 mg daily and DIS 500 mg every other day both result in blood levels of DIS that irreversibly inhibit aldehyde dehydrogenase, leading to an accumulation of acetaldehyde, a metabolite of alcohol, if even small amounts of alcohol are consumed. This leads to a highly aversive visceral reaction, including nausea, flushing, palpitations, headache, dizziness, confusion (the DIS-alcohol reaction). This reaction can occur up to 2 weeks after stopping DIS, because of the high lipid solubility of active metabolite and because of the time required for aldehyde dehydrogenase to be re-synthesized.

Both for safety reasons, and because DIS works through a psychological mechanism of perceived risk, it is necessary for patients to be fully instructed about the risk of alcohol use while taking DIS. This instruction will be given by a physician at several time-points during the study: 1) during the consent procedure; 2) after receiving the first dose of DIS 500 mg, prior to discharge from the inpatient unit; 3) at the second

clinic visit during the 10-day DIS treatment phase, after being observed taking DIS 500 mg; 4) at each weekly clinic visit during the 30-day DIS treatment phase. Either a physician or a nurse will provide instruction about the DIS-alcohol reaction at each clinic visit. The instructions will include 1) a list of the symptoms that can occur if alcohol is consumed during DIS treatment; 2) instruction that the DIS-alcohol reaction can occur for up to 2 weeks after the last dose of DIS, such that non-adherence between supervised doses at the clinic visits will not diminish the risk of the DIS-alcohol reaction. Additionally, patients will be given a card with these instructions, to carry with them at all times, which will also contain the phone number for the on-call physician at STARS.

Option to Extend DIS Treatment After 30 Days:
On the 4th weekly clinic visit of the 30-day DIS treatment phase, patients will be offered the option of continuing to receive DIS treatment in the STARS clinic at no charge for another 30 days. Patients who opt for an additional 30 days of treatment will return the following week for the first of 4 additional weekly visits, utilizing the same procedures as during the initial 30-day treatment period. The decision to opt for continuation of treatment will be a secondary outcome of the study.

Study Termination:
At the end of the 30-day DIS treatment, or at the end of the 30-day extension phase for patients who opt for extending treatment, patients will be offered referrals to a number of outpatient treatment programs where they can receive ongoing treatment for relapse prevention, as well as a list of local Alcoholics Anonymous groups. **At this time, blood will be drawn (10cc, or 2 tablespoons) to assess liver functions and CBC at the end of study.**

MRI Scanning:
Participants will undergo two fMRI scanning sessions at the Center for MRI Research at NYSPI: The first will occur on the last day of the inpatient lead-in phase, just before the first dose of DIS (the pre-DIS MRI scan). The second will occur after the last clinic visit of the 10-day DIS treatment period (the post-DIS MRI scan), which will be approximately 10 days after the first scanning session. The procedures for both fMRI scanning sessions will be largely identical.

Functional MRI scanning sessions at the 3-Tesla Research MRI at NYSPI will be scheduled through the MRI facility website (http://rfmh.nyspi.org/MRI/). The process involves viewing the calendar to see available time-slots and reserving open slots as needed. The scanner is open Monday-Sunday from 8am until 8pm. There is a request form on which time-slots are requested. After submitting this form, appointments are confirmed as soon as possible by the Institute. Time-slots generally do not entirely fill up for an entire day, so it is not required to hold a standing reservation for future scanning appointments.

Participants will be instructed to abstain from eating food for 4 hours prior to the scans (they will be allowed to drink non-alcoholic beverages), and to abstain from all drugs of abuse for at least 1 week prior to the scan.

For the pre-DIS scan, participants will be escorted from the inpatient unit to the MRI scanner in the same building at NYSPI by the RA. For the post-DIS scan, patients will be taken via taxi from STARS to the MRI scanner at NYSPI, after completing the clinic procedures for that day.

Upon arrival at MRI facility, participants will meet with a research assistant, who will administer all of the procedures during the fMRI scan. A physician will not be present for the MRI scans, consistent with usual MRI center policies for scans that do not involve contrast agents or medications being administered during the scans. Participants will be screened for metallic devices and implants using a metal detector (a self-report screening will have occurred prior to enrollment). The urine sample obtained at the STARS clinic will have been tested for pregnancy. Participants will be administered the Alcohol Craving Questionnaire (ACQ) to assess the current level of alcohol craving, the Food Craving Questionnaire (FCQ) to assess the current level of food craving/hunger. The scanning procedure will be reviewed and the participant will be free to ask questions prior to the scan.

During each of the scans, participants will be undergo the Cue Exposure task (20 minutes). This is a previously validated passive cue-exposure task that involves showing the participants pictures of alcohol and food cues in randomized order, and then asking them to rate their desire to consume the depicted item on a 1-5 Likert scale after each cue. The Cue-Exposure task is expected to increase cravings for alcohol and food, and the analysis of brain activity will focus on how DIS treatment changes cue-induced craving and cue-induced neural activity in response to alcohol and food cues, respectively. Additionally, participants will undergo a resting fMRI scan (10 minutes) and an anatomical MRI scan (5 minutes).

Following each scan, patients will complete the DIS-Risk questionnaire to assess for the level of belief that alcohol use will lead to the DIS-alcohol reaction.

The MRI scanning procedure will take approximately 1.5 hour, including 1 hour within the scanner. Participants will be paid $50 for the first fMRI scanning session and $100 for the second fMRI scanning session, whether or not they complete the scanning procedures.

You can upload charts or diagrams if any
Ativan taper schedules.pdf
Instructions to patients taking disulfiram.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation
Early Discontinuation During the Inpatient Lead-In Phase:
Patients who demonstrate worsening psychiatric symptoms, such as the emergence of severe depression, anxiety or significant suicide risk, will be removed from further participation and provided the appropriate level of care in the inpatient unit, followed by referral to appropriate treatment. Patients who develop signs and symptoms of severe alcohol withdrawal (e.g. delirium, requiring > 16 mg Ativan over 24 hours, CIWA-Ar>15 at any assessment) will be transferred to a medical unit for detoxification in coordination with the Milstein Hospital Medicine service, as per usual 5S unit protocol, and then removed from study participation The usual aftercare following discharge for medical detoxification at Milstein Hospital includes referrals to appropriate treatment. Patients who sign out of the hospital against medical advice during the inpatient lead-in phase will be removed from further participation and provided referrals for appropriate treatment.

Early Discontinuation During 10-Day or 30-day DIS Treatment:
Certain patients may be required to discontinue DIS and will thus be removed from study participation, but will be allowed to continue receiving treatment in the STARS clinic if they so choose. These include patients who repeatedly drink heavily while taking DIS; any female participant with a positive pregnancy test; and patients who develop intolerable side effects from DIS (e.g. severe sedation). For these patients, DIS will be discontinued and they will be offered to continue treatment at STARS for the remainder of the study period. This treatment will include weekly meetings with a psychiatrist who will administer appropriate behavioral (e.g. CBT and Motivational Interviewing) and/or pharmacological treatments (e.g. naltrexone, acamprosate, topiramate) for Alcohol Use Disorder.

Patients who demonstrate clinical worsening that requires a higher level of care than can be provided at the STARS clinic will be removed from study participation and provided appropriate referrals. Clinical worsening will be determined by the judgment of the STARS psychiatrist in consultation with the PI, and will include the emergence of serious withdrawal symptoms (e.g. seizures or delirium tremens), serious medical consequences (i.e. physical symptoms requiring emergency room visits, liver failure), dangerous behaviors (e.g. physical aggression), significantly worsening depression or anxiety (increase in HAM-A or HAM-D by more than 15 points from baseline), active suicidal or homicidal ideation or behavior, or clinical deterioration indicated by a CGI-I of 6 or above on 2 consecutive sessions. The psychiatrist will make a determination of the need for a higher level of care, or to an emergency room, and will provide referrals as appropriate.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

	Time to Complete (minutes)	Screening	Inpatient admission	Pre-DIS MRI scan	10-day DIS treatment (every visit)	10-day DIS treatment (final visit)	Post-DIS MRI scan	Weekly during 30-day DIS treatment (including optional extension)	End of 30-day DIS treatment	Weekly during optional 30-day DIS treatment extension
Breath alcohol testing	1	RA	RA		RA		RA	RA		RA
Urine drug/EtG screen	1	RA		RA		RA		RA		RA
Urine pregnancy	1	RA		RA			RA			

screen										
Vital signs	1	RA	RN	RA	RA	RA	RA	RA		
Blood test	1	RA				RA			RA	
EKG	10	RA								

RA=Research Assistant RN=Nurse

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

At screening, the RA will administer a 30-day Timeline Followback (TLFB) to quantify alcohol use and will include the Montreal Cognitive Assessment (MOCA) to assess cognitive functioning. The psychotherapist will administer the Mini International Neuropsychiatric Instrument (MINI) to diagnose Alcohol Use Disorder and other psychiatric disorders. The psychiatrist will administer a psychiatric evaluation; the Hamilton Depression Inventory (HAM-D); the Hamilton Anxiety Inventory (HAM-A); the Clinical Institute for Withdrawal Assessment - Revised (CIWA-Ar); the Clinical Global Impression Scale (CGI); and the Treatment Services Review (TSR).

During the inpatient admission the patients will complete the following self-report questionnaires: The Barratt Impulsiveness Scale (BIS) will assess the level of trait impulsivity. The Alcohol Dependence Scale (ADS) will assess the severity of Alcohol Use Disorder. The Obsessive Compulsive Drinking Scale (OCDS) will assess the level of alcohol incentive salience. The Readiness to Change Questionnaire (RCQ) will assess the motivation to reduce drinking. The Alcohol Abstinence Self-Efficacy Scale (AASE) will assess the level of self-regulation of alcohol-seeking motivation. The Drinker Inventory of Consequences (DrInC) will assess prior experiences with negative consequences from alcohol. The Domain Specific Risk Taking Scale (DOSPERT) will assess the level of risk aversion/preference in a variety of domains. The DIS-Risk scale will ask two questions rating the perceived likelihood and unpleasantness of the DIS-alcohol reaction.

The OCDS, RCQ, AASE will be repeated on the last day of the 10-day DIS treatment, at the STARS clinic, prior to the post-DIS MRI scanning session. The ACQ, FCQ and the DIS-Risk will be administered right before the MRI scans.

Citations for these instruments, as well as the schedule for administration, may be found in the section "Assessments".

The DIS-Risk is the only non-standard instrument. It comprises the following two items: (1) “How certain are you that drinking alcohol today would result in an unpleasant physical reaction?” (1 = “I am completely certain that I will not have any reaction”; 10 = “I and completely certain that I will have a reaction”) and (2) “Assuming that this reaction will happen, how unpleasant/painful do you think it will feel?” (1= “It won’t be unpleasant at all;” 10 = “It will be the most painful feeling I have ever had”).

Please attach copies, unless standard instruments are used
Assessments.pdf

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
Patients will be provided appropriate referrals for AUD treatment at the end of study.

Clinical Treatment Alternatives

Clinical treatment alternatives
The study provides a standard, evidence-based treatment for alcohol dependence. Disulfiram is a an FDA-approved medication for Alcohol Use Disorder that has been available for over 75 years, and will be provided at no cost during the study by psychiatrists who are trained in addiction treatment. In addition to the treatment provided by the study, participants will be allowed to participate in a 12-step program such as Alcoholics Anonymous.

Participants will be informed of alternatives to participation in the proposed trial. The alternative procedures available are individual counseling by other clinicians, or more intensive treatment for heavy drinking such as inpatient or outpatient detoxification, inpatient rehabilitation, or intensive outpatient programs. Additionally, there are a number of alternative medications that may aid in relapse prevention, including naltrexone (Revia) and acamprosate (Campral). More intensive treatment will be indicated if the study treatment is not helpful in the reduction of drinking, if drinking increases substantially during the study period, or if serious psychiatric symptoms (severe depression and anxiety, suicidal ideation) emerge during the course of the study.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Screening and Consent:
During the screening and consent process, there is a risk that patients may arrive either severely intoxicated to the extent that they pose a danger to themselves or others (e.g. falls, aggression, suicidal ideation), or in alcohol withdrawal that poses a threat to their physical safety (e.g. dehydration, seizures, delirium tremens). Patients will also undergo screening EKG's, Breathalyzers, blood tests and urine tests. The blood tests will require venipuncture, which will be associated with mild discomfort and a small risk of bleeding and

infection.

Inpatient Lead-In Phase:
Patients will be hospitalized briefly on an inpatient unit. This will be inconvenient for some patients, especially those who are working and/or who have childcare responsibilities. The physical risks of the inpatient lead-in phase are primarily related to the risk of alcohol withdrawal syndrome that may emerge upon sudden cessation of alcohol use. All of the baseline assessments, including self-reports and structured interviews, are all non-invasive and add no special risk, although they do cover sensitive areas. The major disadvantages are the time taken to complete them, and possible breach of confidentiality. Our past experience indicates that these measures and tests are acceptable to participants.

Disulfiram Treatment:
Disulfiram is an FDA-approved medication for AUD that has been used in clinical practice for over 75 years. The most common risks are related to the DIS-alcohol reaction, which occurs when patients use alcohol while taking DIS, even in small amounts. The DIS-alcohol reaction includes flushing, throbbing in head and neck, headache, shortness of breath, nausea, vomiting, sweating, thirst, chest pain, palpitation, dyspnea, hyperventilation, tachycardia, hypotension, syncope, marked uneasiness, weakness, vertigo, blurred vision, and confusion. In severe reactions there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death. The intensity of the reaction varies with each individual, but is generally proportional to the amounts of disulfiram and alcohol ingested. The duration of the reaction varies from 30 to 60 minutes, to several hours in the more severe cases, or as long as there is alcohol in the blood.

Additional adverse effects of disulfiram are unrelated to the consumption of alcohol, i.e. they are direct effects of disulfiram. Serious adverse reactions that have been reported include optic neuritis, peripheral neuropathy, psychosis and hepatic failure. Hepatic failure is the most serious and life threatening of adverse effects, and has an incidence of between 1/10,000 and 1/30,000 patient-years of disulfiram treatment, and appears to be mediated by an idiosyncratic immune-mediated mechanism that is distinct from alcohol-induced liver injury (11). Less serious, but more common, adverse reactions include benign rash, transient fatigue, impotence, headache, tremor, mild liver function abnormalities and a metallic taste. These more common adverse effects are usually transient and improve spontaneously after 1-2 weeks, and also with dose reduction. Psychotic reactions have been noted, attributable in most cases to high dosage, combined toxicity (with metronidazole or isoniazid), or to the unmasking of underlying psychoses in patients with underlying risk factors (e.g. a prior history of schizophrenia or bipolar disorder). Additionally, rare hematologic reactions have been reported (e.g. agranulocytosis, thrombocytopenia).

In addition to specific risks related to taking disulfiram, there are general risks associated with treating AUD. For example, patients may demonstrate an escalating pattern of alcohol use that can lead to serious adverse medical, legal and interpersonal problems. These risks are presumably lower than for patients who are not seeking treatment, so they do not represent an increased risk due to study participation. Some patients may demonstrate worsening psychiatric symptoms, such as depression, anxiety and suicidal ideation, either as a result of ongoing or worsening alcohol use, or as a result cessation of alcohol use (i.e. withdrawal-related).

fMRI scanning:

fMRI scans pose "Minimal Risk" to participants assuming that all precautions are taken, e.g. subjects must be free of implanted metallic devices or any metal fragments/objects in the body. Participants will be screened a total of 3 times for metallic devices, implants or other contraindications to scanning (once during screen assessment, once prior to first scan, and once prior to the second scan). All female subjects will be asked to take a urine based pregnancy test that will be administered prior to the scans by a female nurse on site at the fMRI Research Center.

While there are no known risks or harmful long-term effects of being placed in a magnet of the strength used in the study (3 Tesla), it is possible that some subjects might experience minor discomfort by the confined and noisy conditions typical of an MRI scanner. All equipment is FDA approved for use in an MRI environment. Brain imaging in this study will be performed on GE 3Tesla MRI scanner dedicated to fMRI research and located in the MRI Facility at the NYSPI. All equipment is FDA approved for clinical MR scanning, commercially available. The fMRI procedure is noninvasive and involves no known incremental risk. MRI devices with a magnetic strength less than 8 Tesla and within FDA specified parameters fall in the category of non-significant risk devices for all persons over the age of one month (http://www.fda.gov/cdrh/d861.html).

The MRI system, using both hardware and software constraints, automatically limits the power and rates of change of magnetic fields according to FDA regulations (http://www.fda.gov/cdrh/ode/guidance/793.html). The specific absorption rate (SAR) will not be greater than: (1) 4 W/kg averaged over the whole body of any period of 15 minutes, (2) 3 W/kg averaged over the head for any period of 10 minutes, (3) 8 W/kg in any gram of tissues in the head or torso, (4) 12 W/kg in any gram of tissue in the extremities for any period of 5 minutes. MRI and fMRI studies that do not involve sedation may be considered minimal risk assuming the proper exclusionary precautions have been taken (e.g., metal implants).
Describe procedures for minimizing risks
Screening
The screening procedures involve evaluation by a psychiatrist, including psychiatric evaluation (including a detailed history of prior alcohol withdrawal symptoms), medical examination and physical examination. This is being done specifically to identify alcohol withdrawal, intoxication or psychiatric symptoms that pose a significant risk (e.g. suicidal or homicidal ideation). The psychiatrist will make a determination of whether the participant requires immediate referral to an emergency department. The blood samples will be collected by RA's and RN's who are trained in venipuncture.

Inpatient Lead-In Phase
The inconvenience of the inpatient admission will be minimized by having as much of the admission as possible occur over the weekend, based on patient preference. The risks of alcohol withdrawal will be minimized by careful screening by a psychiatrist to exclude participants who have a history of significant withdrawal symptoms. This will include checking the breathalyzer result and the CIWA-Ar at the screening and excluding patients with a BAL = 0 who also have a CIWA-Ar > 8. Patients with any history of severe alcohol withdrawal (e.g. seizures or delirium tremens) will be excluded regardless of the CIWA-Ar or BAL at screening.

Together, these screening procedures will minimize the number of patients requiring detoxification during the inpatient hospitalizations. However, despite these procedures, a small number of patients may require detoxification. These patients will be quickly identified using CIWA-Ar given every 4 hours on the first 24

hours of admission. A standard symptom-triggered detoxification protocol will be initiated at the first signs of alcohol withdrawal (CIWA-Ar >8). Avoiding Friday admissions will allow the physician on the inpatient unit to determine the effectiveness and safety of the detoxification medications administered in the first 24 hours and make appropriate adjustments and schedule a taper for the duration of the hospital admission. This physician will also be able to address whether the patient is at risk of severe withdrawal requiring a medical admission. These are all procedures that are commonly utilized on dual-diagnosis and detoxification units in clinical settings, such that study participation will not pose any added risk of withdrawal that is greater than if the patients were to undergo standard inpatient treatment for alcohol use disorder.

The self-report baseline assessments will be administered in a private area, to minimize the chance that confidentiality will be violated. Also, standard practices to preserve patient confidentiality that are employed on 5-S will be in place for this study.

Minimizing the Risks of Disulfiram Treatment

We will exclude patients with significant co-morbid medical illnesses, such as heart disease, diabetes, hypothyroidism and pre-existing liver disease. The inpatient lead-in phase ensures that patients have initiated abstinence prior to starting DIS, and will also increase the likelihood of maintaining abstinence, compared to an outpatient DIS induction procedure. Patients will be fully informed repeatedly that even a small quantity of alcohol use during disulfiram treatment will result in the DIS-alcohol reaction, and that this reaction can occur for up to 2 weeks after taking disulfiram. Patients will also be told to avoid alcohol-containing medications and cosmetics, as even these forms of alcohol can cause the reaction. All patients will be assessed for alcohol use at every visit, along with whether they experienced the disulfiram-alcohol reaction. Patients who resume persistent heavy drinking despite developing significant symptoms of the DIS-alcohol reaction will be removed from the study and provided other treatment.

Study physicians will meet with patients on day-6 of the 10-day disulfiram treatment and every week during the subsequent 30-day disulfiram treatment. At each visit, the physician will assess for alcohol use, psychiatric symptoms, and adverse effects of disulfiram, especially symptoms of hepatitis, such as fatigue, anorexia, nausea and vomiting, abdominal pain, rash, jaundice. Any such symptoms will lead a check of liver function tests. For all patients, liver functions and CBC will be assessed prior to beginning disulfiram treatment, after 10 days of disulfiram, at the end of the 30-day treatment period and, for those who continue disulfiram for a second 30-day period, after 60 days. Any liver function abnormalities (AST or ALT) that are 3 times above the normal limit will result in immediate cessation of disulfiram and removal from the study, with referral to a gastroenterologist for management. The physician will complete the CGI-I at each session. On day-6 of the 10-day disulfiram treatment, the physician will administer the HAM-D and HAM-A to determine the severity of any worsening depression or anxiety.

Minimizing the Risks of fMRI

Participants will complete standard clinical questionnaire to rule out the presence of metal implants in the body. Female participants will undergo urine-based pregnancy tests. Mirrors are provided so that participants can see out of the scanner to reduce claustrophobic feelings. In addition, they will be given earplugs to reduce noise. The scan is monitored by a trained technician the entire time and is in constant communication with the participant. In the event that a subject no longer wishes to continue the MRI scan, the scanning session will be terminated. A member of the research team will explain the MRI procedure in

detail before the scan and will be present throughout the scan. Technicians, nurses, and physicians are present at the fMRI Research Center who are extremely well versed in helping patients cope with the discomforts of the fMRI process. If, however, a participant needs more intensive help in coping, a licensed mental health clinician (one the Research Psychiatrists) will be available by phone.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
To avoid breach of confidentiality, participants' names will appear only on a consent form, a telephone screening form and a "key" form kept by the PI in a locked cabinet. All forms that contain identifying information will be kept double locked (i.e., in a locked cabinet, in a locked room) to maintain their security. All study data forms will contain only the participant's unique study identification number, using a reference system maintained by the PI. Completed study forms will be kept in a locked cabinet, the key to which will be available only to the PI and study research staff. Participant visits will be scheduled, and no information about the participant will be provided to anyone (except in emergencies as defined above) in person or by telephone. The study will be conducted on an inpatient psychiatric unit and an outpatient clinical trials clinic. In both settings, treatment is provided to participants who have a variety of psychiatric problems, not limited to substance abuse.

All electronic files (e.g., database, spreadsheet, etc.) containing identifiable participant information are password protected. All computers hosting such files have a BIOS password to prevent access by unauthorized users. Furthermore, for systems not running Windows 2000/XP, a password-protected screen saver will be installed and configured to activate ten minutes after the computer has been idle. When participant data are exchanged with others, the data will be coded. If identification is necessary, then the data will be encrypted while en-route to the recipient with strong encryption levels (128 bits for symmetric encryption (DES) and 1024 bits for asymmetric encryption (RSA).

Confidentiality will also be maintained for electronic data sources, such as the computer-based questionnaire response files, digital video and audio recordings, entered data from in-person portions of assessment interviews).

At the MRI Facility, all electronic data from the scans and the tasks are de-identified and stored on servers protected by the NYSPI firewall or PsyIT-approved security systems. Data is protected by user group. Access to files is based on user privilege and password-protected. As per lab policy, all consent forms and signed questionnaires obtained for experimental purposes are stored in locked file cabinets.

Our procedures also adhere to HIPAA guidelines. As described above, all data is secured in locked file cabinets or electronically on protected servers located within the MRI Facility located at NYSPI. A minimum of 5 years after publication of the study findings, identifying data will be disposed of by shredding and deletion of identifying electronic files.
Will the study be conducted under a certificate of confidentiality?
Yes, we will apply for the Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
Participants who complete the study will receive treatment with disulfiram, which is an effective, FDA-approved medication for AUD. They will be evaluated for psychiatric and medical co-morbidities and, for those who are excluded for these reasons, provided referrals to high quality psychiatric and medical treatment. The disulfiram treatment will be provided by licensed psychiatrists, most of whom are board-certified in addiction psychiatry and who possess extensive experience treating AUD with disulfiram. Furthermore, participants will be allowed to attend 12-step programs, such as Alcoholics Anonymous, during treatment.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Participants will be paid $50 for completing the pre-DIS fMRI Scanning Session and $100 for completing the Post-DIS fMRI scan. Participants will be paid $10 at each clinic visit, in order to reimburse for travel expenses.

Total compensation for participants who complete the entire study will be $210-$250, depending upon whether they continue disulfiram treatment beyond 30 days.

Reimbursement will be made in cash at the end of each scheduled session that the participant arrives for.

Payment is meant to compensate the participants for time and effort required to complete the study. A higher level of compensation is provided for the post-DIS fMRI scan in order to provide an incentive for participants to complete this scan.

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