1) Protocol Title (01/30/2018)

Modafinil for the treatment of alcohol use disorder: targeting impaired response inhibition (Version 01/30/2018)

2) Principal Investigator

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3) Funding Agency

National Institutes of Health (NIH) [specifically, National Institute of General Medical Sciences (NIGMS), a subdivision of NIH]

4) IRB Review History

Previously approved by University of New Mexico, Human Resources and Review Committee, transferred due to change of employer of the Principal Investigator. At the time of transfer, 5 participants have been consented, 4 discontinued (deemed ineligible based on stop signal reaction time), 1 enrolled but not yet initiated on treatment or randomized.

5) Objectives

Hypotheses and Specific Aims:

Alcohol use disorders (AUD) are pervasive and have significant individual and societal costs[1]. While three FDA approved medications are available for the treatment of AUD, effect sizes tend to be modest, and results frequently inconsistent[2-6]. Important to recognize, AUD medication effects may be masked by heterogeneity in patient samples and by specific sub-types within the AUD spectrum[2,4-17]. An NIH-wide initiative, Precision Medicine[18], has recently embraced the importance of patient-treatment matching to produce optimal patient outcomes, a central theme of the Mechanisms of Behavior Change conference in 2016 at the Research Society on Alcoholism. Responding to this initiative, this application seeks to prospectively investigate the promising moderating effects of response inhibition on a new medication for the treatment of AUD.

Modafinil is FDA-approved to treat narcolepsy, is safe, and works by increasing synaptic dopamine and norepinephrine[19,20]. In the only study in which modafinil was tested for the treatment of AUD, no main effect was found supporting that modafinil reduced alcohol consumption[21]. Likewise, in the treatment of other SUD, studies of this medication have shown mixed effects on substance use[22-32]. However, preliminary evidence suggests that modafinil matches to the particular characteristic of impaired response inhibition (i.e., a reduced ability to withhold a pre-potent response)[21] which is a characteristic of approximately 60% of individuals with AUD[21](C.1). Specifically, in a post hoc analyses of the single study of modafinil in AUD[21], individuals with impaired response inhibition [as defined by a stop signal reaction time (SSRT) of > 233] had a reduction in drinking with a fairly large effect size [effect size time to relapse (TTR) d=.84, percent days abstinent (PDA) d=.50] which are much larger than effect sizes of naltrexone (FDA-approved for the treatment of AUD) on heavy drinking observed from a meta-analysis (0.19)[5]. **The primary goal of this study is to offer the first prospective test of the effect of modafinil on drinking in individuals with AUD with impaired response inhibition compared to individuals with normal response inhibition.**

Establishing biological mechanisms of treatment (target engagement) in clinical trials is also an NIMH-wide initiative[33] endorsed by NIAAA; response inhibition is a likely target for SUD[34]. To be a mechanism, a target must both be 1) mobilized by the treatment, and 2) changes in the target must predict changes in the outcome of interest[33]. Regarding the former (1), there is evidence that modafinil improves response inhibition[35-38] and related metrics such as working memory and attention[37-44] in a variety of populations. However, curiously, while response inhibition was a

matching variable (predicted response to treatment) in the aforementioned modafinil trial in AUD[21], response inhibition was not altered by active treatment, even in the impaired response inhibition subgroup, although self-reported impulse control improved. Further work using a wider array of potentially more sensitive measures (response inhibition in the presence of emotional/alcohol cues), and other related metrics of cognitive function (working memory), obtained at a higher frequency are needed to test for target engagement in AUD undergoing treatment with modafinil. Regarding the latter (2), although individuals with impaired response inhibition do worse in treatment[45-47], improvements in response inhibition correlate with drinking reductions[48,49] and treatments targeting response inhibition predict drinking reductions in heavy drinkers[50] no study has demonstrated that improvement in response inhibition predicts reductions in drinking in AUD. **Our second set of goals will be to explore the mechanisms of effect of modafinil on alcohol use outcomes in AUD.**

There is reason to believe that blood-oxygen-level dependent (BOLD) signal during response inhibition [obtained by performing a task while undergoing a brain functional MRI (fMRI) scan] may be a more sensitive predictor of substance use[51,52] and other clinically-relevant outcomes[53] than task performance. Hypoactivation in dorsomedial prefrontal cortex (dmPFC) and lateral prefrontal cortex (lPFC) are markers of impaired response inhibition in a variety of populations[46,54-56]. Moreover, modafinil increases dmPFC activation during response inhibition tasks after a single dose in AUD[38].

25 treatment seeking adults with AUD will be recruited from local treatment centers and randomized to treatment with either placebo or 300 mg of modafinil daily for 6 weeks in a **double-blind placebo-controlled trial.** Measures of response inhibition[21], other cognitive domains, impulsivity, and drinking will be collected at baseline, 2 and 4 weeks. fMRI scans will be obtained at baseline and 2 weeks after initiation of either medication or placebo (2 scans per participant) while performing an emotional Go/No-Go (GNG) task[57].

Aim 1: To investigate the effects of modafinil on alcohol use outcomes in treatment-seeking AUD. Modafinil will improve alcohol use outcomes relative to placebo in individuals with impaired response inhibition (SSRT>233) with a larger effect size than individuals with normal response inhibition (SSRT<233). If effect size calculations show a moderate to large effect in the expected direction, this will provide pilot data for an NIH application.

Aim 2: To investigate the mechanisms of effect of modafinil on relevant self-report, neuropsychological testing, and fMRI measures and to establish the most robust measure of its mechanism in AUD with poor response inhibition. Modafinil will improve response inhibition relative to placebo and improvements in these metrics will predict reductions in alcohol use and will mediate the beneficial effect of modafinil on alcohol use outcomes, in individuals with impaired response inhibition. Modafinil treatment relative to placebo treatment will improve response inhibition (performance) and increase dmPFC and lPFC activation during response inhibition (No-Go vs Go trials) to both neutral and aversive stimuli.

6) Background

The promise of Precision Medicine in AUD: Alcohol dependence accounts for 4% of the global disease burden[1], and, although effective pharmacotherapies for AUD exist, effect sizes are often small[5] and findings do not replicate from study to study[3-6]. AUD is heterogeneous, and medications for the treatment of AUD may be more effective if particular subgroups are targeted[2,4-17]. Indeed, Precision Medicine[18] is an initiative that is being pushed not only in AUD, but across NIH divisions, with the recognition that **heterogeneity may be masking treatment effects across a variety diagnoses.**

Modafinil as a medication for which client heterogeneity may be masking effects during AUD treatment: Modafinil has been most studied in SUD populations as a treatment for stimulant use disorder (StimUD). In these studies, effects of modafinil on substance use outcomes were mixed[22-32], with only 3 studies showing effects of treatment on substance use in the whole

sample. However, subgroup analyses showed that poor adherence[28,29,32], too high of a dose[27,29-31], and comorbid other SUD[28] may have contributed to negative findings. Especially important, however, is that **none of the trials in StimUD reported on whether response inhibition was a predictor of response to modafinil**. There has only been a single treatment trial of modafinil in AUD thus far[21]. In this study, individuals undergoing residential treatment also received 300mg modafinil treatment for 10 weeks. Individuals were still in residential treatment during most of the trial. Although there was no significant effect of modafinil in when the whole sample was analyzed, SSRT predicted treatment response, such that individuals with poor response inhibition (SSRT>233) had greater increases in PDA on modafinil relative to placebo (p=.07, d=.50) and prolonged TTR (p=.02, d=.84). **Targeting AUD with poor response inhibition may significantly enhance effects of modafinil on alcohol use outcomes.**

The importance of establishing target engagement early on in treatment studies: Identifying the mechanisms by which a treatment works, which involves establishing that the treatment improves a measure of the mechanism, and that changes in the mechanism predict changes in the disorder, is another incentive within NIH[33,34]. **Establishing target engagement during early phases of pharmacotherapeutic treatment studies in AUD will inform future research and clinical practice.** Successful target engagement (i.e., modulation of response inhibition by modafinil) even in conjunction with a failed trial (i.e., no change in drinking) would suggest that the proposed mechanism is not related to outcome. Moreover, the absence of target engagement with a concurrent positive clinical effect would indicate that the treatment is not working via the hypothesized mechanism. Response inhibition falls within the Cognitive Systems domain of the Research Domain Criteria (an NIMH-initiative to organize functional dimensions of behavior and treatment targets)[58].

Response inhibition, cognitive control, and impulsivity: In SUD, response inhibition is impaired. Furthermore, it is considered to be a biological mechanism, and is therefore a likely treatment target[34,46]. Defined as the ability to withhold a pre-potent behavior, it is commonly measured with Stop Signal (SST) or a Go No-Go (GNG) task[46] . Response inhibition falls into the broader category of cognitive control, which includes working memory, and has been found to be related to response inhibition in terms of task performance and the neural circuitry involved [34,41,46]. Furthermore, response inhibition is often correlated with self-reported impulsivity and delay discounting, the latter a measure of the ability to delay reward[46,59-61]. In summary, response inhibition, cognitive control, and impulsivity are related constructs, but the relative importance of their roles in AUD is still not entirely clear.

Response inhibition as a likely target of modafinil treatment: Modafinil is FDA-approved to treat narcolepsy and works, in part, by increasing synaptic dopamine and norepinephrine[19,20,62-64], neurotransmitter systems which regulate response inhibition[65-67]. Modafinil improves response inhibition in rodent models with low levels of response inhibition[68] and in single-dose studies in non-substance disordered humans[35,36]. The beneficial effects of modafinil on response inhibition[37,38], impulsive decision making[41], and other cognitive control tasks[40,42-44,69] carry over into AUD and other SUD both in single dose studies[37-41] and in studies where the medication is given over days to weeks[42-44]. This is especially true for individuals with more room for improvement (greater SUD severity, higher impulsivity, or poorer baseline task performance)[37,40,42,43,69]. In single-dose studies modafinil normalizes the neural circuitry recruited during tasks of response inhibition[38] and related cognitive functions[39,41] in AUD and StimUD[70], changes which were also associated with improvements in performance. **Modafinil may improve response inhibition and related metrics in AUD** especially in individuals with poor response inhibition. Notably, although baseline SSRT was a matching variable in the single clinical trial of modafinil in AUD[21], SSRT did not decrease even when the subgroup with poor response inhibition was targeted. However, **working memory, when targeting those with the lowest levels worst working memory at baseline, did improve in this same population on modafinil[42]** and in other populations[43,44]. The absence of an effect of medication on SSRT may have been due either to the fact that the SSRT was obtained too infrequently (every 5 weeks), that abstinence-related effects on response inhibition in the whole sample masked medication

effects and/or that the task was not sensitive enough to measure the underlying construct of interest. To address these, we will test cognitive function more frequently, and we will include a larger array of measures, which will include tests of working memory and tests of response inhibition during exposure to alcohol or aversive stimuli. Response inhibition performance can be profoundly affected by environmental cues such as drug/ alcohol cues or during emotional arousal[56,71-86]. **By obtaining more sensitive measures of response inhibition at more frequent intervals, we will improve our chances of finding effects,** if present.

Brain activation during response inhibition as an important target for AUD treatment: Response inhibition is defined as the ability to withhold a pre-potent behavior and is most commonly measured with stop signal, go no-go or continuous performance tasks[46]. There is reason to believe that blood-oxygen-level dependent (BOLD) signal during response inhibition may be a more sensitive predictor of substance use[51,52] and other clinically-relevant outcomes[53] than task performance. These tasks activate lateral PFC (lPFC) [dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC)/inferior frontal gyrus (IFG) (BA 44/45)], inferior parietal lobe (IPL), dorsomedial prefrontal cortex (dmPFC), [dorsal anterior cingulate cortex (dACC), pre-supplementary motor area (pre-SMA) and supplementary motor area (SMA)], dorsal striatum, and thalamus[46,54,55,57]. Decreased activation in lPFC and dmPFC during response inhibition is observed in clinical groups with higher impulsivity, higher rates of past and future substance use and poor response inhibition[46,51,54,55,87,88]. In addition, individuals with AUD compared to controls, or with greater AUD severity, demonstrate lower activation in dmPFC and lPFC[46,88-90] and in subcortical regions (putamen[38] and thalamus[88]). Therefore, for our purposes, **an increase in dmPFC and lPFC activation during response inhibition will indicate normalization of brain function in this subgroup with known behavioral deficits.**

Change in response inhibition as a likely mechanism by which treatments for AUD work: Impaired response inhibition theoretically contributes to greater AUD severity by increasing sensitivity to drug cue-induced craving[91,92] or by globally impairing the ability to withhold a pre-potent response, like reaching for a drink, in the context of cue-exposure[93]. Indeed, impaired response inhibition is predictive of later development of SUD[94,95] as well as poorer response to treatment in AUD[45-47]. Relatedly, brain activation during response inhibition[96-98]predicts worse treatment outcome. Importantly, treatments or trainings which increase response inhibition are also associated with improvements in drinking in AUD[48,49]and heavy drinkers[50,99], but whether these associations are driven by reductions in response inhibition (establishing it as a mechanism) or whether the drinking reductions are driving the improvements in performance in AUD[48,49] is not clear. Therefore, although studies indicate it is a good mechanistic candidate, **no study has definitively established response inhibition as a mechanism.**

Preliminary Data: Our previous work demonstrates we can successfully carry out the proposed project. First, in terms of retention, the PI has recently completed a 6-week randomized placebo-controlled clinical trial of prazosin for the treatment of AUD in which individuals received a battery of self-report, neuropsychological tests, and an fMRI scan before and after 3 weeks of treatment (K23 AA021156; PI Dr. Wilcox). 78% of the 36 individuals initiated on medication were available for collection of follow-up data at 6 weeks. Second, data was collected from 10 participants with AUD who underwent a SST identical to the task which identified response inhibition as a moderator[21] and the task we will use as our matching variable in the proposed study. Approximately 60% of participants had a SSRT>233, which is similar to what was seen in the clinical trial in AUD[21]. Third, we are well-prepared to do the study and the analyses, having conducted two definitive reviews on the roles of cognitive control and emotion regulation in SUD[46,84], and treatment implications. A manuscript is in preparation for the clinical outcomes analyses on the prazosin dataset, and analyses are complete. Fourth, together the three Intensive Outpatient Treatment Programs (IOPs) we will be recruiting from enroll approximately 50 AUD per month, 30 of which would likely meet criteria for screening, of which 60% would be likely to have impaired response inhibition.

7) Inclusion and Exclusion Criteria

Inclusion Criteria. Participants will be required to meet the following criteria to be eligible for enrollment: 1) males and females age 18-65 meeting DSM-V criteria for moderate or severe AUD in the past year; 2) interested in reducing or quitting drinking; 3) able to provide voluntary informed consent; 4) have at least 4 heavy drinking days (≥ 5 drinks per day for men, and 4 for women) in the past 60 days.

Exclusion Criteria. Participants will not be eligible for enrollment (excluded) if they meet the following criteria: 1) severe neurological conditions (severe TBI[100]/stroke/active seizure disorder); 2) heart disease [mitral valve prolapse, left ventricular hypertrophy, cardiac arrhythmias, angina, myocardial infarction, unstable angina, cardiac syncope or pre-syncope, any electrocardiogram (ECG) finding that suggests the presence of one of these conditions]; 3) uncontrolled hypertension (SBP >160, DBP >100); 4) heart rate greater than 70% of the maximum expected for age [0.70(220-age)]; 5) chronic renal or hepatic failure; 6) recent pancreatitis; 7) insulin-dependent diabetes; 8) other urgent medical problems; 9) elevated liver function tests (AST or ALT greater than 4 times normal; modafinil is metabolized primarily by the liver[101]); 10) schizophrenia, schizoaffective disorder, Bipolar I disorder, suicidal thoughts in the last month; 11) current moderate or severe other SUD (except nicotine or marijuana); 12) active legal problems with the potential to result in incarceration; 13) pregnancy or lactation, or child bearing age and not on birth control; 14) current daily use of anti-craving medications, stimulants, benzodiazepines, opiates, anti-psychotics; current daily use of tricyclic antidepressants, bupropion, monoamine oxidase inhibitors, serotonin and norepinephrine reuptake inhibitors, or therapeutic doses (for bipolar disorder) of mood stabilizers; 15) taking a medication contraindicated for use with modafinil; 16) meet safety criteria to undergo an MRI scan; 17) taking the following medications: acebrophylline, asunaprevir, axitinib, bedaquiline, bosutinib, cobimetinib, dasabuvir, deflazacort, elbasvir, flibanserin, grazoprevir, iobenguane I, neratinib, nisoldipine, olaparib, ranolazine, simeprevir, sofosbuvir, sonidegib, velpatasvir, venetoclax.

Modafinil can interact with metabolism of several medications, either increasing or decreasing the levels of these medications. Some of these are listed in the exclusion criteria because they are exclusionary for other reasons (psychiatric medications that could affect the fMRI signal or impulse control such as tricyclic antidepressants, monoamine oxidase inhibitors, antipsychotics, benzodiazepines). For each participant, prior to initiating study medication, the study physician will research all possible interactions with any medications a participant is taking, and on a case-by-case basis, determine whether it is safe to proceed with initiating the study medication, whether increased vigilance is needed during monitoring for side effects, and, if necessary, whether medication doses need to be adjusted (of either study medication or of the medications they are taking for other conditions, in collaboration with the participant's prescribing physician, with participant permission).

In addition, modafinil can decrease concentrations of hormonal contraception. Therefore, participants will be required to utilize additional modes of contraception (e.g. barrier methods) while on study medication.

Criteria for undergoing the MRI scan: All participants must have a negative urine pregnancy test and no contraindications to receiving an MRI scan (MRI safety screening form) in order to undergo the MRI scans. Participants with positive urine drug screen for marijuana, cocaine, amphetamine, opiates or benzodiazepines plus reported use within the last 24 hours; for alcohol use within the last 24 hours; or who have a CIWA[102] >= 8 will be asked to reschedule their assessment visit within the next 4 days.

8) Multi-Site Research

N/A

9) Study Timelines

Individual participant's involvement will last a total of 14.5 hours over approximately 11 weeks. It is estimated to take approximately a year to complete enrollment.

10) Study Endpoints

Primary endpoints occur at week 2, 6 and 10. The study will close to enrollment after at least 25 participants have completed all study procedures.

11) Study Methods

Study Overview Table:

Week		-1	-.5	0 (baseline)	1	2	3	4	6	10
Intervention	Phone Screen	Consent, SST, SCID I, TLFB, Vitals	History & Physical, Lab Draw, ECG, Vitals	Initiate Meds, Assessment, Vitals	Med Visit, Vitals	Med Visit, Assessment, Vitals	Med Visit, Vitals	Med Visit, Assessment, Vitals	Assessment	Phone assessment
Compensation ($)	0	30	30	60		70		70	40	40
Time (hours)	.25	2.5	1.5	3.5	.5	3.0	.5	1.5	1	.5

Adverse Events will be evaluated for at week 1,2,3,4,6,10.
SST: Screening stop signal task.
TLFB: Timeline follow-back for daily alcohol and other drug use history.
SCID: Interview for exclusionary psychiatric diagnoses and other substance use disorder diagnoses.

- Initiate Meds: Symptom checklist, BAL, urine drug screen, urine pregnancy test, CIWA[102] for alcohol withdrawal.
- Med Visit: Symptom checklist, BAL, urine drug screen, adherence and pill counts, CIWA[102] for alcohol withdrawal, urine pregnancy test.
- Week 0 Assessment: TLFB between screening visit and current date, impaired control[103] and craving[104]. Emotional and Alcohol Go No-Go, digit span task[42,105], Kirby Delay Discounting task[106], the PROMIS anxiety, depression, and anger scales[107],the State Difficulties in Emotion Regulation Scale[108] an emotional n-back task[109], and the Pittsburgh Sleep Quality Index[110] and Epworth Sleepiness Scale[111]. Rivermead Post-Concussion Symptoms Questionnaire[112], Alcohol Dependence Scale[113], Fagerstrom Test for Nicotine Dependence[114], AUDIT[115], intelligence (WTAR[116]), Barratt Impulsiveness Scale (BIS)[59], UPPS[117], the Adult ADHD Self-report scale[21,29], motivation (Stages of Change Readiness and Treatment Eagerness Scale[118]), Treatment Services Review[119], Difficulties in Emotion Regulation Questionnaire[120] and Emotion Regulation Questionnaire[121], urine pregnancy test, urine drug test, MRI safety screening form, fMRI scan.
- Week 2 Assessment: TLFB between Week 0 and current date, impaired control[103] and craving[104]. Emotional and Alcohol Go No-Go, digit span task[42,105], Kirby Delay Discounting task[106], the PROMIS anxiety, depression, and anger scales[107],the State Difficulties in Emotion Regulation Scale[108], the stop signal task, an emotional n-back task[109], and the Pittsburgh Sleep Quality Index[110] and Epworth Sleepiness Scale[111], urine pregnancy test, urine drug test, MRI safety screening form, fMRI scan.
- Week 4 Assessment: TLFB between Week 2 and current date, impaired control[103] and craving[104]. Emotional and Alcohol Go No-Go, digit span task[42,105], Kirby Delay Discounting task[106], the PROMIS anxiety, depression, and anger scales[107],the State Difficulties in Emotion Regulation Scale[108] an emotional n-back task[109], and the

Pittsburgh Sleep Quality Index[110] and Epworth Sleepiness Scale[111], urine pregnancy test.

- Week 6 Assessment: TLFB between Week 4 and current date, impaired control[103] and craving[104]. PROMIS anxiety, depression, and anger scales[107],the State Difficulties in Emotion Regulation Scale[108] Pittsburgh Sleep Quality Index[110] and Epworth Sleepiness Scale[111], urine pregnancy test.
- Phone Assessment: TLFB between Week 6 and Week 10, impaired control[103] and craving[104].

Screening/Consent Visit (Week -1)

At the first visit, participants will undergo a consent process. Participants will meet with the coordinator if they pass the phone screen and will go over any questions about the consent and study with the coordinator at this first in-person visit. Individuals will indicate their consent to participate in the study by signing and returning the informed consent form. If they consent to be in the study, they will then undergo the Screening SST to establish which response inhibition subgroup they belong to (impaired=SSRT>233[21], normal=SSRT<233) followed by a Structured Clinical Interview (SCID) for Psychotic, Anxiety, Mood, and Drug and Alcohol Use Disorders[122] to establish whether they have moderate to severe AUD and/or exclusionary SUD and psychiatric disorders. A 90 day timeline follow-back (TLFB)[123] will also be performed to establish adequate drinking levels for inclusion. If participants are experiencing clinically significant active alcohol withdrawal (CIWA>8[102]) they will be asked to have their withdrawal treated before returning to initiate treatment in the study. All participants will complete the safety screening form for fMRI to determine eligibility for undergoing the fMRI portion of the study. All research forms will be labeled with a code and all identifiers will be securely kept separate from the research forms.

Screening Physical (Week -.5)

All participants will then undergo a screening physical at which they will have a medical history and physical exam by the study physician to determine safety for initiation of modafinil. Blood work, EKG, vital signs, and a urine pregnancy test will be obtained at this visit.

Randomization

All individuals who pass the screening will be randomized to receive: 1) modafinil, or 2) placebo. Urn randomization procedures will be utilized to ensure groups are matched on recruitment site and response inhibition subgroup (impaired: SSRT > 233, normal: SSRT < 233). The PI will generate the randomization scheme and the pharmacist will perform the randomization. Besides the pharmacist, all study personnel will be blinded to condition.

Study Intervention and Assessment Procedures: (Week 0-10)

Intervention: At the screening visit, if the participants are likely to qualify pending lab test results, the physician will describe in detail the possible side effects with modafinil, dosing regimen, and will develop a medication adherence plan. Once labs confirm they meet study criteria, participants will be randomized to active treatment or placebo using an urn technique (stratified by recruitment site). The placebo group will receive capsules which look identical to capsules filled with active treatment, and will receive the same number of capsules. Only the study pharmacist will be un-blinded, and the pharmacist will not interact with any of the participants. Modafinil will be given at 100mg orally per day for the first 4 days, then 200mg for 4 days, and then 300mg for the remainder of the treatment based on previous work[21].

The dose will be adjustable at the discretion of the medical practitioners (Dr. Wilcox or covering provider) and dispensed weekly (See IDS plan). Specifically, at the Week 0 visit, the participant

will receive the first 11 days of study medication, at the Week 1 visit the participant will receive the subsequent 7 days of study medication, at the Week 2 visit the participant will receive the subsequent 7 days of study medication, at the Week 3 visit the participant will receive the subsequent 7 days of study medication, and at the Week 4 visit, the participant will receive the final 10 days of study medication. If we adjust the dose at a particular medication visit we will simply inform the participant to take the appropriate dose from their bottle (all capsules are 100 mg modafinil and so we will just inform them to take 2 capsules instead of 3 capsules if we are suggesting a dose decrease from 300 mg to 200 mg for example), and we will also call the pharmacist to tell them that for the next prescription the participant should have a lesser quantity dispensed. We will note any dose adjustments at that visit, and will expect the participants to return the appropriate number of pills to us at the subsequent visit. All non-consumed pills will be returned to the pharmacist. If we make an adjustment in the dose before the medication has been prepared by the pharmacist, for example following a phone consultation initiated by the participant, then we will call the study pharmacist to request that she dispense the lower dose at the next dispensation.

Dose adjustments will only be made at the discretion of either Dr. Wilcox or covering provider based on participant symptoms and signs. Dose adjustments cannot be made by the research coordinator or nurse, but the research coordinator or nurse will be expected to report any and all participant complaints, side effects, vitals, physical signs, and adverse events to study physicians for final dosing decisions to be made at each medication visit.

Adherence will be monitored with pill counts at all med visits, primarily by the research coordinator or nurse, but also by study physicians if needed. All participants will be asked to record adherence in a daily log, and to bring in their pill bottles for pill counts at all visits. Unused pills will be returned to the pharmacist. Study personnel (nurse, research coordinators, study physicians) and the pharmacy will count pills remaining in bottles and record these values.

All individuals will be screened for side effects at the weekly visit (Med Visit) with a nurse or research coordinator. During these four follow-up Med Visits (15 minutes), individuals will undergo a review of side effects, and an assessment of alcohol consumption and medication adherence. Serious adverse events will be documented on the serious adverse events form and will be followed with the serious adverse events follow-up forms until resolution.

Note: for community recruited participants, we will provide individuals who are not currently in treatment for their AUD 4 sessions of a widely-accepted evidence-based psychosocial intervention for AUD called Motivational Enhancement Therapy (MET)[124]. Specifically, all individuals who are not undergoing active treatment will be offered 4 sessions of this intervention at Week 0, 2, 4, and 6, and the therapy will be administered by the PI.

Assessment Measures: *Clinical Measures:* Based on their association with modafinil treatment in past work[27-29,125], rash [with a possibly, but not definitively increased frequency over background rates of Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)], euphoria, craving for the medication, chest pain, tachycardia, headache, nausea, dizziness, depression, anxiety, psychosis, irritability, insomnia, arthralgia, dry mouth, appetite changes will be assessed at each Med Visit and at week 6 using a standardized form[126]. Vitals, breath alcohol (BAL), urine drug screen (UDS) and CIWA[102] will be checked at each visit and urine pregnancy will be checked at the screening physical exam visit, baseline, and at each in-person follow-up visit, including prior to each MRI scan. At week 4 participants will be asked whether they think they were in the placebo or the modafinil group to test blinding. *Screening SST:* Designed after the SST used in the single clinical trial in AUD, this will be used to distinguish those with impaired response inhibition (SSRT>233)[21] from those without impaired response inhibition. Go trials require the participants to perform a two-choice reaction time task on a computer screen. Stop trials are identical to go trials but in addition a visual stop signal (screen turns from black to red) cues participants to inhibit their response. An adaptive tracking algorithm accomplishes 50% successful inhibition for each participant by varying the delay [stop signal delay; (SSD)] between

presentation of the arrow and the stop signal. The dependent variable (SSRT) is calculated by subtracting the SSD (the mean time between the appearance of the arrow and the stop signal) from the mean reaction time to go stimuli. *Primary Outcome Variables:* We will derive PDA, TTR, drinks per drinking day (DPDD) and drinks per week (DPW) at every assessment visit using the TLFB[123]; even though effects on DPDD were not seen in in previous work we will still measure it[21]. We will also measure impaired control[103] and craving[104] at every assessment. *Primary Mediators, response Inhibition:* The task we will use to measure target engagement (obtained at every assessment) is a validated emotional Go No-Go task[57,127,128] and will have additional trials preceded by aversive[74] alcohol[72,129] or neutral stimuli. *Exploratory Mediators:* At every assessment participants will also perform a digit span task[42,105], Kirby Delay Discounting task[106], the PROMIS anxiety, depression, and anger scales[107],the State Difficulties in Emotion Regulation Scale[108] an emotional n-back task[109], and the Pittsburgh Sleep Quality Index[110] and Epworth Sleepiness Scale[111]. *Nuisance Variables:* At baseline, we will obtain the Rivermead Post-Concussion Symptoms Questionnaire[112], Alcohol Dependence Scale[113], Fagerstrom Test for Nicotine Dependence[114], AUDIT[115], intelligence (WTAR[116]), Barratt Impulsiveness Scale (BIS)[59], UPPS[117], the Adult ADHD Self-report scale[21,29], motivation (Stages of Change Readiness and Treatment Eagerness Scale[118]), Treatment Services Review[119], Difficulties in Emotion Regulation Questionnaire[120] and Emotion Regulation Questionnaire[121]. Adherence (self-report/pill counts), and presence of moderate TBI (loss of consciousness >30 minutes and <24 hours) will be controlled for. Treatment site will be a nuisance variable.

Magnetic Resonance Imaging (MRI): MRI scan(s) taking less than an hour will involve performing a cognitive task (emotional GNG task designed after previous work[57], approximately 20 minutes), a resting state task during which they are asked to gaze at a fixation cross and think about nothing in particular for 6 minutes, and a structural, diffusion weighted imaging and arterial spin labeling scan during which they are not required to perform any task. Participants will lie down on a table and be placed into a long donut-shaped magnet.

If a participant appears to a visit intoxicated (BAL >.08%) the assessment (both research assessments and clinical assessments) will not proceed, and the participant will not receive their medication refill until they can be assessed under the legal limit. Furthermore the participant will not be allowed to drive home until under the legal limit. In cases of intoxication, the assessment will be rescheduled to occur as quickly as possible. There will be a 4-day flex window for rescheduling an assessment for intoxication. Similarly, there will be a 4-day flex window for rescheduling for no-shows. If it is impossible to reschedule an assessment or a no-show within that period of time, then participants will be given one chance to restart the study from the day after the baseline visit if the lapse occurred between Week 0 and Week 2 (redoing all subsequent research and clinical assessments and re-initiation of modafinil up-titration if it has been more than 3 days since their last modafinil dose). If the lapse occurs between Week 2 and Week 4, they will be given one chance to restart the study from the day after the Week 2 visit, but they will be required to restart the modafinil up-titration at 100 mg if it has been more than 3 days since their last modafinil dose. If a lapse happens a second time, they will be discontinued from the study.

There will be no change if the participant drops out of SOC treatment (IOP's or study-provided motivational interviewing) and we will be happy to provide the participant with further referral information to explore at their discretion, and they are more than welcome to engage in other non-pharmacologic alcohol use disorder treatment options and self-help group attendance (Alcoholics Anonymous etc.) while also still undergoing the study protocol.

Data Analysis

1. *Neuroimaging Methods: Task:* All participants will complete the emotional GNG task designed after previous work[57] at baseline, and at 2 weeks.

2. *Neuroimaging Acquisition and Analyses:* Standard pulse sequences will be utilized to collect high-resolution anatomical (T_1) and whole brain echo-planar images. Functional images will be generated using similar methods previously published by the PI and mentor, and evoked analyses will follow standard pre-processing techniques[130-133]. Deconvolution analyses will be performed (AFNI, 3dDeconvolve) and individual-subject percent signal change (PSC) maps will be generated for four trial types (aversive NoGo, neutral Go trials, neutral NoGo, aversive Go), regressing out error-related signal. No-Go minus Go contrasts will be calculated at the individual-subject level for both aversive and neutral stimuli. *DTI:* To probe for effects of modafinil on neuroinflammation, we will also obtain fractional anisotropy and axial diffusivity measures using DTI[134,135]. Analyses methods will mirror those performed in previous work by Dr. Mayer[136-138]. *Arterial Spin Labeling (ASL):* A pulsed Arterial Spin Labeling (pASL) image will be collected to measure mean cerebral blood flow (CBF) in significant clusters, which can be used to correct for vascular effects of modafinil (modafinil has weak cardiostimulatory effects, and could globally effect CBF[125,139,140]) and to distinguish those from the neural effects[141-146]. Analysis methods will mirror those performed in previous work by Dr. Wilcox[130,147].
3. *Statistical Analyses:* Data will be inspected for normality and outliers; when appropriate, slight deviations from normality will be transformed whereas rank analyses will be performed for severe violations. *Aim 1:* First, we will test the effects of medication in the whole sample in which medication, response inhibition subgroup and an interaction term (medication condition*response inhibition subgroup) will be entered as a predictor, to test for a matching effect. Because the sample size is small, regardless of whether the interaction term or condition term are significant in the whole sample, we will also test for an effect of medication in the sample with impaired response inhibition separately from the sample with normal response inhibition. Using latent growth curve modeling (LGCM), we will be able to examine the main effects of medication on PDA, DPDD, and DPW at baseline, 1, 2, 3, and 4 weeks. LGCM is an extremely flexible modeling approach that allows the examination of linear and non-linear changes over time amongst both normally and non-normally distributed outcome measures. To test for medication effects on TTR, a Cox regression analysis will be performed for the time to first heavy drinking day (≥ 4 drinks/day for women, 5 for men)[8]. *Aim 2:* To test our hypothesis that modafinil will improve response inhibition (GNG errors of commission) relative to placebo a series of 2x3x3 ANCOVAs will be performed with fixed factors for treatment group (modafinil vs. placebo) time (baseline, 2, 4) GNG trial type (alcohol cue vs. aversive cue vs. neutral cue), and the nuisance variables as covariates. Similar analyses will be performed for exploratory targets/mediators, and repeated in the non-impaired group. To test for mediation we will use parallel process LGCMs which examine simultaneous growth (i.e., change) in the mediators and outcomes and can be used to examine both concomitant and prospective mediation models. In these models, the total, direct, and indirect effects of treatment on alcohol outcomes via putative mediators will be estimated using the bias-corrected bootstrap based on 10,000 bootstrapped samples[148], which provides a powerful test of mediation[149], and is robust to small departures from normality[150]. For both aims, baseline drinking quantities and medication group will be entered as main effect predictors, as will nuisance variables that differ between active and placebo groups at baseline, and missing data will be handled using full information maximum likelihood procedures[151,152]. For fMRI analyses, contrast images (No-Go minus Go) will be entered into a 2x2x2 mixed measures ANOVA [Group(modafinil, placebo), Time (baseline, week 2), Stimulus(aversive, non-aversive)] which will permit examination of Aim 1 hypotheses (i.e., GroupxTime interaction with null effect for Stimulus). Appropriate measures will be enacted (i.e., parametric thresholding and spatial clustering) as we have done in previous work[130-133] to correct for false positives for all voxel-wise comparisons. For all analyses, the null hypothesis will be rejected in the event of a significant GroupxTime interaction. *Additional Analyses:* Chi square analyses and t-tests will be used to compare rates of individual and overall number of reported side effects and adherence (pill counts) in each treatment arm.

4. *Power Analyses:* Based on our previous studies (Preliminary Data), we expect 20% attrition, leaving a total of 20 participants completing the study. Approximately 12 of these will have impaired response inhibition based on preliminary data (see above). Our primary test will be whether or not modafinil reduces percent days abstinent and time to relapse in those with impaired response inhibition with a larger effect size than those with normal response inhibition. Previous studies[21] have demonstrated effect sizes of .5 and .8, respectively, for effects of modafinil on these metrics in individuals with impaired response inhibition. The other tests are essentially secondary aims and we will not expand on this here. Using 1-tailed hypotheses, we will have 80% power to detect an effect of size of .8 with an alpha of .2. We will first be able to determine whether the directionality of effects are in the expected direction (e.g. if modafinil increases time to relapse and percent days abstinent rather than reducing it). Then we will be able to determine if there is evidence of benefit of similar effect size comparable to that seen in previous work, and whether or not pursuing further funding is worthy with our sample size. We acknowledge that this study is not powered to definitively determine whether or not the medication is effective for the treatment of AUD, and that modafinil is not minimal risk. However, in general it is a relatively safe medication, and the potential benefits to the participants who get assigned to active treatment and the potential value to the field and future patients with AUD outweigh the risks of being on this medication. Aim 1: We would require 24 participants per medication group in the impaired response inhibition subgroup to be adequately powered (80%) to detect an effect of the size seen for TTR (d=.84 using a pooled SD of .37) and 64 per medication group to be adequately powered to detect a similar effect for PDA (effect size .50)[21] in the previous modafinil study. We are not adequately powered to detect an effect, but we will test medication effects by measuring effect sizes. **However, previous pilot studies of other pharmacotherapeutic agents in AUD have measured effects sizes as large as d=2.8, which we would be adequately powered to detect** with 6 per group[153]. Aim 2: We have mentioned that in the previous trial of modafinil in AUD, that SSRT was not altered by treatment[21]; however, there was a medication effect on working memory in individuals with impaired working memory at baseline[42] (d=.52). Moreover, previous work has shown a correlation (r=.39, d=.85) between changes in response inhibition and changes in alcohol use during pharmacotherapeutic treatment[48]. If there is a large effect, as defined by d>.59, for medication on mediator, and for changes in mediator and alcohol use outcome, then we would need total sample sizes of 34 to have 80% power using bias-corrected bootstrapping to detect a significant (p<.05) mediating effect[149]. We will therefore be underpowered to detect an effect, but we will have 80% power to detect a trend (p<.15) with 20 participants completing. Moreover, our design (more frequent testing of potential mediators, and participants being in their natural environments, amongst drinking triggers) may further increase effects from those observed in previous work. *Power analyses for fMRI task:* The only single-dose study of effects of modafinil on brain activation during response inhibition did not include means and standard deviations from which to derive effect sizes[38]. In StimUD, modafinil elicited activation in lPFC and dmPFC (learning task) with effect sizes ranging from 0.7 to 1.0[70]. Our sustained dosing approach should result in larger effects[20]. We will be adequately powered (80%) to detect similar effects (effect size 1.0) of medication on BOLD signal with our sample size of 25 if we use a liberal alpha of 0.15 for our spatial clustering procedure during the whole brain analysis and a 2x2 mixed measures ANOVA, leaving stimulus type out of the model. In summary, we will certainly have enough participants to determine if an R01 application is warranted and project necessary sample sizes.

12) Compensation

Participants will compensated for their time for research visits as follows: Consent and screen visit $30, history, physical, and screen visit $30, baseline assessment $60, second assessment (week 2) $70, third assessment (week 4) $70, fourth assessment (week 6) $40, Phone assessment ($40). Participants will not be compensated for medication visits that don't co-occur with an assessment. Payments will be in the form of merchandise gift cards, pre-paid visa cards (or similar) or cash to equal a total of $340 (if all visits are completed). If participants do not complete the study, they are paid for visits completed and all payments occur immediately at the conclusion of a study visit.

13) List of Appendices

Impaired Control Scale initial
Impaired Control Scale followup
Difficulties in Emotion regulation questionnaire
Barratt Impulsivity Scale
AUDIT
Emotion Regulation Questionnaire (ERQ)
StateDERS
Promis Anger/Anxiety/Depression
SOCRATES – alcohol questions
UPPS
FTND
PACS
PSQI
Adult ADHD self report scale (ASRS)
ESS
Drinker Inventory of Consequences (pages 43-46 in the pdf)
ADS (Alcohol Dependence Scale)
CondMedsMod
CIWA
Demographic Form
Edinburgh Handedness Questionnaire
MedHx2
MRI Screening Form no contrast
Phone Screen Modafinil 12_31_17
Physical Exam
Post Scan Questionnaire
Pre Scan Questionnaire
Rivermead Post Concussion Symptoms Questionnaire
SAE report
SAE f/u
SAFTEEmodafinil
SCID V
Treatment Review Questionnaire
WTAR recording
WTAR word card

2015ModafinilPrescribing Info
IDS Plan 9/12/17

PIND

Online ad Mod 12_31_17
Modafinil for Alcohol Use Disorder MRN Website 12_31_17
Modafinil Flyer 12_31_17
Narrative Modafinil 12_31_17
Newspaper Add Modafinil 12_31_17
Newspaper Color Add Modafinil 12_31_17

14) Data and Specimen Banking

No specimens will be banked as part of this protocol. Participants will be given the option of having their data stored in the MRN Data Repository (see HRRC# 06-387, PI: Roberts).

15) Data Management

Consent Forms: Signed consent forms are stored in a locked cabinet in a locked office at MRN.

Questionnaire Data: All data are coded with a unique research subject identifier (URSI) number. Electronic data is stored on a drive only accessible by the research team on a secure MRN server. For non-computer based forms, such as the neuropsychological assessments, the data collection sheets are stored in a locked cabinet in a locked office at MRN.

Behavioral and Imaging Data: All data is coded with the URSI, and collected and stored electronically. Electronic data is stored on a drive only accessible by the research team on a secure MRN server (any standardized forms/assessments that have a space for "name" are labeled with URSI only, e.g. Epworth sleepiness scale and PSQI). The MRI screening form is labeled with name and date of birth, and stored separately from any research data which is necessary for safety screening by the MRI technologists. De-identified data resulting from this study may also be presented at meetings, published in journals/books, used in classrooms for training/teaching purposes, and may be shared with other researchers including scientists at other universities and institutions.

Study Closure: At the time of study closure, all participant identifiers (name, address, etc.) will be made inaccessible to the research team. MRN retains the link between identifiers and URSI indefinitely for the potential future benefit to the research participant. Specifically, it may become medically advantageous in the future for a former participant to have access to the clinical information that may be present in radiological scans and reviews. For example, if a participant has been diagnosed with a neurological condition (e.g., multiple sclerosis, glioblastoma, etc.) it may be clinically beneficial for the participant's physician to have access to a research scan that was performed at an earlier time-point to determine disease course and severity.

16) Provisions to Monitor the Data to Ensure the Safety of Participants

General Considerations: The risks are greater than minimal risk. Although the safety profile of modafinil is reasonably well established, modafinil has only been studied in alcohol dependent populations in a single study, and there were no serious adverse study-related events. The data and safety monitoring plan is therefore designed both to ensure that the risks of medications and study-related procedures are minimized for patients, and to minimize any doubt that there

are adequate safeguards in place to minimize this risk. The FDA has determined this medication to be exempt from needing an IND (see attached IND exemption letter).

Every effort will be made to address adverse events as they arise from the medication treatment. The study physician will be allowed to decrease the dose, or discontinue the study medication as deemed necessary. Similarly, every effort will be made to address adverse events as they arise from the assessments including anxiety from exposure to the affective stimuli. If there are any serious adverse events we will take appropriate measures.

If a participant does experience excessive craving or anxiety as a result of the assessments, or neuropsychological testing, or expresses suicidal thoughts, Dr. Wilcox or covering medical provider will be available at any time to assess safety and make an attempt to help the patient. Although no aspects of the study are expected to be unduly upsetting or risky, established procedures are in place for the occurrence of such an emergency. Support will be available to deal with any anxiety, fatigue or increased urge to use drugs associated with behavioral testing. There will a physician available any time by phone to talk with participants for any emergent medical adverse events from the medication. A standardized suicide risk assessment protocol is in-use by this team to assess for safety when participants report past or current suicidal thoughts, and Dr. Wilcox or covering medical provider will be called, and one of them will be available at any time to respond, if the protocol warrants their involvement.

Every effort will be made to protect the confidentiality of participants' records. However, complete confidentiality of records cannot be guaranteed as records may be examined by authorized personnel from the approving IRB. Participants will be informed of this possibility prior to signing the consent forms. Otherwise, records will be kept strictly confidential and will not be inspected by any other agency unless required by law. Loss of confidentiality will be minimized by assigning a randomized number to each participant upon entry into the study. This number will be used for all correspondence between study investigators and all data collection and analysis after the initial screening visit. MRN has state-of-the art IT networks with all necessary security mechanisms in place for data storage. Any personal information entered into computers is password protected and monitored for suspicious activity. Moreover, all information will be in double-locked rooms per privacy specifications. The results of this research may be presented at meetings or in publications; however, participants' identity will not be disclosed. This research study has a Certificate of Confidentiality from the National Institutes of Health (NIH).

Participants will be clearly informed of their right to withdraw from the study at any time and still receive full compensation.

Adverse events (AEs) will be collected on an AE case report form when they come to the awareness of study staff. The form will include an assessment of clinical significance and study relatedness. AEs will be reported in accordance with federal law and policies and the IRB. Reporting procedures vary depending on the severity of the AE, and will follow the policies in the IRB manual. In particular, adverse events and other reportable events that are unanticipated and deemed related to research procedures will be reported to the IRB within 7 days of discovery, regardless of whether they qualify as SAEs. In addition, information on adverse events will be captured in the study data system as follows.

There are no known health risks associated with the proposed MRI aspect of the study. A two-way intercom system and a video monitoring system provide continual monitoring of the participant's condition at all times. If discomfort or concern is expressed, or detected, the

experiment will be stopped and the participant will be given the option to discontinue at any time. Absolute caution will be implemented to ensure that only non-ferrous objects are present during all of the MRI sessions. Participants will be asked to change into hospital scrubs prior to being placed in the scanner to ensure that they do not introduce any metallic objects into the imaging environment. Participants will also be screened for the presence of a pacemaker or any other metallic objects in their body, such as an aneurysm clip, ear implant, or nerve stimulator. Participants with these or other metallic devices will not be allowed to participate in any of the previously described studies. Ambient scanner noise will be below the current recommended guidelines.

Data Safety Monitoring Committee

Data and Safety Monitoring Committee: Data and Safety Monitoring Committee will be established comprising the study physician, the research coordinator, and an external physician reviewer who is not otherwise affiliated with the study and does not report directly or indirectly to the PI. This committee will meet at least quarterly to review data quality, recruitment and retention, and to review all serious or clinically significant adverse events. In addition, the committee will review safety data before each dose increase in the study, and following any serious adverse event that appears to be study related. The DSMC members will be blinded for participants who are currently enrolled, but not blinded for participants who have been informed about what group they were assigned to (e.g. once the participants knows what group they were assigned to, which will occur after their final assessment, all study team members and the DSMC members will know what group a particular participant was assigned to). For all SAE's, investigators will consider and discuss the need for unblinding, based on the nature of the SAE, and based on whether or not knowing the group assignment would alter treatment of the SAE, within 48 hours. Patterns of adverse events as well as individual events may indicate the need for operational changes, protocol modifications, a decrease in dose, or, conceivably, discontinuation of the trial. An example of a pattern of adverse event that could result in discontinuation would be greater rates of cardiac events (severe tachycardia) in the active treatment group compared to the placebo group. Either the PI, or a single member of the DSMC could recommend protocol modifications or discontinuations.

All side effects and adverse event information will be monitored for using a standardized checklist at all medication visits with the nurse or research coordinator. Study data will be reviewed quarterly, or more frequently as deemed necessary by the PI.

On a quarterly basis, just before each DSMC, we will review the literature, searching PubMed for new studies of "modafinil + alcohol use disorder", and "modafinil + safety" and if any new information about risks or benefits is found on such a search that was not included in the consent, and that might change the participants' mind about participating, we will inform all participants who are currently enrolled in the study.

Adverse Events

For the purpose of this study, the following AEs will not require reporting in the data system but will be captured in the source documentation (progress note) as medically indicated:
All adverse events due to study medication will be captured at weekly visits with the nurse or research coordinator, or more frequently, on a validated form designed to capture adverse events. The following symptoms will be directly asked about at each visit: rash, euphoria, craving for the medication, chest pain, tachycardia, headache, nausea, dizziness, depression, anxiety, psychosis, irritability, arthralgia, dry mouth, appetite changes. These and those listed on the consent would be deemed expected. Adverse events that are unanticipated and deemed

related to research procedures will be reported to the IRB within 7 days of discovery, regardless of whether they qualify as SAEs.

Serious Adverse Events

Adverse events (AEs), when present, will be collected on an AE case report form at the end of each drug administration session and at all subsequent visits. The form will include an assessment of clinical significance and study relatedness. Serious Adverse Events (SAEs) will be documented on a separate SAE form. SAEs will be reviewed by the Data and Safety Monitoring Committee at its quarterly meetings. These will also be reported to IRB within 48 hours.

17) Participant Complaints

If a participant wishes to issue a complaint or request information about the research, they may notify the research coordinator at 505-510-4351 or the PI, Dr. Claire Wilcox, at 505-633-8105 (Dr. Wilcox will be available 24/7 for patients to call regarding side effects). Participants may also contact the UNM Office of the IRB, (505) 277-2644, irbmaincampus@unm.edu. Website: http://irb.unm.edu/

Depending on the nature of the complaint, the problem will be resolved directly with the participant, if possible, in a confidential and timely manner. Complaints that constitute a reportable event will be submitted to the IRB within 7 days. Participant complaints will be coded with a unique research subject identifier (URSI) and kept in their respective study folder in a locked office for record-keeping purposes.

18) Withdrawal of Participants

It is not anticipated that circumstances will arise during the course of the study for which the participants will need to withdraw from the study. The consent form will fully inform the participants that they can refuse to answer any questions, participate in any procedures (e.g., neuropsychological testing), or withdraw from the study at any time. If a participant refuses to participate in a portion of the research, they can still participate in the other parts of the study. If a participant withdrawals from the study completely, they will be informed in the consent that the data they have provided up to that date will be maintained as a part of their study record. Participants can withdraw from the study at any time.

19) Risks to Participants

The risks of the interventions used in this study are greater than minimal risk.

Risks of Modafinil

The main risks of this study are probably related to possible effects from modafinil which are: rash [with a possibly, but not definitively increased frequency over background rates of Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)], euphoria, craving for the medication, chest pain, tachycardia, headache, nausea, dizziness, depression, anxiety, psychosis, irritability, arthralgia, dry mouth, appetite changes. Additionally, in the consent we have listed the following potential risks:

Occasional (Between 5-20% more often than placebo) side effects include: headache, nausea.

Rare (2-4% more often than placebo) side effects include: nervousness, anxiety, vasodilation (orthostatic dizziness), paresthesia (tingling), high blood pressure, chest pain, dry mouth, sore throat, decreased appetite, insomnia.
Extremely Rare (1% or less) side effects include: rhinitis (runny nose), back pain, diarrhea, dizziness, dyspepsia (stomach upset or reflux), liver function test changes, constipation, depression, palpitation, sleepiness, rapid heart rate, vision changes, agitation, asthma, chills, confusion, movement changes (dyskinesia, hyperkinesia, hypertonia), edema, emotional lability, high eosihophil levels on blood count, bloody nose, flatulence, risk of death, mouth ulcers, sweating, changes in taste, thirst, tremor, changes in urination, vertigo, rash, euphoria, craving for the medication, depression, psychosis, irritability, body aches.
http://www.rxlist.com/provigil-drug/side-effects-interactions.htm

Risks of Assessment Procedures
It is possible that discussion of substance use and consequences may cause emotional discomfort in some participants. The only risk associated with the assessments and neuropsychological testing is fatigue or anxiety. In particular, the affective stimuli in the emotional GNG are emotionally intense and the alcohol stimuli could trigger craving. To minimize such discomfort, the following steps will be taken. The consent form will fully inform the participants about the nature of the information to be disclosed in the protocol, the nature of the cognitive tasks they will be undertaking, and the participants will be informed in the consent form that they can refuse to answer any questions or withdraw from the study at any time. Participants will be informed that all information is confidential, and the steps taken to guard confidentiality, as well as the limits to confidentiality, will be described. One of the study investigators will be available to meet with any participant who becomes distressed about any aspect of the protocol and wishes to discuss this.

Risks to Confidentiality and Potential Legal Consequences
Records which identify participants and the consent form signed by participants may be inspected by the IRB. Because of the need to release information to this party, absolute confidentiality cannot be guaranteed. The results of this research project may be presented at meetings or in publications. However, the identity of individual participants will not be disclosed in those presentations.

MRI: Radio and magnetic waves associated with MRI scans are not associated with any known adverse effects. MRI is non-invasive and considered minimal risk by the FDA and OHRP. However, the scanner is a large magnet, so it could move objects containing ferrous metal in the room during the scan. All participants are screened using the MRI safety screening form prior to be being scanned. Participants may be bothered by feelings of claustrophobia (uncommon). The MRI also makes loud 'drum' beating noises during the study. Headphones or earplugs are provided for protection. Rarely, large or recent tattoos can heat up during an MRI scan and cause skin irritation like a sunburn (uncommon). No long-term harmful effects from MRI are known. However, since the effect of MRI on early development of the fetus is unknown, participants who are pregnant will not be allowed to go in the MRI. All females will undergo a urine pregnancy test prior to scanning. The test results will only be shared with participant. All MRI sequences used are within FDA approved parameters, including specific absorption rate. Due to the very high sensitivity of MRI in detecting abnormalities, there is a risk of false-positive findings, identifying something on imaging studies that may or may not be important. This may result in anxiety and a referral for additional medical testing, possibly including a recommendation for clinical scans at the participant's cost.

Another main risk of this study, especially given the questions regarding drug use and psychiatric symptoms and disorders, would concern confidentiality, so we will de-identify data as appropriate. Although we do not intend them to be, such questions could also be upsetting to individuals.

As with any study that collects personal information, there is a risk of loss of confidentiality.

There may also be side effects or risks to study participation that are unforeseen and not known at this time.

20) Potential Benefits to Participants

Participants may or may not have benefit from the study. Knowledge gained through this study may aid the development of more effective treatments for individuals with alcohol dependence and other addictive disorders. There are also potential direct benefits to participants in this study. All individuals (whether assigned to the active treatment with modafinil or placebo group) are receiving treatment (either in the intensive outpatient program upon enrollment or will be offered four sessions of motivational interviewing by the PI), and will also be offered a referral list upon completion of the study. If the medication being tested works, then individuals assigned to the intervention group may also benefit from the treatment. Also, being in a research study may provide benefit, as may taking a placebo pill; individuals who undergo a series of assessments in a research study oftentimes reduce their drinking even if they are not on active treatment. Moreover, at the end of the study, individuals will be informed about whether they were assigned to active treatment or placebo. If assigned to active treatment, and if they experience benefit, they are welcome to approach their primary care provider to explore the possibility of off-label treatment. Other aspects of study participation that may be beneficial include receiving free medical and psychiatric evaluations and the attention and support of participating in a clinical trial.

21) Vulnerable Populations

This study will not include vulnerable populations. Incidentally, we have chosen to keep the monetary compensation levels low to avoid undue coercion. As is discussed in the previous sections, potential participants will be informed of the purpose of the study, voluntary nature of participation, and ensured that their decision to participate (or not) will have no effect on their treatment.

22) Community-Based Participatory Research/Field Research

N/A

23) Sharing of Results with Participants/Incidental Findings

Incidental Findings: Regarding incidental findings from blood draws, all blood work will be done at CLIA certified labs. We will communicate all abnormal results to the participant, by phone if possible. If the participant is unreachable by phone (3 tries) we will mail them a letter asking them to contact us about their blood work. If the participant requests, we will also call participants' providers with abnormal blood work results at the participant's request after having them sign a release of information. Regarding incidental findings from MRI scans, all research MRI scans will be read by a neuroradiologist (a doctor with experience reading MRI scans) unless the participant has been scanned at MRN in the previous six months. If the scan is read, an e-mail notification is sent to the participant letting them know new results are available. The participant can securely log in to the Collaborative Informatics and Neuroimaging Suite (COINS)

Homepage to access their MRI radiology report. No sensitive or identifying information is sent via e-mail. If an abnormality that requires follow-up is identified, such as a Doctor Referral recommendation, a hard copy of the report may be mailed to the participant in addition to the e-mail notification. In these cases, the MRN Medical Director may also attempt to contact the participant by phone to explain the information and help answer questions. There is no plan to share study progress and results will not be shared with participants except for lab results and MRI results as described above.

24) Research Setting

All study procedures will take place at the Mind Research Network with the exception of the University of New Mexico research pharmacy.

UNMH research pharmacy:

Research at the University of New Mexico Health Sciences Center (HSC) is supported by the Investigational Drug Services (IDS) Pharmacy. By responsibly managing and dispensing investigational drugs for clinical trials, IDS enhances the smooth functioning and compliant operation of these studies. In many cases, this process spans the entire study life-cycle, beginning in the early design and planning stages and continuing through study close-out.

IDS activities may include, but are not limited to inventory management, maintenance of drug accountability records, blinding and/or randomization of study medication, development and preparation of matching placebo, procurement, dispensation of study medication to research staff, and the secure, temperature-monitored storage of investigational product.

25) Resources Available

Five private, closed door rooms are available to research staff for study visits at MRN. These assessment rooms have white noise generators outside of the doors to prevent conversations from being overheard. These are reserved by investigators as needed, and are easily accessible. The imaging facilities also have private changing rooms with lockers for personal items. All MRN research staff are trained in regards to the HIPAA Privacy Rule. All individuals will be trained to administer the same consenting and study procedures. Further, all study personnel will have current CITI and HIPAA training throughout the period of the study.

John Phillips serves as MRN Medical Director. UNM hospital is less than a mile away and, as a public hospital, will serve as a treatment facility for unexpected participant emergencies. Located on UNM's north campus, MRN is a 501(c)3 non-profit organization consisting of an interdisciplinary association of scientists focused on state-of-the-art imaging technology and its emergence as an integral element of neuroscience investigation.

26) Prior Approvals/Attachments Requiring Signatures

A COBRE pilot grant (PI Dr. Vince Calhoun, MRN) has been awarded for this study by the NIH. Also MRN Departmental Review is included with the submission.

27) Recruitment Methods

Recruitment: Individuals with AUD (N=25) will be recruited from local treatment centers with flyers and by word of mouth or from the community through newspaper advertisements, flyers

posted in the community, posting on online community websites, Johnny Boards etc. If recruited from treatment programs, potential participants will be recruited from one of three intensive outpatient treatment programs (IOPs) (Sage Neurosciences or Presbyterian or Turning Point; letters of support attached). Through collaborations with site staff and flyers posted at the site, potential participants will be identified and asked if they are interested in participating in this study. If an individual is interested in participating in the study, they will be given the phone number to speak with the study coordinator to then undergo a phone screen. All existing treatment facility clients and subsequent new enrollees will be informed about the study. Interested participants will be given a study flyer and study description with contact information. They will call the coordinator at which point they will undergo a phone screen. Up to 100 participants will be recruited over the course of the study to achieve a final sample of 25 participants (12-13 per group).

28) Local Number of Participants

As many as 100 participants will be enrolled in this study locally to obtain a final sample size of 20 people who complete the treatment with either placebo or active medication (accounting for 20% attrition). Specifically, we will only be initiating participants on treatment who pass the screening history and physical examination. Individuals will initially be consented, then undergo some further screening with a computerized task (stop signal task) and assessment for comorbid psychiatric disorders and recent drinking history to assure that they qualify for the study. Preliminary data (see above) indicates that 60% of participants screened will qualify based on the stop signal task.

29) Confidentiality

All participants are assigned a study ID (URSI) that links their data with their name and other identifying information. All study data (with the exception of the consent form and payment receipt) are coded only with this number. The information is maintained in a secure, restricted access database (COINS). After completion of data analysis, the linking code will be made inaccessible to the research team. De-identified data will be retained until data analysis activities are complete.

30) Provisions to Protect the Privacy of Participants

Five private, closed door rooms are available to research staff for study visits at MRN. These assessment rooms have white noise generators outside of the doors to prevent conversations from being overheard. These are reserved by investigators as needed, and are easily accessible. The imaging facilities also have private changing rooms with lockers for personal items.

31) Compensation for Research-Related Injury

No commitment is made by the MRN to provide free medical care or money for injuries to participants in this study. This is clearly stated in the consent form. Within the consent, participants will be informed that if they have an injury or illness that is caused by participation in this study, reimbursement for all related costs of care will be sought from their insurer, managed care plan, or other benefits program. Within the consent they will be informed that if they do not have insurance, they may be responsible for these costs and that they will also be responsible for any associated co-payments or deductibles required by their insurance.

32) Economic Burden to Participants

Participants will not be charged for any of the experimental study procedures, including MRI scans. If incidental findings from the study result in the need for further evaluation/treatment, the participant or their insurance company will be responsible for additional clinical evaluation/treatment that may be needed. Also, incidental finding information is disclosed only to the individual participant. However, if a participant chooses to disclose such information also to their personal physician, this may become part of their medical record which may or may not have an effect in the future on getting health or life insurance.

33) Consent Process

Upon initial contact, the study will be briefly introduced to the participant by a member of the study team. Participants will then be screened over the phone. We are requesting a waiver of consent for screening purposes only to screen and recruit for potential participants. It would not be practicable to carry out the study if we did not have this waiver. We will need to ask a variety of questions including questions about substance use and psychiatric history to determine if the participant is eligible to be in the study before inviting them for the first in-person visit, and the numbers we will need to screen over the phone will likely greatly exceed the number that qualify for the study, making in-person post-consent initial screening infeasible. We are requesting permission to save data for people who screen out of the study to review reasons for exclusion for future studies, and to keep identifying information for people who were ruled out to avoid the same people calling back and changing answers.

If the participant meets inclusion criteria, the study visit will be scheduled and documented consent will be obtained from all participants. Trained study staff will review the consent with participants and be available to answer any questions that arise as a potential participant reads the consent. The consent process will take place at MRN in a private room with a study team member only. The consent form will fully inform the participants about the nature of the information to be disclosed in the assessments, and the participants will be informed in the consent form that they can refuse to answer any questions or withdraw from the study at any time. Participants will be informed that all information is confidential, and the steps taken to guard confidentiality, as well as the limits to confidentiality, will be described. One of the investigators of the project will be available to meet with any participant who becomes distressed about any aspect of the protocol and wishes to discuss this. Patients indicate their consent to participate in the study by signing and returning the informed consent form. Interested patients can choose to keep the consent to review, there is no time limit on how long they have to decide if they are interested in participation. All participants are required to sign consent prior to participation in any aspect of the study. If there are any changes to the consent during the course of the study, these changes will be submitted to the IRB. No coercion or undue influence will be used. If there are no further questions, the consent form is signed and stored in a locked cabinet in a locked office at MRN. A copy will be given to the participant. Source documents will be stored in locked cabinets in an office which will be locked when the office is not in use.

Name, address, phone number and email are routinely collected from all study participants for the purpose of providing the radiology review letter and future contact, if needed.

Participants not fluent in English Potential participants must be fluent in English to participate in the study as many of the assessments are only available in English.

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative Individuals who have significant impairment of cognition or judgment (as observed by study staff) rendering the person incapable of informed consent. (e.g., traumatic brain injury, delirium, intoxication) are not eligible to participate.

Participants who are not yet adults (infants, children, teenagers) All participants will be 18 and older.

34) Drugs or Devices

All medications will be stored and handled by the research pharmacy and only the pharmacy personnel or staff trained to dispense medications including research coordinator or nurse, or study physicians will dispense medications.

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