Research Protocol: Citalopram Effects on Craving and Striatal Dopamine Availability in Alcohol Dependence

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A. Introduction

Alcohol abuse and dependence represent a spectrum of maladaptive behaviors with enormous public health impact, especially for the U.S. veteran population (Calhoun et al, 2008). Depressive symptoms are frequently comorbid with alcohol use disorders, and the use of serotonin reuptake inhibitors (SSRIs) to treat these symptoms is common in clinical practice (Nunes and Levin, 2004). Clinical trials with SSRIs for alcohol use disorders, however, have yielded mixed results concerning their impact on drinking behavior (Nunes and Levin, 2004; Kenna, 2010).

The characterization of alcohol-dependent subjects on the basis of demographic variables, severity of addiction, and psychiatric symptomatology has revealed a divergence in response to treatment with SSRIs among different subtypes of alcoholics (less severe "Type A" vs. more severe "Type B" alcohol dependence; Kampman et al., 2007). Type A alcoholics exhibit a trend toward decreased drinking behavior in clinical trials with SSRIs, whereas type B alcoholics show a trend in the opposite direction (Kampman et al., 2007). The literature does not offer an explanation for this divergence, and therefore, it is not clear how these research findings can be applied clinically.

Citalopram is an SSRI that is commonly used as a first-line medication for the treatment of depression (Bezchlibnyk-Butler et al., 2000). Intravenous (*iv*) citalopram infusion (40 mg) bypasses hepatic metabolism, and a single infusion is well tolerated and produces a clinically relevant concentration of the medication in the human brain (Smith et al., 2009). A single infusion reduces striatal dopamine (DA) receptor availability (presumably through an action to increase intrasynaptic dopamine) by a magnitude comparable to the effect of chronic oral citalopram treatment, as measured by positron emission tomography (PET) (Smith et al., 2009). The subjective experience of craving for alcohol in alcohol-dependent individuals has been associated with decreased dopamine receptor availability in the striatum, as demonstrated with PET imaging (Heinz et al., 2004).

In the proposed project, we will examine the effect of the SSRI citalopram on intrasynaptic DA concentration using PET in participants with alcohol dependence. Specifically, 20 research volunteers in each of 3 groups (Type A alcohol dependence, Type B alcohol dependence, and healthy control subjects) will be recruited for a double-blinded, placebo-controlled, within-subjects, outpatient study with *iv* citalopram (40 mg and saline, in counter-balanced order) and [^{18}F]fallypride PET scanning. Typology among alcohol-dependent subjects will be assessed *post hoc* as in Pettinati et al. (2000).

The goal of the project is to assess whether SSRI effects on drinking behavior in alcoholic subtypes is mediated by altering the level of craving for alcohol and/or via changes in intrasynaptic dopamine in the striatum. Results of this study will have clinical importance in the treatment of alcohol dependence, by providing an increased understanding of the neuropsychopharmacology of practical treatment options for this condition in Veteran clinical populations.

B. Methods

B.1. Summary of experimental design. This project proposes to study 20 completing individuals in each of 3 groups (Type A alcohol dependence, Type B alcohol dependence, and healthy control subjects) for a double-blinded, placebo-controlled, within-subjects, outpatient study with *iv* citalopram (40 mg and saline, in counter-balanced order) and [^{18}F]fallypride PET scanning. Participants will be non-treatment seeking. Participants will be in good physical

health, have no history of complicated alcohol withdrawal symptoms (e.g., seizures, delirium tremens), be 21-55 years of age, and taking no psychoactive medications. Typology among alcohol-dependent subjects will be assessed as per Pettinati et al. (2000). U.S. Veterans will be encouraged to participate in the study, and are expected to be highly represented in the enrolled participants, given that alcohol dependence is more common among Veterans than in the U.S. civilian population.

After screening, qualified participants will be undergo a structural MRI (sMRI) scan at the Greater Los Angeles VA Medical Center, which will be used for co-registration of subsequently obtained PET images. Participants will then have two separate procedure days on which they will receive a double-blinded *iv* infusion of one of the two test compounds (citalopram 40 mg or saline control, counter balanced). Participants will be randomly assigned to either condition on the first procedure day. After each infusion, participants will undergo ~15 min of assessment of both baseline and cue-induced craving for alcohol, followed by ~45 min of paper- and computer-based questionnaires designed to assess measures of mood and other psychiatric symptoms. Subsequently, participants will undergo [^{18}F]fallypride PET scanning (~90min) to assess striatal $D_{2/3}$ receptor availability. After PET scanning on the first procedure day, participants will be sent home, with at least one week separating procedure days to allow for washout of first test compound and radiotracer. Participants will then return to the VA for the second procedure day, with the second test compound infusion (citalopram 40 mg or saline control, opposite of first procedure day) and PET scan. After completion of both infusions and PET scans, participants will be discharged from the study.

B.2. Participants

***Note**: To comply with VA-funded research guidelines, potential study participants will be restricted to U.S. Veterans.*

B.2.1. Selection criteria for alcohol dependent subjects. Initial selection criteria for alcohol-dependent subjects will be consistent with Kampman et al. (2007).

Inclusion criteria are: (1) age between 21 and 55; (2) meeting DSM-IV diagnostic criteria for alcohol dependence; (3) report drinking at least 48 standard drinks in a 30-day period, during the 90 days before enrollment, and must have had at least 2 days of heavy drinking (at least 5 drinks/day for men, 4 drinks/day for women) in the last 30 days.

Exclusion criteria are: (1) current treatment for alcohol problems or a history of treatment in the 30 days before enrollment or are treatment seeking; (2) a current (last 12 months) DSM-IV diagnosis of dependence on any psychoactive substances other than alcohol and nicotine.

B.2.2. Initial Screening criteria for typology in alcohol dependent subjects. In order to provide for approximately equal numbers of participants in the Type A and B groups *a priori*, alcohol dependent participants will be enrolled in the study following the criteria of Kampman et al. (2007). However, final typological classification for all alcohol dependent participants will be conducted *post hoc* with K-means clustering of clinical and demographic variables for potential participants following an updated protocol based upon the original classification of Babor et al. (1992; Pettinati et al., 2000). Type B alcohol dependence will be conditionally classified as those who: drink more than 12 drinks per day on average for males, 10 for females over the last 90 days prior to study, and have at least one of the following: 1. Age of onset of alcohol dependence prior to age 25; 2. A HAM-D score of greater than or equal to 14 at study entry; 3. Meeting three or more childhood criteria for Antisocial Personality Disorder. Alcohol dependent participants during screening and recruitment who are not provisionally classified as Type B will be provisionally classified as Type A (Kampman et al., 2007), again pending final *post hoc* typological clustering, at which time all participants will be assigned to their correct typological grouping (Babor et al., 1992; Pettinati et al., 2000).

B.2.3. *Post hoc* final typological classification. Given that the diagnostic criteria for Type A vs. Type B classification used in screening may have some level of diagnostic uncertainty with regard to the original definition based upon statistical clustering, *post hoc* K-means clustering will be performed on all alcohol dependent subjects after study completion, utilizing a streamlined version of the typological procedure to ensure accuracy of typological classification (Pettinati et al., 2000). This updated procedure has shown to produce identical results to the method of Babor et al. (1992), while utilizing only validated rating scales as input measures (Pettinati et al., 2000). Specifically, information from thirteen separate intake assessment data sources will be standardized to a common metric range, and then K-means cluster analysis will be performed on these data from all randomized participants, using SAS software, (Babor et al., 1992; Brown et al., 1994; Pettinati et al., 2000). The assessments utilized will be (after Pettinati et al., 2000):

(1) Addiction Severity Index (ASI; McClellan et al., 1992), number of first degree relatives with current or past alcohol problems;

(2) Number of childhood conduct disorder problems as determined by the SCID-II Antisocial Personality Disorder module;

(3) Life Change Index score for "life crisis level" based on lifetime psychosocial stressors (Holmes, 1967);

(4) ASI Alcohol Composite score;

(5) ASI Drug Composite score;

(6) Obsessive-Compulsive Drinking Scale score (Anton et al., 1996);

(7) Average number of drinks per drinking day, last 90 days by Time Line Follow Back (TLFB; Sobell, 1992);

(8) Short Michigan Alcohol Screening Test score (MAST; Selzer et al., 1975);

(9) Medical ASI Composite score;

(10) Legal ASI Composite score;

(11) Family ASI Composite Score;

(12) Psychiatric ASI Composite score;

(13) 24-item baseline HAM-D score.

B.2.4. Selection criteria for healthy control subjects:

(1) age between 21 and 55;

(2) no Axis I DSM-IV diagnosis (except for nicotine dependence);

(3) report drinking less than 10 drinks weekly over the past 90 days prior to study entry by TLFB.

Exclusion criteria are:

(1) Any history of treatment for alcohol or other substance use disorders;

(2) any history of DSM-IV diagnosis of dependence on any psychoactive substances other than nicotine;

(3) any history of DSM-IV diagnosis of Axis I mental illness.

B.2.5. Exclusion criteria for all subjects:

(1) a current (last 12 months) DSM-IV diagnosis of schizophrenia, bipolar disorder, other psychotic disorder, eating disorder, panic disorder with or without agoraphobia;

(2) current use of psychoactive drugs, other than occasional marijuana use ($\leq$ 3 uses per week), as determined by a positive urine screen for narcotics, amphetamines, or sedative hypnotics;

(3) serious alcohol withdrawal symptoms as indicated by a score > 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA);

(4) clinically significant physical abnormalities as indicated by physical examination, hematological laboratory assay, or urinalysis, defined as: hematology and chemistry laboratory tests that are within normal (+/- 10%) limits with the following exceptions: a) liver function tests

(total bilirubin, ALT, AST, and alkaline phosphatase) ≤ 3 x the upper limit of normal, and b) kidney function tests (creatinine and BUN) ≤ 2 x the upper limit of normal;

(5) A screening ECG that demonstrates anything other than normal sinus rhythm, normal conduction, and no clinically significant arrhythmias;

(6) history of epilepsy, seizures, or severe head trauma;

(7) history of alcohol intoxication delirium, alcohol withdrawal delirium or seizure, alcohol-induced persisting dementia, or alcohol-induced psychosis;

(8) treatment with any of the following medications within the last 30 days prior to randomization: antidepressants, anti-convulsants, hypnotics, antipsychotics, psychomotor stimulants, anti-anxiety agents, or cimetidine;

(9) previous treatment with citalopram discontinued due to an adverse event;

(10) pregnancy, nursing, or refusal to use reliable barrier method of birth control, if female;

(11) the presence of metal fragments, pacemaker, or other ferromagnetic material which would prevent safe completion of an MRI scan;

(12) Recent history of radiation exposure which would make exposure to radiation from serial PET scans contraindicated;

(13) Non-zero breath-alcohol level on screening. We will exclude participants who present to study appointments intoxicated, as active alcohol intoxication may interact unpredictably with citalopram and produce unreliable results in assessments of mood or alcohol craving (e.g. Ray and Hutchison, 2007; Ray et al., 2011; see *preliminary data C.2.* above);

(14) Resting vital signs on any study visit outside of acceptable parameters: Pulse of 50-105 bpm, Blood pressures of 90-160 mm Hg systolic, 55-100 mm Hg diastolic;

(15) Any indication of suicidal ideation (i.e. as assessed by question 9 on the BDI-II), or elevated index of depressive symptoms, as evidenced by BDI-II score of ≥20;

(16) Presence in the body of a metal device (e.g., pacemaker, infusion pump, aneurysm clip, metal prosthesis or plate) that could either interfere with the acquisition of the MRI scan of the brain or for whom the MRI scan would pose a potential risk will be excluded.

(16)Radiation exposure: Participation in any other research study involving exposure to ionizing radiation in the past year if the total cumulative exposure from the past research studies and the current research study would exceed the limits described by the FDA in 21 CFR 361.1. Specifically, the total cumulative dose to the whole body, active blood-forming organs, lens of the eye, and gonads must remain below 5 rems, and the cumulated dose to all other organs must remain below 15 rems over the last year.

(17)Baseline QT prolongation (QTc> 455 ms): Given that citalopram has been found to be associated with a dose-dependent risk of ECG QT interval prolongation, in order to avoid the potential risk of causing ventricular arrhythmias including Torsades de Pointes, we will exclude participants from the study who exhibit baseline QTc prolongation.

B.2.6. Criteria for Discontinuation Following Initiation

1. Positive urine drug screen or breath test indicating use of cocaine, methamphetamine, alcohol, opiates, or other abused drugs on any study day;
2. Inability to comply with study procedures;
3. Meet discontinuation criteria due to severe side effects from citalopram infusion;
4. BDI-II score of 20 or greater and/or indicating any suicidal thoughts.
5. Vital signs outside of acceptable range: SBP <90 or >160 mm Hg, DBP <55 or >100 mm Hg, or P <50 or >105 bpm.
6. CIWA score of >10 on any testing day.

B.2.7. Gender, minority, and child representations. Both men and women of all ethnic backgrounds will be recruited for this project. Generally, about 70% of alcohol dependent individuals are men. Research shows no gender differences in cue reactivity for alcohol

(Rubonis et al., 1994; Ray and Hutchison, 2004). However, studies of gender differences on alcohol-related variables in response to *iv* citalopram have not been reported. Thus, we will conduct analysis of gender differences. We will encourage participation of all ethnicities and racial minorities, and anticipate a diverse participant population (See *section E, Human Subjects* for more details). Children will not be studied because the safety of citalopram for alcohol use in children/adolescents has not been demonstrated, and alcohol is illegal for individuals under the age of 21 in the state of California.

B.3. Procedures

B.3.1. Recruitment and informed consent procedures. Participants will be recruited from the community through advertisements, such as flyers and advertisements on the internet (e.g., Craigslist). These procedures have been used successfully to recruit alcohol dependent individuals in previous studies with heavy alcohol drinkers by the consultant, Dr. Lara Ray (Ray and Hutchison, 2007; Ray et al., 2007; Ray et al., 2011). The ads will target non-treatment seeking alcohol-dependent and healthy control men and women.

People who call about the study will receive an individual telephone screen for self-reported inclusion and exclusion criteria and the nature of the study will be further explained. Treatment-seeking individuals will be provided an appropriate referral. Those who appear eligible will be scheduled for an appointment with our staff for an in-person screening session in which we will obtain a medical history and physical exam, administer a battery of individual differences measures, and complete a psychiatric diagnostic interview. A separate consent form will be used for the medical screening. If, after completing the medical history and diagnostic interviews the potential participant still appears eligible, the study will be fully explained including all aspects of procedures, potential side effects, and those who continue to be interested will have blood drawn and a urine sample collected for the laboratory tests outlined for medical eligibility. The P.I. will review each participant's screening results and if those preclude participation, the individual will be telephoned and the reason why the participant cannot continue in the study will be explained.

B.3.2. Incentives for participation. Per VA research guidelines, participants will be compensated for their participation. Recruits will receive $50 for participating in the initial screening interview, since it requires approximately four hours plus blood and urine samples. Participants will be paid $40 for the sMRI scan, $50 for each of the laboratory infusion sessions (i.e., citalopram or saline infusion followed by mood and cue-reactivity assessment), up to $30 each for computer tasks to be done after infusions, $100 for each PET scan, plus a $50 bonus for completing the entire study. Therefore, completing participants may receive up to $500.

B.4. Citalopram Infusions.

B.4.1. General procedures. Participants will be blinded for infusions (citalopram and saline). Infusions will occur in the VA West Los Angeles CRC, on the 3rd floor of the hospital. VA pharmacy staff will provide double-blind study compound on infusion days. An intravenous line will be placed using sterile technique by CRC nursing staff, and citalopram (40 mg or saline control in 250 ml saline) will be infused via perfusion pump over 1h, after Smith et al. (2009). The P.I., a board-certified psychiatrist, will be present during all infusions to monitor for any physical or psychiatric side effects.

B.4.2. Medical monitoring. All infusions will be monitored by the P.I. Participants will be given a 24-hour telephone number for calling the P.I. to discuss side effects which may arise subsequent to infusion days, and office hours will be available as needed. All participants will meet with the P.I. on infusion days to review side effects, discuss ways to manage possible side effects, and to assess for possible complications.

B.5. Assessments: Interviews and Questionnaires

B.5.1. Screening measures. The following will be used to screen for inclusion and exclusion criteria:

(1) Alcohol dependence and other psychiatric diagnoses will be assessed using the *Structured Clinical Interview for DSM-IV* (SCID-IV; First et al., 1995) in order to determine inclusion based on diagnostic criteria. Additionally, age of onset of alcohol dependence and additional axis I DSM-IV diagnoses will be recorded. Research Assistants (RAs, with at least bachelor-level education) will receive formal training on the sensitivity and specificity of psychiatric diagnoses and the SCID algorithm by rating 10 video interviews (www.scid4.com). To ensure inter-rater reliability, ratings will be compared against expert or "Gold Standard" ratings and an overall kappa of .85 across the 10 videos must be achieved prior to participating in SCID administration. RAs will be observed annually by the P.I., and together they will co-rate a live interview to avoid rater drift. Every diagnostic evaluation will be discussed in a weekly meeting led by the P.I.

(2) A *medical history form* to screen for medical conditions that contraindicate taking citalopram. The P.I. will review each participant's history along with laboratory tests.

(3) *Physical examination form* conducted by the P.I. includes a comprehensive physical exam, vital signs, weight, and review of medical systems.

(4) *Blood and urine samples* will be collected to assess: (a) blood LFTs, (b) urine drug screen, (c) blood chemistry screen (including assays for potassium and magnesium) (e) urine pregnancy screen (females only). All tests will be conducted by the hospital laboratory. A urine pregnancy test will also be conducted immediately prior to each procedure day.

(5) *ECG*: a clinical electrocardiogram will be performed as part of the intake physical exam (see exclusion criteria above).

(6) To ensure that participants are not seeking treatment, they will be asked whether they want to receive any treatment now or have received any treatment for alcohol problems (including formal treatment and/or use of self-help groups) in the past 30 days, and will be excluded for positive answers.

(7) Screening questions about quantity and frequency of drinking will be assessed using the 90-day *Time Line Follow Back* (TLFB), (Sobell and Brown, 1996).

(8) *Depression*: the *Hamilton Rating Scale for Depression* (HAM-D 17) is a 17-item measure of depressive symptoms, previously used in studies of pharmacotherapies for alcoholism (e.g., Kampman et al., 2007; Pettinati et al., 2000);

(9) *MRI Safety Screen*: A 1 page questionnaire to screen for any potential risk factors for MRI, including metal implants, fragments, pacemaker, etc.

B.5.2. Measures of baseline alcohol and drug use at Screening

(1) The 90-day *TLFB* interview (Sobell et al., 1980) is a calendar-assisted self-report method with high reliability and validity that will be used to obtain a detailed baseline of quantity and frequency of drinking.

(2) *The Alcohol Dependence Scale* (ADS; Skinner and Allen, 1982) will be used to assess severity of alcohol dependence at baseline. This 25-item scale measures alcohol dependence symptoms over the past 12-months and has been shown to contain items that are relevant for alcohol dependent drinkers (Kahler et al., 2003).

(3) *Addiction Severity Index (ASI-lite):* The ASI-lite is the interviewer's estimate of the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological).

The Lite version is a shorter version of the ASI that retains all questions used to calculate the ASI composite scores.

(4) *Obsessive-Compulsive Alcohol Disorder* scale (Anton et al., 1996). Information from this validated instrument will be used to determine *post hoc* Type A/B cluster membership for alcohol dependent participants.

(5) *Short Michigan Alcohol Screening Test* (Selzer et al., 1975). Information from this validated instrument will be used to determine *post hoc* Type A/B cluster membership for alcohol dependent participants.

B.5.3. Other individual differences measures at screening

(1) Demographic information will be collected, including age, gender, ethnicity, education level, and employment.

(2) Current smoking will be assessed by asking (a) number of cigarettes per day and use of any other form of tobacco, and (b) the *Fagerstrom Test for Nicotine Dependence* (FTND; Heatherton et al., 1991). Although not directly related to any aim, this measure will be investigated for possible interaction with the effects of citalopram, and as dependent measures in their own right given findings that medication affecting drinking behavior and urge to drink often also affects tobacco use and nicotine craving (e.g., Ray et al., 2007).

(3) Conduct disorder symptoms and adult antisocial personality disorder symptoms will be assessed using the *Antisocial Personality Disorder Module of the Structured Clinical Interview for DSM-IV Personality Disorders* (SCID-II; First et al., 1997).

(4) *The Cognitive Reflection Test* (Frederick et al, 2005) is a 3-item questionnaire designed to assess the degree to which a participant relies on impulsive cognitive styles for routine tasks, which has been shown to be largely uncorrelated to measured IQ or scholastic achievement testing.

(5) *Barratt Impulsivity Scale* (BIS-II; Patton et al, 1995): This is a 30-item questionnaire that is self-administered during screening. The questionnaire assesses trait measures of impulsivity, broken up into attentional, motor, and non-planning domains.

(6) *Delay Discounting Task* (~5-8 min): Subjects are given a number of choices between smaller, immediate rewards, and larger, delayed rewards. The results provide an estimate of how steeply individuals discount the future value of money compared to their estimation of the present value. Rates of delay discounting (DD) have been demonstrated to be independent of measured IQ. An increased rate of DD (signifying a steeper discounting of the future value of money) has been observed in alcoholics, heroin addicts, cocaine addicts, smokers, and pathological gamblers;

(7) *Satisficing/Maximizing Behavior Assessment*: (Schwartz et al., 2003) A survey measuring the extent to which participants explore different options while making decisions.

(8) *Life Change Index* score for “life crisis level” based on lifetime psychosocial stressors (Holmes, 1967), which will be used to determine alcohol dependence typology in alcohol-dependent participants.

B.5.4. Baseline and repeated assessments. The following measures will be administered at baseline and then prior to procedures on every procedure day.

(1) Breath Alcohol assessment via *breathalyzer*, and *urine drug screen* (with *urine pregnancy test* for female participants).

(2) *Drinking behavior*: the *TLFB* (Sobell et al., 1980) will be the primary measure of prior drinking behavior in the study.

(3) *Beck Depression Inventory, Revised* (BDI-II) is a 22-item measure of depressive symptomatology, widely used in psychological research and practice.

(4) *Brief Symptom Inventory* (BSI) is a 53-item measure of global psychiatric symptomatology, used in psychiatric research to assess for psychiatric symptoms.

(5) *Alcohol craving*: the *Penn Alcohol Craving Scale* (PACS) is a 5-item, self-report measure of craving for alcohol during the previous week (Flannery et al., 1999).

(6) *Clinical Institute for Withdrawal from Alcohol scale* (CIWA): This is a 10-item rater-administered scale which assesses for common signs and symptoms of alcohol withdrawal. Participants who score ≥10 on any study day will be excluded from the study and referred immediately for medical treatment (See exclusion criteria, above).

(7) *Adverse Events*: An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the study medications. For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluations. Clinically significant blood pressure elevations and changes in psychiatric symptomatology (including suicidal ideation) will be classified as AEs. If an AE is reported to study personnel that requires medical attention, it will be reported to a study physician immediately. Study physicians will assess subjects for any medical or psychiatric side effects. All AEs will be recorded on an adverse event case record form that is updated at least weekly. Unresolved AEs will be assessed daily by study personnel starting as soon as subjects give informed consent.

B.5.5. Magnetic Resonance Imaging Protocol

An MRI scan of the brain will be obtained prior to infusion procedures, on a 1.5-T scanner (Signa; GE Medical Systems, Milwaukee, WI) in the same building as the CRC and PET scanner, in order to aid in localization of regions on the PET scans. The MRI will have the following specifications: three-dimensional Fourier-transform (3DFT) spoiled-gradient-recalled acquisition with TR=30ms, TE=7ms, 30 degree angle, 2 acquisitions, 256 x 192 view matrix. The MRI scanning procedure typically lasts ~ 30 minutes. The acquired volume will be reconstructed as roughly 90 contiguous 1.5-mm thick transaxial slices.

B.5.6. Infusion assessments.

(1) *Profile of Mood States* (POMS)*, short version*. A self-report questionnaire that measures dimensions of affect or mood. It consists of 65 adjectives to which the client responds according to a 5-point scale ranging from ‘not at all’ to ‘extremely’. The POMS will assess changes in mood states from pre- to post- infusion (McNair et al., 1971).

(2) *Alcohol Urge Questionnaire (AUQ)*. The AUQ is an 8-item scale where subjects rate their craving for alcohol at the present moment. Participants will be asked to use a 7-point Likert scale expressing agreement with statements such as “I crave a drink right now.” The AUQ is appropriate for use in laboratory investigations examining state levels of urge to drink (Bohn et al., 1995; Mackillop, 2006).

(3) Heart rate and blood pressure will be measured prior to infusion, and 1 hour after infusion, to ensure that vital signs remain within safety parameters (see *B.2.5.* above.)

B 5.7. Cue reactivity assessment (CR)

CR Procedures. (~15 min total time) In this trial, the CR will follow each of the intravenous infusions (i.e., citalopram 40 mg or saline control). Specifically, participants will receive standardized instructions about the assessment while becoming acclimated to the laboratory and psychophysiological monitors. Sessions will begin with a 3-minute relaxation period, in which participants are asked to sit quietly and do nothing. Participants will then hold and smell a glass of water for 3 minutes as a standard procedure to control for the effects of simple exposure to any potable liquid, followed by another 3-minute relaxation period. Next, the participant will hold and smell a glass of a preferred alcoholic beverage for three 3-minute trials. During each trial, the participant will be asked to sniff the beverage for 5 seconds each time a tone sounds: 13 tones sound during each 3-minute block of time with variable intervals to ensure that all receive the same olfactory exposure. Order is not counterbalanced because of carryover effects that are known to occur (Monti et al., 1987) and that would interfere with determination of CR. The water trial provides a baseline that controls for all aspects of stimuli and movement except the nature of the beverage.

CR Measures. After every 3 minutes of exposure, each participant will rate his/her urge to drink alcohol level on an 7-point Likert scale via the AUQ, from "no urge at all" to "extremely strong urge." The term urge to drink is explained to the participant as "want, desire, craving, thirst for, or wish to drink." Urges ratings will be the primary outcome variable for *Specific Aim 2.*

B.5.8. Post-Infusion Assessment of Mood, Personality, and Decision-Making

These assessments will occur over approximately 45 min, immediately after the CR measures described above. The following assessments will be administered by the RA:

(1) *Delay Discounting Task* (~5-8 min): Subjects are given a number of choices between smaller, immediate rewards, and larger, delayed rewards. The results provide an estimate of how steeply individuals discount the future value of money compared to their estimation of the present value. Rates of delay discounting (DD) have been demonstrated to be independent of measured IQ. An increased rate of DD (signifying a steeper discounting of the future value of money) has been observed in alcoholics, heroin addicts, cocaine addicts, smokers, and pathological gamblers.

(2) *Simple Reversal Learning Task* (SRLT, ~10 min): Participants perform a simple categorization task with reversal stages. Participants learn to make one of two key-press responses to a set of abstract visual patterns on the basis of trial-by-trial feedback. Participants are trained on stimuli that have varying numbers of trials before reversal, and reversals occur throughout most of the training sessions, but not all, in order to make them unpredictable. Subjects view the stimuli (which are novel visual patterns) and must make a key press. Immediately after the response, feedback will appear on the screen: "correct", "incorrect", or a "no response recorded" message if no response is made within the response window. In order to minimize the effect of practice on performance, we will use different sets of stimuli in each test run. Performance on RLTs has been shown to be sensitive to serotonergic pharmacology.

(3) *Loss Aversion Gambling task* (LAG, ~10 min): Participants will first be presented with a possible gamble (i.e., "Would you choose $10 for sure or a 50% chance to win $25?") and asked to judge whether they would accept the gamble by pressing one of two keys. Participants will receive one of several stipend types, plus an incentive-compatible payment depending upon their choices during the decision making task and the outcome of relevant chance gambles. Although some gambles will entail the possibility of monetary loss, no participant will ever experience actual monetary loss during the task. The total money that a participant could win in this task is $15.

(4) *Balloon Analogue Risk Task* (BART, ~10-12 min): The BART is a computer based assessment of risk taking behavior. A subject uses a computer mouse to click a balloon pump that inflates a balloon on the screen. Subjects are informed that the objective of the task is to get the largest amount of money possible while avoiding balloon explosions. Participants are not

given any detailed information about the probability of the balloon exploding. Each pump of the balloon without an explosion places money into a money reserve. Should the subject pop their balloon they lose all money and another balloon appears. At any time during a trial the subject can click "collect money" and transfer all money from a temporary bank account to a permanent account where a new total is updated. Participants may earn up to $15 based upon their performance in this task.

B.7. PET Scan Acquisition and Analysis

After the collection of the measures of mood state and decision-making on infusion days, participants will be escorted to the basement of the hospital where the PET scan is located. CR-induced craving for alcohol quickly subsides after a peak ~6 min into the CR procedure (Monti et al., 1993). Given that > 45 min will have elapsed between the end of the cue-induced craving session and the beginning of the PET scanning procedures (which includes ~30 min of mood state assessments), CR procedures will not affect the results of subsequent PET scanning (~90 min duration); indeed, alcohol CR-induced craving in alcohol dependent subjects has previously been shown to produce no change in subsequent PET scan signals, compared to a non-CR baseline (Lingford-Hughes et al., 2006). [^{18}F]fallypride will be synthesized in the Cyclotron Facility of the VA by procedures currently in use for ongoing studies. [^{18}F]fallypride will be synthesized via nucleophilic substitution of tosyl-fallypride with [^{18}F]fluoride ion, supported by Investigational New Drug (IND) Application no.78,226 to Dr. London. Each batch of radiotracer will be tested for quality control including (radiochemical purity, specific activity, apyrogenicity).

After placement in the PET scanner, participants will be given a bolus injection of [^{18}F]fallypride (~5 mCi in 30 sec). PET scans will be obtained on a Philips GEMINI TruFlight Positron Emission Tomography and Computed Tomography (CT) system (Philips Medical Systems, Eindhoven, Netherlands), with CT scans being acquired for attenuation correction. Scans will be acquired in the 3-dimensional mode, with the scanner having a diameter of 90 cm and an axial field of view set to 18 cm. The transverse and axial resolutions of this scanner are 4.8 mm at the center. Scans will be acquired as series of 8 10-min frames with a short break for participant comfort (~90 minutes total time).

[18F]fallypride will be prepared and administered by an established method (Mukherjee et al., 1995), as in previous and ongoing studies by Dr. London (e.g., Lee et al., 2009; see *preliminary data C.5.*).

PET analysis will be performed using ROIs drawn on MRIs by a trained research assistants using a Macintosh-based software program (PACE) that has been used in many clinical studies (e.g., Brody et al., 2010). ROIs will be reviewed in team meetings with the mentors, Dr. Brody and Dr. London. Based on prior reports and our preliminary studies, ROIs will include the dorsal and ventral caudate (Cd) and dorsal and ventral putamen, with the cerebellum being drawn as a reference region (Lee et al., 2009; Brody et al., 2010). The dorsal and ventral halves of both Cd and putamen will be drawn in approximately 6 planes. Cerebellum will be drawn in approximately 14 planes. ROIs transferred onto PET from MRI will be visually inspected to ensure no gross misalignments of the co-registered images. Hand drawn ROIs have been shown to have consistent findings between those drawn on MRI and transferred to PET and those drawn directly on [^{18}F]fallypride PET images (Lee et al, 2009; Brody et al., 2010).

B.8. Statistical Methodology

The distributions of raw and change scores (for clinical rating scales and ROI measures) will be examined for suitability for parametric analyses. Analysis of PET data will be performed for binding potential (BP) in the two primary ROIs, where BP = $C_{ROI}/C_{cerebellum} - 1$ with C = mean counts, and the two primary ROIs are the ventral Cd and putamen. The same calculations will also be performed for the dorsal Cd and putamen, which are easily visible on [^{18}F]fallypride

scans. Statistical calculations will be performed using the software package SAS (v. 9.2; SAS Institute Inc., 2008).

B.9. Sample Size Power Calculation.

The group sample sizes for this study (n=20 each of Type A, Type B, and healthy controls) were chosen based upon the following statistical considerations, in order to have an adequately sized sample to be able to detect a group difference given expected experimental differences in the context of expected variance in the data. Power analyses were conducted to determine the sample size needed to achieve a power of 0.80 at a two-tailed alpha level of 0.05, utilizing *Java Applets for Power and Sample Size* software (Lenth, 2009).

B.9.1. Aim 1. *Decreased dopamine $D_{2/3}$ receptor availability with citalopram in Type B alcoholics compared to healthy control subjects*. Based upon data from Smith et al. (2009), a single dose of *iv* citalopram (40 mg) resulted in a decrease in striatal dopamine receptor availability from 3.81+/-0.29 to 3.64+/-0.27 (mean +/- s.d.) compared to placebo. Given that the difference to be observed between groups would be of a comparable magnitude, with a similar variance, adequate power to detect a group difference is achieved with sample sizes of n=16.

B.9.2. Aim 2. *Craving with citalopram will be increased in Type B alcoholics compared to healthy control subjects*. Based on data from section C.1. (Zorick et al., 2011b) from methamphetamine-dependent individuals who had a poor response to the SSRI sertraline, we expect increased craving for alcohol in Type B alcoholics taking who receive an SSRI compared to those who receive placebo. Given the magnitude of the 1st week difference in craving in the methamphetamine study, and the sample variances of the levels of craving for the population (4.2±1.5 vs. 3.1±2.1 for worse-sertraline vs. placebo; Visual Analogue Scale craving score (0-10 range) ± s.d.), adequate power to detect a similarly sized group difference with similarly sized variances is achieved with sample sizes of n=14 each.

B.9.3. Aim 3. *Striatal dopamine $D_{2/3}$ receptor availability in Type B alcoholics will be correlated to measures of craving for alcohol after citalopram infusion*. Based upon data from Heinz et al. (2004), for the correlation of striatal dopamine receptor availability and craving for alcohol in alcohol-dependent individuals of -0.9, adequate power to detect a correlation at least as strong as that observed is achieved with a sample size of n=12.

B.10. Data Analysis Plan

In order to examine the study hypotheses of group differences and treatment effects, statistical analyses will be conducted using SAS software. K-means clustering for final group membership of all study participants will be performed on the 13 individual data sources discussed in B.2.3 above. Briefly, scores from all instruments will be normalized to a common metric range to avoid overrepresentation of any individual score, and then data on all 13 instruments will be utilized in a K-means clustering algorithm (Babor et al., 1992; Pettinati et al., 2000).

Aim 1: To determine change in striatal dopamine receptor $D_{2/3}$ receptor availability (measured with the radiotracer [^{18}F]fallypride and PET scanning) from before to after iv citalopram (40 mg, compared to iv saline control) among different subject groups. Similar to prior research (see sections C3-5, preliminary data), dopamine $D_{2/3}$ receptor availability from hand-drawn ROIs will be extracted from striatal regions using the cerebellum as a reference tissue. For group comparisons, a mixed linear procedure will be utilized that represents a generalization of the standard linear model (GLM) procedure, such that the data are allowed to exhibit correlation and non-constant variability. The mixed linear model permits the modeling not only the means of the data, but their variances and covariances as well. This approach is consistent with that of Kampman et al. (2007) and with our previous work in pharmacotherapy studies for addictive disorders (e.g., Zorick et al., 2009). Demographic variables which differ between groups (e.g., age, gender, smoking status, lifetime drinking history) will be utilized as covariates.

Aim 2: To test the effect of citalopram (40 mg iv vs. saline iv control) on measures of alcohol craving and mood among different subject groups. A MANOVA will be performed, using changes in craving and mood assessments as dependent variables, and group membership (Type A/B or control) as an independent variable. Demographic and laboratory variables (such as age, smoking status, gender, lifetime drinking history) will be compared between groups, and will be used as nuisance covariates, if there are group differences in these variables. Post-hoc t-tests will be used to determine which independent variables account for significant findings.

Aim 3: To assess whether changes in striatal $D_{2/3}$ receptor availability with iv citalopram (40 mg, compared to iv saline control) are related to measures of craving for alcohol. For correlations, Pearson's moment correlation will be performed using SAS with adjustment for covariates that may differ between study groups (such as age, smoking status, gender, lifetime drinking history). Region-specific dopamine $D_{2/3}$ receptor availability in each participant in each study condition will be correlated with the VAS measure of cue-induced alcohol craving.

B.11. Timeline of Proposed Activities

Based upon prior experience with recruitment of subjects for studies of addictive behaviors, we anticipate that we will have a 60% drop out rate for alcohol-dependent participants, and about a 50% drop out rate for healthy control subjects. This estimated rate of study non-completion includes those recruited individuals who pass phone screening who either fail the medical safety screen (for active medical issues, e.g.), who drop out for procedural reasons (i.e. illicit drug use during the study), who voluntarily withdraw their participation for personal reasons, or any other reason. Therefore, to achieve the final goal of 40 completed alcohol-dependent participants (20 each Type A and Type B), we anticipate screening 100 participants, and to achieve the final goal of 20 completed healthy control participants, we anticipate screening 40.

Table B.11. Timeline for Study Activities. Abbreviations: Alcohol-Dependent Participants: AD; Healthy Control Participants: HC.

	Year 1	Year 2	Year 3	Year 4	Year 5	Totals
Screened	10AD/4HC	20AD/8HC	32AD/16HC	16AD/4HC	8AD/4HC	100AD/ 40HC
Completed	4AD/2HC	8AD/4HC	16AD/8HC	8AD/4HC	4AD/2HC	40AD/ 20HC
Ongoing Activities	IRB Approval/ Education and Training first 6 months	Data fidelity checks and preliminary analyses	Data fidelity checks and presentation of preliminary findings at conferences	Data analysis and manuscript preparation	Manuscript submission and future grant writing, last 6 months	

C. **Human Subjects Participation**

C.1.1. Subject Participation Overview: 20 completing subjects will be recruited in each of 3 subject groups (20 Type A and 20 Type B alcohol dependent subjects, along with 20 healthy control subjects) for this 5-year study. Recruitment will be accomplished by using flyers, print ads, and radio advertisements. These media will direct potential participants to call a phone number for additional information if they are interested in participating.

Those who call the toll-free number will be informed about the general requirements of the study. Appointments for face-to-face screening interviews will be scheduled for those who maintain interest. During these screening interviews, participants will read the informed consent document and discuss any questions or concerns they have with research staff, including the P.I. Participants who remain interested in taking part will sign the consent document. At several times during this screening process, participants will be informed that treatment is available and referrals will be provided if desired. Enrolled participants who meet the inclusion criteria will be scheduled for a session of structural MRI scanning (~1 h; see Table C.1.).

C.1.2. Procedures (see Table C.1.): Research subjects will enter the study upon completion of an interview and questionnaires on drug use history and a screening evaluation, which will include a comprehensive medical history, physical examination, EKG testing, and laboratory blood and urine screening. They must provide urine samples negative for any illicit substance and report no current or prior drug dependence (other than nicotine dependence). We will collect a urine sample for drug testing, and test for alcohol breath level in each participant immediately after we receive informed consent. Urine samples will also be collected on procedure days for all subjects to screen for cocaine, amphetamine, MA, opiates, cannabinoids, and benzodiazepines.

We will also assess for evidence of possible psychiatric disorders, status of neuropsychological functioning, and current use of medications. During the study, they will be required to refrain from illicit and prescription drug use; compliance will be confirmed with urine drug screen and breath alcohol level testing on all procedure days. Prior to each procedure day subjects will be asked to remain abstinent from alcohol and other illicit substances.

On infusion days, participants will be escorted to the VA WLA Clinical Research Center (CRC) for infusions and assessment of mood and craving. On each infusion day, each subject will participate in a study arm with citalopram 40 mg *iv* or matched saline control infusion, double-blinded. The second infusion day will occur at least 1 week after completion of the first infusion. After infusion of each test compound (citalopram 40 mg or saline, *iv*), subjects will self-rate alcohol craving, followed by a 15 min session to elicit measures of alcohol cue-induced craving. Next, participants will answer a series of paper- and computer-based questionnaires about their mood state that will last about 30 min. Subsequently, participants will be escorted to the VA PET facility (in the basement of the same building as the CRC) for PET scanning with [^{18}F]fallypride (~90 min).

Table C.1. Timeline for Study Procedures

Study Day	Procedures
Intake	Consent, eligibility, SCID, Medical History and Physical (~4 h)
Participants released to the community	
sMRI Scanning	Structural MRI scanning (~1 h).
Participants released to community	
Infusion day 1 (40 mg citalopram or saline, iv)	
Test compound 1	IV infusion over 1 h.
Craving Assessment	Baseline and cue-induced craving for alcohol assessment (~15 min)

Mood, Personality, Decision-Making State Testing	Paper and computer-based questionnaires and tasks (~45 min)
[^{18}F]fallypride PET Scan 1	~90 min

Participants released to community >1 week

Infusion day 2 (40 mg citalopram or saline, iv), opposite of test compound 1	
Test compound 2	IV infusion over 1 h.
Craving Assessment	Baseline and cue-induced craving for alcohol assessment (~15 min)
Mood, Personality, Decision-Making State Testing	Paper and computer-based questionnaires and tasks (~45 min)
[^{18}F]fallypride PET Scan 2	~90 min
Participants will be discharged from the study after completion of Infusion day 2	

Nausea, headache, fatigue, and tachycardia may be side effects of citalopram. High doses of citalopram have been associated with a risk of ECG QTc prolongation, and concomitant risk of ventricular arrthymias, including Torsades de Pointes. To minimize the risk associated with citalopram administration, the study procedures include a plan for careful participant assessment and monitoring. A medical screening will be conducted that consists of a history and physical, baseline ECG, as well as blood tests including hematology, chemistry, renal and hepatic function tests. In order to qualify for the study, participants must have vital signs that fall within the acceptable range, must have a normal ECG and baseline QTc<455 ms, and participants must continue to meet inclusion criteria to remain in the study (see *section B.2.5.* above for vital signs criteria).

Participants will also have blood samples taken for RPR, HIV and Hepatitis C testing, and will also have a PPD placed during medical screening, to be read by CRC nursing staff in 48-72 h. If subjects are PPD positive, a chest x-ray will be performed to rule out active pulmonary lesions indicative of active tuberculosis

Participants will be required to refrain from illicit and prescription drug use for the duration of the study and this will be confirmed with urine toxicology testing on testing days. Participants will be required to refrain from drinking on testing/procedure days during the study, and this will be confirmed by breath alcohol testing on testing days.

Caffeine will be restricted on study days for least 2 h prior to infusion days and MRI scan day. Participants will be permitted to drink their normal daily intake of caffeine, given the caveat above. Cigarette smoking will be permitted during the study. The incorporation of smoke breaks during testing days assures that acute nicotine withdrawal does not negatively impact performance on cognitive tests or neuroimaging.

C.2. Characteristics of Subjects

C.2.1. Number of subjects: Over the course of the project, a total of 100 alcohol-dependent subjects and 40 healthy control subjects will be recruited as potential participants, with the final sample (with complete data) to be 20 subjects in each group (Type A and B alcohol-dependent, and healthy control subjects). We estimate that about 60% of the alcohol-dependent participants we enroll will either voluntarily leave the study, wash out, or be lost to follow up during the study; and, that roughly 50% of the healthy control participants enrolled will go on to complete the study. Based upon the study's location at the West Los Angeles VA, Veterans will be recruited as participants, and will be expected to be highly represented in the study population.

C.2.2. Gender and ethnicity: Alcohol dependence is more common among men than women, but we intend to recruit a representative sample of the population for the study. Minority subjects are expected to be represented at about 40% based upon prior studies with substance using populations in the West LA area.

C.2.3. Age range: Subjects will be between the ages of 21 and 55 years old, as the target population is adults with histories of alcohol dependence, and to avoid age- and alcohol-related cognitive changes in older individuals.

C.2.4. Health status: Potential subjects will be those individuals who are in adequate health to permit their participation in study procedures without likelihood of experiencing undue harms or risks (see *Inclusion Criteria, Exclusion Criteria* and *Criteria for Discontinuation* above).

C.3. Sources of Research Material Obtained from Human Subjects

C.3.1. Specimens and safety measurements: Blood and urine will be taken for laboratory tests, and blood pressure, heart rate, and oral temperature will be measured upon admission and on each procedure day. Blood samples and urine samples for laboratory examination will be disposed of in standard fashion.

c.3.2. Mood and craving state assessment: Participants will complete several pen and paper and computer-based questionnaires to assess their current mood state and levels of craving for alcohol on procedure days. Computerized data will be stored on a laptop computer and backed up to a main database in the Brody lab. Other behavioral measurements and paper questionnaires will be stored for entry into the Brody lab computer database using double entry for accuracy.

C.3.3. Structural Magnetic Resonance Imaging: Participants will complete an sMRI scan for use in PET scan co-registration. Electronic images from the scan will be transferred to the Brody lab imaging database.

C.3.4. Positron Emission Tomography: Participants will undergo PET scanning with [18F]fallypride as a radiotracer. Electronic images of the time evolution of radiotracer binding will be transferred to the Brody lab imaging database for storage.

C.3.5. Medical records and data: Clinical features that characterize each subject's alcohol use history and details of their personal history will be recorded. These data will be obtained through the SCID to determine diagnoses, and the Time Line Follow Back (Sobell et al., 1996). Demographic data (age, ethnicity, gender) and general medical data (other medical diagnoses, non-psychotropic medications, etc.) will also be recorded. Subjects will complete at intake and on infusion days the Beck Depression Inventory (BDI-II), a 21-item self-report inventory that focuses on subjective feelings of depression.

C.3.6. Maintenance and security of research material: The research material obtained will be data in the form of digital images and coded files, which will be used for further analysis. Risks to confidentiality from the proposed research will be minimized by using a coding system for all data collected, with personal identifying information kept in a secure area accessible only to the investigators. Results of measurements and tests will be stored as data that are associated with a unique subject identification number; one CD will be retained on-site in a locked office accessible to the P.I. (Dr. Zorick), and mentor (Dr. Brody) and the other is kept in a secure, off-site location for backup, accessible to the P.I. and the co-investigators. After processing, all data are exported into spreadsheets. All clinical data are scored, transferred to a summary sheet, and then entered into a database system on a local area network keyed to the same unique identification number, and to be used specifically for research purposes per authorization of the P.I. exclusively.

C.4. Recruitment of Subjects and Consent Procedures

C.4.1. Recruitment, Screening and Enrollment: We will recruit non-treatment-seeking subjects from the greater Los Angeles area by newspaper, Internet, and radio advertisements and flyers. In telephone interviews, we will describe the study and obtain information about subject eligibility. Veterans will be particularly encouraged to enroll, and are expected to be highly represented in the subject population. Volunteers who meet initial criteria will be invited to read the consent form and if willing to participate, give informed consent, as approved by the VA

Institutional Review Board (IRB). After providing informed consent, subjects will undergo an evaluation that will include physical examination and medical history, psychiatric diagnostic interview, self-report questionnaires, and urine and blood tests.

C.4.2. Consent procedures: The consent form, outlining procedures, potential risks and anticipated benefits, right to withdraw, and confidentiality, will be read to each participant, allowing time for questions. During the recruitment and consent process, participants will be told about a Certificate of Confidentiality obtained from NIDA under PL 94-255, which limits the collected data from being used in any criminal or legal proceedings. If the subject agrees to participate, two consent forms will be signed by both the study participant and the principal investigator, indicating a mutual understanding of the purpose of the study and confidentiality precautions. The study participant will be provided with a signed copy of the consent form, which will contain contact addresses and telephone numbers for the investigators and the VA IRB.

C.4.3. IRB approval: All procedures proposed in this study will be approved by the VA IRB. The equipment and methods to be utilized have been employed in several VA- and NIDA-supported projects. All participants will receive a copy of the Subject's Bill of Rights prior to giving consent to participate.

C.5. Potential Risks to Subjects

C.5.1. Risk of blood sampling during screening: When having blood drawn participants may experience some discomfort as a result of the needle prick in the arm. Some bruising or slight bleeding may occur. Although infection is possible, it is extremely rare, because the needle is sterile and disposable. Occasionally, people feel lightheaded or faint when blood is drawn, but the volume taken will be small (around 10 ml per blood draw).

C.5.2. Risk of abstinence from alcohol: Initiating acute abstinence from alcohol in alcohol-dependent individuals can cause serious withdrawal symptoms, which may include behavioral agitation, hypertension, lowered seizure threshold, and in severe cases, delirium tremens. Therefore, we will exclude subjects with a history of severe alcohol withdrawal symptoms, or active severe alcohol withdrawal symptoms (see exclusion criteria above).

C.5.3. Risks of intravenous saline infusions: When having an intravenous line placed, some discomfort, bruising, or bleeding may occur. With intravenous saline infusions, infiltration of the intravenous line site is possible, which can result in swelling, pain, inflammation, and localized cellulitis or superficial thrombophebitis.

C.5.4. Risks of citalopram administration: Based upon randomized controlled trials, the following side effects have been to occur more frequently in individuals taking citalopram than in placebo-treated individuals (in order of declining frequency): nausea, dry mouth, somnolence, insomnia, dizziness, diarrhea, tremor, and sexual side effects (including ejaculatory delay, decreased libido, and impotence). Postmarketing surveillance of pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. As a result, the FDA has included the following "black box" warning in the package insert of all serotonergic antidepressants prescribed to patients in the US:

> *Suicidality and Antidepressant Drugs*
>
> *Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of citalopram or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase*

in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Citalopram is not approved for use in pediatric patients.

The SCID-IV will be used on all subjects to exclude those with any active Axis I clinical disorder (except alcohol and nicotine dependence), in order to reduce the possibility that participants with active mood disorders will receive study procedures. Also, all participants will be screened with the BDI-II on screening and all procedure days, and those individuals with suicidal thoughts and/or elevated depression scores will be excluded from further study participation (see exclusion criteria above).

Based upon evidence from post-marketing surveillance, the FDA found that citalopram is associated with a dose-dependent prolongation of the ECG QTc interval, which increases the risk for ventricular arrhythmias, including Torsade de Pointes. As a result, they released the following additional "black box" warning for healthcare professionals, originally on 8/24/11, and subsequently modified on 3/27/12:

- *Citalopram causes dose-dependent QT interval prolongation. Citalopram should no longer be prescribed at doses greater than 40 mg per day.*
- *Citalopram should not be used in patients with congenital long QT syndrome.*
- *Patients with congestive heart failure, bradyarrhythmias, or predisposition to hypokalemia or hypomagnesemia because of concomitant illness or drugs, are at higher risk of developing Torsade de Pointes.*
- *Hypokalemia and hypomagnesemia should be corrected before administering citalopram. Electrolytes should be monitored as clinically indicated.*
- *Consider more frequent electrocardiogram (ECG) monitoring in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval.*
- *20 mg per day is the <u>maximum</u> recommended dose for patients with hepatic impairment, who are greater than 60 years of age, who are CYP 2C19 poor metabolizers, or who are taking concomitant cimetidine (Tagamet®), because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes.*
- *No dose adjustment is necessary for patients with mild or moderate renal impairment.*
- *Advise patients to contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking citalopram.*
- *Report adverse events involving citalopram to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.*

In order to minimize the cardiac risk to participants, we will utilize only a single 40 mg dose of citalopram, and only to healthy participants between 21 and 55 years of age. All study participants will undergo an extensive medical screening procedure, which will include a full history and physical examination, including baseline ECG and laboratory studies, which will include assays for potassium and magnesium. Participants with any history of cardiac disease,

arrhythmia, abnormal laboratory values, or abnormal screening ECG will be excluded from the study. Participants taking cimetidine will be excluded from the study. Participants with baseline QTc prolongation (QTc > 455 ms) will also be excluded from the study to minimize the risk of citalopram administration.

C.5.5. Risk of MRI: There are no known risks associated with the MRI scanning procedures; however, the magnetism of the machine does attract certain metals. Therefore, if a subject would fail to make the investigator aware of the presence of such a device (e.g., cardiac pacemaker, artificial heart valve, implanted infusion pump, cochlear implant, spinal cord stimulator) in his or her body and were to be scanned, the magnetism could affect or stop the device from working properly.

C.5.6. Risk of PET: The PET scan entails exposure to a small amount of radiation. The maximum total amount of radiation per scan is 606 mrem. The maximum radiation dose for the entire study (two PET scans) is 24% of the annual limit for those people who work with radiation (e.g., x-ray technicians, radiologists etc.). The legal radiation limit for these people is 5000 mrem/year. The radiation dose received in this study is well below the levels that are thought to result in significant risk of harmful effects. The radioactivity disappears very quickly; half of the radiation will disappear within 2 hours and the remainder will disappear within 24 hours.

C.5.7. Psychological Risk: The interview instruments request information of a personal nature; some respondents might experience embarrassment and unease because of items about medical conditions, health-related behaviors, or stigmatized behaviors such as alcohol or drug use. Subjects are forewarned of this remote possibility and notified that discomfort with questions may be dealt with by discussing the resultant discomfort with the P.I. to help resolve the issue or, in some cases, by declining to answer particularly troubling questions.

During the MRI or PET scans, subjects may experience some anxiety or claustrophobia associated with confinement in the scan apparatus. Both the MRI and PET scanning procedure requires that the subject be confined in a small, partially enclosed space. The sound of the MRI scanner can be loud, but will be reduced by special earplugs. The scan procedures may be boring or difficult. All efforts will be made to assist the subject in remaining calm and as comfortable as possible.

Testing in the CRC and the administration of rating scales are procedures with minimal risk to subjects. Typical risks associated with these procedures involve fatigue, boredom, and frustration. Subjects will be counseled to be prepared for the experience and encouraged to bring reading materials or other items that will help them pass the time.

Participants may experience some symptoms from brief alcohol abstinence. These may include restlessness, anxiety, depressed mood, irritability, or difficulty concentrating.

C.5.7. Risk Classification: Based on the procedures described, the overall risk of this research is classified as "more than minimal risk". Based on the HHS/FDA Regulations (45 CFR 46), a classification of "minimal risk" is given when the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological exams or tests.

C.6. Procedures for Protecting against or Minimizing Potential Risks

C.6.1. Safety Procedure Overview: Subjects will be fully informed of potential risks (described above), which has been considered and addressed in extensive previous human research. Attempts will be made to make the subject as comfortable as possible during his or her participation in the study. Attempts will be made to make the subject as physically comfortable as possible while undergoing laboratory and physical assessments and tests. For example, a pillow and blanket will be provided when possible, as will refreshments following

blood draws or before and after lengthy procedures. Subjects will be told that they can request breaks when needed during assessments that can be interrupted without compromising results.

To minimize the potential risk of exposure to a magnetic field, subjects will be queried as to whether they have any metals or devices (see above) implanted, and if so, will be excluded from participation. Safety screening forms based on guidelines distributed by the International Society for Magnetic Resonance in Medicine will be used. Subjects will also be informed of the consequences that could result in undergoing an MRI scan with such an implanted device present. To minimize any potential for exposure of a fetus to low levels of magnetic activity, pregnant women will be excluded and fertile women will be required to use acceptable birth control methods as described above.

To minimize the potential risk of exposure to the small amount of radiation from the PET scans, subjects will be queried as to their recent history (over the last year) of radiation exposure. Any individual indicating that they have received exposure to more than 5 rems of radiation over the last year will be excluded from the study.

Risks associated with citalopram treatment will be minimized through careful assessment and monitoring. Psychiatric screening will consist of a diagnostic interview with the SCID, and screening for depressive symptoms and suicidality with the BDI-II. Medical screening will consist of a history and physical exam, including ECG, and blood tests including hematology, chemistry, renal and hepatic function tests. Subjects will be seen by P.I. on every infusion day to assess for possible side effects during the study. The duration of treatment with citalopram is extremely brief (only 1 dose of active compound, *iv*).

The dose of citalopram chosen for the study (40 mg *iv*) is a standard therapeutic dose for a ~75 kg human subject (Smith et al., 2009). Vital signs will be monitored on each procedure day for participants; participants with persistently elevated vital signs (>5 min. duration; *see section C.6.2.* below for criteria) will be withdrawn from the study.

C.6.2. Safety Procedures: All trials conducted by both the Brody and London laboratories use a set of safety procedures to ensure safe participation during the research trial. The P.I. assumes primary medical responsibility for each participant and personally evaluates any significant complaints, clinical adverse events, and abnormal laboratory findings. Weekly rounds are held with the full study team and the status of each participant is reviewed to assess medical and psychiatric safety, and data completion. Consistent monitoring of participant progress provides one level of safety procedures. Another level of safety procedures involves evaluation of data collected (especially item 9 of the BDI-II that assesses suicidal intentions) and of verbal reports of suicidal and/or homicidal intent to staff members. Participants assessed by the P.I. at any point to be a danger to self or others or who are judged to be in grave danger due to extreme psychiatric problems will be discontinued from the study and connected with an appropriate treatment facility. All staff receive training in identifying suicide/homicide risks and/or signs of intoxication and in following the steps needed to appropriately respond to these signs. Vital signs including heart rate and blood pressure will be checked on infusion day visits during the study. Any vital sign abnormalities during study visits meeting the criteria for high-risk cardiovascular status (see *section B.2.5.* above) will prompt immediate notification of the study physician who will assess the patient and take appropriate clinical action.

C.6.3. Provisions for addressing risks and possible adverse effects: In addition to those measures to protect subjects noted above, careful clinical procedures will be followed to avoid any potential harm to subjects from possible adverse medical reactions or from study conditions such as infusion procedures in the CRC. Subjects will be monitored closely by the medical staff upon induction into and throughout the study. They will be withdrawn from participation if they show signs of serious adverse reactions that pose a threat to their physical or psychological health. In the unlikely event that a subject experiences a medical emergency, the VA CRC is fully prepared to respond to any situation that may arise. It is located on the third floor of the West Los Angeles VA Medical Center and is fully staffed with physicians and nurses. The

general and psychiatric emergency rooms are located two minutes away on the 1st floor of the hospital. There is a 24-h medical Emergency Code team in the hospital. Physicians and nurses in the CRC are fully trained to respond to all types of medical and psychiatric emergencies. A fully equipped crash cart is located on the unit. All potential risks will be thoroughly discussed with each subject during the pre-enrollment interview.

C.6.4. Protection of Confidentiality: All patient information and identifying materials will remain confidential and will kept in locked storage locations and will be accessible only to authorized study personnel. An HHS certificate of confidentiality will be obtained from NIDA which will further reduce the possibility of violations of patient confidentiality. All of the staff have received required training in research ethics, including risks associated with breaches in confidentiality. In addition, all staff members have received HIPAA training, further enhancing this aspect of patient protection. Patients are informed during the informed consent interview of the exceptions to confidentiality mandated by California state law, which include a study participant being deemed imminently suicidal or homicidal, or making statements alluding to their involvement in the perpetration of child or elder abuse.

C.6.5. Reporting of Serious Adverse Events: The intervention being studied poses minimal-moderate safety risks to study participants, and there is a low probability of adverse events occurring given the careful assessments incorporated in the study design. The investigator will classify all adverse events as serious or non-serious and appropriate reporting procedures followed. Serious Adverse Events (SAEs) are defined as any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, any event that requires or prolongs inpatient hospitalization, or any congenital anomaly. This category also includes any other important medical event that a study investigator judges to be serious because it may jeopardize the subject or require intervention to prevent one of the above reportable outcomes, or which would suggest a significant hazard, contraindication, side effect, or precaution.

All investigators in this study will promptly report all SAEs to the VA Institutional Review Board. Expedited reporting of Serious Adverse Events to the VA IRB will adhere to the appropriate guidelines.

C.6.6. Safety-Potential Risks for Participants: Overall, the risk in this study is “more than minimal.” This will be addressed in all consent/assent forms and IRB applications. During the consent process, clients are informed that they have the right to refuse to answer any question or to stop their participation in the study at any time. Some client interviewees may experience anxiety or embarrassment when answering sensitive questions about alcohol and drug use history, treatment history, and related behaviors. The study staff will be trained to respond appropriately to subject safety issues. All research personnel will be able to provide local hotline and referral phone numbers where immediate help is available.

C.6.7. HIPAA- Confidentiality/Privacy: Participants’ medical information obtained during the study is confidential, and disclosure to third parties is prohibited. Research personnel will complete HIPAA training, as well as training on the “Protection of Human Research Subjects” in order to ensure understanding and compliance with HIPAA and confidentiality requirements. All study personnel will be required to sign a confidentiality agreement, and certificate of confidentiality will be obtained from the Department of Health and Human Services. No medical information will be provided to any other person or agency except as required by law. Research records may be reviewed by Dr. Zorick and pertinent study personnel, the Veterans Administration and its contracted agents, and monitors or auditors or other agencies, such as the Department of Health and Human Services (DHHS). Data from this study that are sent by mail and electronically to data repositories will be coded with initials and/or a number, and not the participants' names. No identifying participant information, including names, will be

disclosed in reports, publications or presentations. At the participant's request, medical information may be given to his/her personal physician.

C.6.8. Data monitoring to ensure subject safety and confidentiality: None of the data collection procedures will present significant physical or psychological risks to the subjects. Data files on the medical histories of subjects will be kept in a locked file cabinet in the P.I.'s offices, accessible only to Todd Zorick, M.D., Ph.D. as needed. Electronic media (i.e., computer-stored data, and data stored on CDs) will be password-protected via encrypted code key known only to the senior study personnel. Furthermore, all subject information will be coded with a unique numerical identifier. Protections of privacy of subjects' medical information will be described to the prospective subjects as part of the enrollment interview and the informed consent procedures.

C.7. Possible Risks in Relation to Anticipated Benefits

C.7.1 Benefits to subjects: This project is not a treatment study, and there are no anticipated physical, medical or psychological benefits associated with study participation. It is possible, however, that some subjects may experience some benefit from education about the effect of alcohol on their body while they are enrolled in the study. It is also possible that subjects may, in some instances, benefit from the knowledge of their psychological, medical, and/or laboratory test results (i.e., medical disorder previously unknown to subject, detected through study participation).

C.7.2. Potential risks: The major medical risks are those associated with abstinence from alcohol, exposure to citalopram, exposure to radioactivity as part of [^{18}F]fallypride PET scanning, and strong magnetic fields as part of MRI scanning. These risks are described above; substantial precautions will be taken to reduce these risks as much as possible.

C.7.3. Benefits to society and to the knowledge base: Alcohol dependence is an enormous global public health problem. The potential benefit to society, particularly to the component of society with alcohol dependence, from which some study participants will be drawn, is a better understanding of the response to pharmacological treatment seen in alcohol dependence and of the neurobiological bases for this disorder. The results from this study may significantly improve our ability to identify and develop more effective treatments. As such, the benefits outweigh the risks.

C.8. Data and Safety Monitoring Plan

C.8.1. Responsibility for Data and Safety Monitoring: Over the past several years, research oversight bodies at all levels have expressed concern that the safety of subjects be an aggressive process conducted by the research team locally and by the sponsors of the research (typically a pharmaceutical company and/or NIH). The safety monitoring process at the WLA VA begins with the initial review of the protocol during the study development process. This review is conducted at multiple levels, including the FDA, VA research infrastructure, and the local IRB. Once the trial is initiated, the first and most aggressive action to monitor subject safety involves an initial medical evaluation and review of data forms (e.g., BDI) by research staff. The Principal Investigator and the mentors review these reports regularly and make recommendations about the safe participation of subjects while they are in the trial. Of course, if serious or unexpected adverse events occur during the trial, the Principal Investigator reports these occurrences within the specified time frames to the IRB, VA, and FDA as required.

C.8.2. Frequency of Data Safety Monitoring: At least annually, the PI (Dr. Zorick) and primary mentor (Dr. Brody) will prepare the summary of all Adverse Events. As the Principal Investigator, Dr. Zorick will be ultimately responsible of monitoring the safety and efficacy of this trial, executing the DSM plan, and complying with reporting requirements.

C.8.3. Conflict of Interest: Neither the mentors nor Dr. Zorick have any financial relationships with any organization or corporation related to the study medication. Additionally, Dr. Zorick will not be primarily responsible for the health care of the patients beyond ensuring adherence to the protocol and requirements of the study. At any time during the research, patients may ask for a second opinion about their care from another doctor who is in no way associated with the study.

C.8.4. Safety monitoring activities for SAEs: For the purpose of reporting to the VA IRB, serious adverse events include all adverse events meeting the FDA definition of serious, plus drug overdoses (from the pharmacological investigation under evaluation) that require medical intervention (regardless of severity), instances of suicidal ideation requiring therapeutic intervention, and illegal activity resulting in arrest, incarceration or harm to others. In the assessment of serious adverse events, the local IRB, FDA, and VA administration will receive detailed descriptions that summarize all available information about each case.

C.8.6. Communication plan to IRB, VA, and FDA (if applicable): As stipulated above, all reports of SAEs will be provided to the VA IRB, and the FDA (in applicable situations specific to effects of citalopram, or other study procedures).

C.9. Inclusion of Women and Minorities: We will recruit women aggressively and plan to over-sample women in order to compensate for poor inclusion of women in research. Generally about 25% to 36% of alcohol dependent persons in the community are women, and that about 33% of participants who enroll in studies similar to the ones proposed are women, so we expect about 33% women representation in the proposed study.

Volunteers will be recruited without regard to race or ethnicity. Racial and ethnic group participant will be based on the characteristics of the study population in the general Los Angeles area, which is highly diverse. Based upon similar types of studies conducted in West Los Angeles, we anticipate that ~60% of the participants will be Caucasian, ~25% will be African American, ~10% will be Asian/Pacific Islander, ~5% other racial groups (including Native American), with about ~30% of participants reporting Hispanic ethnicity.

C.10. Inclusion of Children

Children under the age of 21 will be excluded because drinking below that age is illegal in the state of California.

C.11. Study Timeline for Gender Recruitment

First 6 months	Prepare study manual; train staff and implement procedures
Month 6 to Year 4 Month 6	Enroll participants into the study and prepare preliminary results for conference presentations
Last 6 months	Complete data management, analyze data, and publish results

Enrollment Table C.11. Projected Completed Participant Study Flow, Males/Females (Total)

Year	*0-3 mo.*	*3-6 mo.*	*6-9 mo.*	*9-12 mo.*	*Yearly Total*
1	00/00 (00)*	00/00 (00)*	02/01 (03)	02/01 (03)	04/02 (06)
2	02/01 (03)	02/01 (03)	02/01 (03)	02/01 (03)	08/04 (12)
3	04/02 (06)	04/02 (06)	04/02 (06)	04/02 (06)	16/08 (24)
4	02/01 (03)	02/01 (03)	02/01 (03)	02/01 (03)	08/04 (12)
5	02/01 (06)	02/01 (03)	00/00 (00)	00/00 (00)	04/02 (06)

*Reflects start-up time. Grant Total: 40/20 (60)

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