Application for Review of Human Research: IRB Protocol Summary
Biomedical Research **Section II**
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PROTOCOL TITLE

1. ***Full Title*** Baclofen effects on brain and behavior in cigarette smokers Protocol # 817101

2. ***Brief Title*** Baclofen effects in cigarette smokers

STUDY SPONSORSHIP

1. ***Funding Sponsor*** National Institute of Drug Abuse/National Institutes of Health

2. ***Primary Sponsor*** *the primary sponsor is the PI, Teresa Franklin*

PROTOCOL ABSTRACT

Cigarette smoking is the cause of over 400,000 preventable deaths per year in the United States. Smoking cessation could substantially reduce this burden. However, less than 5% of unaided quit attempts lead to successful long-term abstinence. Relapses to smoking are often preceded by a strong desire or craving for a cigarette when exposed to stimuli related to smoking. Knowledge of the mechanisms underlying stimuli- or smoking cue-induced nicotine craving may aid in the search for additional viable pharmacotherapies to help smokers remain abstinent for life.

Functional magnetic resonance imaging (fMRI) is being used to observe the effects of the GABA B agonist, baclofen, on the brain's response to craving. In this study, craving will be induced in subjects by watching videos of smoking-related cues before and during medication. Subjective measures of craving will be collected throughout the cue/fMRI sessions. It is hypothesized that heightened neuronal activation will be seen in the amygdala, the ventral striatum, the anterior cingulate, the prefrontal cortex and the insula and that baclofen will modulate these responses.
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Pharmacogenetics is a promising and novel addition to neuroimaging studies. Twin, family and adoption studies indicate that vulnerability to substance abuse is partially inherited. Individual response to medications will most likely be related to genetic phenotypes. Genetics studies, on their own, require huge sample sizes and are expensive; however, when combined with neuroimaging, which offers a 'picture' of individual brains, we can learn why some individuals respond to a particular medication and others do not. For example, evidence suggests that the rewarding properties of drugs involve activation of the mesocorticolimbic dopaminergic system, and thus, dopaminergic genes will be examined. Candidate dopamine genes include DRD1, DRD2, DRD3, DRD4, DRD5, COMT and DAT. In addition, is also evidence that GABA-ergic mechanisms are involved, particularly the GABA B2 subunit. Therefore, we will examine it as well. The most compelling evidence for a role for variance in dopaminergic components in smoking cue reactivity exists for the dopamine transporter (DAT). Thus, the DAT gene will be our primary focus. The DAT gene has two common polymorphisms. One is the 9 variable number tandem repeat (VNTR) allele and the other is the 10 VNTR allele. Those with the strongest smoking cue responses have at least one 9 VNTR (hetero- or homozygotes) while reduced smoking cue responses occur in those homozygous for the 10 VNTR allele.

OBJECTIVES

1. Overall Objectives

AIM 1 Compare brain and behavioral measures in subjects who are carriers of a dopamine transporter (DAT) 9 (VNTR: 9-repeats) versus 10 VNTR homozygotes (10/10-repeats), actively seeking smoking cessation treatment.

Hypothesis: We will replicate our original findings of differential brain and behavioral responses to cues mediated by variance in the DAT gene. Brain activity will be enhanced in the interconnected ventral striatum and medial orbitofrontal cortex, regions involved in conditioned drug reward, in 9-repeats compared to 10/10-repeats. Brain and behavioral responses will be significantly greater in 9-repeats compared to 10/10-repeats.

AIM 2. Compare brain and behavioral measures following 3 weeks of baclofen versus placebo treatment in treatment seeking subjects.

Hypothesis: Baclofen will modulate resting brain activity—specifically, activity in the lateral orbitofrontal cortex, involved in aversive processing, will be greater in baclofen-treated subjects. Baclofen will modulate smoking cue reactivity: activity in reward-related regions will be blunted in subjects receiving baclofen, while those receiving placebo will display the original signature of craving observed in our well-characterized smoking cue reactivity paradigm. Baclofen will correct vulnerabilities by modulating neural activity in the amygdala and ventral striatum, regions known to respond to reward and in the insula, which is considered an autonomic signaling relay station andplays a role in drug craving. Although overall effects are expected, inter-individual variability in pharmacological response introduced by genetic variance in the DAT will be evidenced.

AIM 3. In a 2 x 2 design (DAT genotype) x (baclofen versus placebo), examine the interaction between allelic variance in the DAT and baclofen-induced neuromodulatory and behavioral responses.

Hypothesis: DAT genotype will underlie the inter-individual variability in brain and behavioral responses to baclofen. 9-repeats receiving baclofen will demonstrate greater reductions in reward-related brain activity and smoking behavior compared to 10/10 repeats.

Optional Sub-Study Aim: Conduct an optional sub-study to examine the effects of baclofen on brain responses to alcohol cues (compared to non-alcohol cues) and drinking behavior compared to placebo following 4 weeks of baclofen or placebo in individuals actively seeking smoking cessation treatment and drink heavily. The goals, rationale, background and study methods for this objective are described in Appendix I.

2. Primary Outcome Variable(s)

Brain and behavioral responses to smoking cues will be significantly greater in 9-repeats compared to 10/10-repeats. Although overall effects are expected, inter-individual variability in brain response introduced by genetic variance in the DAT will be evidenced. 9-repeats receiving baclofen will demonstrate greater reductions in brain activity and smoking behavior compared to 10/10-repeats.

3. Secondary Outcome Variable(s)

Pre-medication outcome variables:

9-repeats may have more difficulty labeling their feelings as measured by higher scores on the Toronto Alexithymia Scale (TAS).

9-repeats may have higher attention deficit (ADHD) symptoms as measured by the ADHD battery.

Exposure to smoking cues will not affect how 10-repeats smoke a cigarette whereas 9-repeats will smoke more of their cigarette following cue exposure, as measured by solanesol content.

During-medication outcome variables:

Following 3 weeks of medication, measures of anxiety and depression may be reduced in baclofen-treated subjects compared to placebo-treated subjects, as evinced by lower scores on the HAM-D and HAM-A.

Throughout treatment, alcohol/other drug craving and use may be reduced in baclofen-treated subjects compared to placebo-treated subjects as measured by lower scores on the Alcohol Urge Questionnaire (AUQ) and reduced days of use as measured by the Time-Line-Follow-Back (TLFB).

Baclofen-treated subjects will show differences in how they evaluate their last cigarette smoked as measured by the modified Cigarette Evaluation Questionnaire (mCEQ).

Post-medication outcome variables

Following the 3-week imaging paradigm and 5 additional weeks of treatment, subjects treated with baclofen will have better treatment outcome, as evinced by reductions in urine cotinine levels, and cigarettes smoked per day compared to placebo-treated subjects, as measured by urine cotinine levels and cigarettes smoked per day.

Females who begin treatment in the follicular phase of the menstrual cycle and who are baclofen-treated will have better treatment outcome than females who begin treatment in the luteal phase who are baclofen-treated, as evinced by reductions in urine cotinine levels, and cigarettes smoked per day.

BACKGROUND and SIGNIFICANCE

The Problem is Relapse, motivated by Craving Cigarette smoking is **the leading cause of preventable death** in the nation and is the direct cause of 87% of lung cancer cases, as well as chronic obstructive pulmonary disease, emphysema and myriad other devastating and fatal diseases. Of the roughly 36 million smokers in the nation, most desire to quit, and 40% make an attempt each year, while less than 5% succeed (1, 2). The deleterious effects of smoking highlight the importance of identifying the genetic underpinnings and the brain targets that will aid in identifying effective treatments that will improve treatment outcomes.

There are a host of factors involved in the motivation to smoke and that promote relapse, including stress, peer pressure, availability, menstrual cycle phase and even weight management (3-7), **however, smoking cue (SC)- and withdrawal (WD)-induced 'cravings' are two major motivators to continued smoking and relapse (8-11).** While abstaining, smokers find themselves fixated on smoking to alleviate what they report as intolerable cravings, induced by nicotine WD and/or reminders to smoke (10, 12-14). WD is a short intense phase of nicotine cessation, caused by the absence of the pharmacological effects of nicotine in the brain. It is characterized by a constellation of symptoms, which include irritability, insomnia, fatigue, inability to concentrate, and headache (14). The WD symptoms inevitably lead to craving, as smokers know that smoking will provide relief. Inability to combat WD-induced craving, which declines within a month (15), plays a major role in *early* relapse. However, smokers report that SCs, such as the smell of a burning match, another person smoking, drinking alcohol, and even internal mood states (stress, fatigue, contentment) repeatedly associated with smoking, can trigger relapse months or even years after quitting. Smokers who possess high 'cue reactivity' may be especially vulnerable to relapse initiated by exposure to SCs (16, 17).

Our group studies appetitive SC-induced motivation, as it occurs long after WD symptoms abate and its link to relapse is not clearly delineated. Further, existing medications such as bupropion, varenicline, and nicotine replacement therapy (NRT) NRT are effective in 'some' smokers (2, 18-25), but they do not help a large majority of smokers, which may indicate the existence of pharmaco-responsive endophenotypes. The variable treatment response to existing medications may indicate heterogeneity in the relative contribution of SCs and WD to the maintenance of dependence. Smokers whose smoking behavior is influenced more by pharmacological WD from nicotine may benefit from the existing medications, whereas, smokers whose relapse is influenced more by cue exposure may receive less benefit. We suggest that the heterogeneity in treatment response is partially mediated by genetic variance in the DAT and possibly other DA-ergic regulating genes indicating a **'pharmaco-responsive-heterogeneity'.** Subsequently, **there is a critical need to identify agents that target cue reactivity to aid cue-vulnerable individuals.**

Why do some smokers find it so hard to quit? Inherited vulnerabilities in neurophysiology may underlie compulsion to smoke. These vulnerabilities may originate in the mesolimbic DAergic system (26, 27). The dopamine transporter

(DAT) is responsible for rapid removal of synaptic DA after its release in response to addictive drugs and to the conditioned cues associated with repeated drug use. Evidence suggests that a functional 40-base pair VNTR polymorphism in the 3' untranslated region of the *SLC6A3* gene, affects DAT availability (28, 29). In molecular studies, the 9-repeat allele is associated with lower expression of the DAT gene, which may lead to slower DA clearance (30, 31). We **hypothesize that a less efficient or less functional DAT may lead to slower reuptake of DA so that it lingers longer in the synapse, prolonging the reward message and strengthening the associations between nicotine and SCs. As the incentive value of SCs is enhanced, so is the craving and associated brain activity triggered in their presence.** Thus, we evaluated the impact of genetic variation in the DAT gene on brain and behavioral responses to SCs. We found that 9-repeat carriers had greater brain responses to SCs (vs. nonSCs) than 10-repeats bilaterally in the inter-connected ventral striatum (VS) and medial orbitofrontal cortex (mOFC) (32). Further, subjective craving scores were increased in 9-repeat carriers and decreased in 10/10-repeats. Recently, we have confirmed these brain finding in a new cohort of smokers (33). However, power was insufficient to link the brain findings to behavioral correlates that will aid in identifying a SC-reactive endophenotype. This link is necessary to assign mechanism to function and could aid in identifying a SC-reactive endophenotype. **Aim 1 of this proposal will provide the link between genes, brain and behavior, which is critical knowledge to determine the functional significance of the neurogenetic findings.**

Evidence of the promise of baclofen as a smoking cessation agent A wealth of preclinical literature examining the neurobiology underlying drug dependence and the cues that signal their availability point to the mesolimbic dopaminergic reward system as a final common brain substrate (34-36). GABA-ergic agents indirectly quiet accumbens afferents (37-41), thereby reducing the self-administration (SA) of psychoactive drugs (42, 43). GABA B antagonists reverse these effects (44, 45). The mechanisms underlying the GABA B antagonistic effects are still under investigation, but one hypothesis is that activation of GABA B receptors located somato-dendritically on ventral tegmental area (VTA) neurons inhibit the release of DA in interconnected regions, such as the VS and prefrontal cortex (44, 46, 47).

Baclofen has been studied quite extensively in animals with consistent results. Baclofen dose-dependently prevented SA of several drugs of abuse (48-50), including nicotine (51-54), and inhibited DA release in nicotine, cocaine and morphine-dependent rats (55). Nicotine self administration was substantially reduced when baclofen was micro-infused into the VTA (45) or into the pedunculopontine nucleus (56), a strong GABAergic VTA afferent. Most recently, Fattore and colleagues reported that baclofen dose-dependently blocked nicotine-induced reinstatement of SA in rats and dose-dependently abolished nicotine conditioned place preference in mice (57). Baclofen reduces drug-reinforced behavior at doses that do not affect responding for food, water, or locomotor activity; this suggests that it is not sedating and does not disturb normal activities (48, 50, 57, 58).

Clinically, baclofen has shown potential for reducing drug-motivated behaviors, including craving and relapse in opiate (59), cocaine (60-62) and amphetamine (63) addictions. However, baclofen was ineffective in a recent NIDA multi-site trial for cocaine treatment (64). The contrast of this result to earlier preclinical and human studies may reflect 1) the trial's focus on abstinence initiation rather than relapse, 2) the need for a higher baclofen dose, 3) and/or genetic makeup of the study population. Baclofen has been studied more extensively in alcohol trials and has shown promise in increasing treatment retention, decreasing WD symptoms, and reducing craving and relapse (65-69). In three case studies of alcoholics using high-dose baclofen, subjects reported complete remission, as indexed by the absence of alcohol craving and use (67, 70, 71). With respect to smokers, **we observed reductions in the number of cigarettes smoked per day in a *Baclofen for Smoking Reduction* clinical trial using a higher dose (80mg/day) than used in previous clinical trials of drug addiction (72).** To our knowledge, there are no published treatment trials of baclofen for smoking cessation.

With respect to imaging, our studies are the only published studies examining the effects of baclofen on drug cues. Using PET, and $O^{15}H_20$, we demonstrated that baclofen reduced cocaine cue-induced craving and brain activity in the amygdala and orbitofrontal and anterior cingulate cortices (73). Recently, we showed that baclofen dampened activity in the brain 'at rest' in the VS, amygdala and OFC(33).

Because of its indirect actions on the DA system, the human and animal data presented above, and the clinical and imaging data from our lab, we hypothesize that baclofen may be an effective tool to delineate a subgroup of smokers whose relapse vulnerability is more strongly influenced by SCs.

Neuroimaging and Cue Reactivity Neuroimaging techniques provide the opportunity to examine the DA-ergic system in humans and demonstrate that drug-related cues elicit DA release in the striatum in humans (74, 75). Also, as aforementioned, we observed that genetic variability in the DAT produces a profound effect on SC reactivity

(76). A consistent neural substrate for cue-reactivity has been observed in cocaine-, heroin-, cigarette- and sexual-cues using a variety of imaging modalities (5, 77-80). In studies of SC reactivity, we characterized and replicated a neuroanatomical brain signature in response to SC exposure, independent of WD, that included activation in the reward-related VS and medial OFC (and other reward-related structures). In accordance with the substantial preclinical literature (81, 82), the most profound effects were found in the interconnected medial OFC/VS (76, 83, 84) Based on consistent findings within our laboratory of a role for the medial ventral aspects of the mesolimbic system in drug cue reactivity and baclofen's actions on these DA-ergic substrates, **we hypothesize that baclofen will diminish SC reactivity in the VS/mOFC. We also expect baclofen to *enhance* activity in lateral prefrontal regions that are involved in suppressing previously-rewarding behavior and behavioral inhibition (85, 86). We predict that baclofen will manifest its effects on CNS responses in both the resting baseline state and during cue exposure and that resting brain responses will predict cue responses.**

Baclofen is FDA-approved and safe Baclofen has been FDA-approved for the treatment of spasticity since the early 1970s (87-89) and does not carry a significant abuse liability (65, 90, 91). A common criticism of the use of baclofen for the treatment of smoking cessation or other addictions is its reputation for possessing undesirable side effects. The most common adverse reaction during treatment with baclofen is transient drowsiness (10-63%, depending on the drug) (RxList The Internet Drug Index, Kemstro, Side Effects and Drug Interactions, 2008). Other adverse events that have been reported with long-term use include: dizziness (5-15%), weakness (5-15%), fatigue (2-4%), confusion (1-11%), headache (4-8%), insomnia (2-7%), hypotension (0-9%), nausea (4-12%), constipation (2-6%), and an increase in urinary frequency (2-6%). However, **in our *Baclofen for Smoking Reduction Trial*, we observed no differences in sedation or any other side effects between placebo- and baclofen-treated subjects. We attribute the absence of adverse events to our innovative dosing schedule which includes 1) an induction period, during which baclofen is titrated to full dose over a period of four days, and 2) a 7-day taper at study end (72).** Further, **in a large multi-site trial of baclofen for cocaine dependence using the dosing schedule developed in our lab, no differences in side effects were observed (72).** The practice of slowly introducing a psychiatric medication for smoking cessation or other illness is gaining acceptance, as it eases the occurrence and intensity of side effects (24).

Despite the abundant evidence supporting the potential utility of baclofen as an anti-relapse/anti-craving agent and its clinical safety profile and clinical tolerability of this readily available FDA-approved medication (66-68, 89-93), ours is the first published clinical treatment trial of baclofen's effects on smoking behavior and indicate the importance of further investigation. Minimizing relapse rates and maximizing abstinence is crucial to the health of our nation and may be hastened by exploiting existing (and safe) medications, such as baclofen, that are potentially beneficial for smoking cessation.

The perfusion fMRI/SC paradigm One factor that may have slowed development of medicinal therapies for smoking cessation is the lack of human experimental models to screen medications early in the clinical development program. An assay that rapidly screens promising smoking cessation medications as candidates worthy of the investment of a clinical trial is crucial to hasten our efforts to conquer this chronic relapsing disorder. **The innovation of the proposed studies is based upon our unique approach that may link a characteristic brain response and underlying mechanism of promising candidate agents to relapse prevention.** Theoretically, **the brain's response to novel compounds 1) may predict treatment response, 2)** aid in selecting optimal doses, and 3) aid in the development of new candidate therapies. Thus, these studies can accelerate progress towards the identification and availability of pharmacotherapies that can benefit individuals inextricably held within the grips of cigarette addiction.

Our approach capitalizes on the neuroimaging technique of pseudo-continuous arterial spin labeled (PCASL) perfusion fMRI. Perfusion fMRI is a non-invasive, non-radioactive technique that is used to measure neurophysiological activity. It uses magnetic field to induce a radio-frequency signal to reflect the brain anatomy and the changes in CBF in near real-time. Changes in CBF result in changes in tissue contrast, measured reliably with MRI scanners. Perfusion refers to the delivery of oxygen and nutrients to tissue by means of blood flow and is regionally coupled to brain metabolism. Perfusion fMRI is distinguished from BOLD contrast, which is acquired via oxygenated vs. deoxygenated hemoglobin. **Perfusion fMRI is quantitative (94) and stable across time (95), which facilitates the measurement of brain responses at various time points, both in response to cognitive and emotional tasks, such as cue exposure (76, 83), and also in the brain in the resting condition (without provocation) (96, 97). As such, perfusion fMRI is ideal for longitudinal studies examining brain modifications induced by pharmacological agents. BOLD fMRI is a relative measure, which can only accurately examine changes that occur within a scanning session, during a task, or other provocation and cannot reveal changes induced by a chronic (or otherwise) treatment.** Another feature of perfusion fMRI is that **noise characteristics are stable over the entire frequency spectrum, which makes it suitable for studying low-frequency events in brain function, such as craving and other emotional states that**

accrue over time (83, 94, 98, 99). Consequently, in our paradigm, **this stable and quantitative technique has distinct advantages over BOLD imaging for revealing the neurobiological mechanisms underlying task performance (i.e., cue exposure) and its modulation by pharmacological agents.**

Other factors involved in smoking behavior:

Besides smoking cue exposure and withdrawal other factors are involved in smoking behaviors such as continued smoking, craving and relapse. These include attention problems – nicotine enhances attention and some smokers smoke to improve attention (100); menstrual cycle phase – because of the enhanced discomfort of pre-menstrual cycle symptoms and decreased self-efficacy, menstrual cycle phase at start of treatment can affect treatment outcome (6); ability to label feelings – we hypothesize that the inability to label the craving state could be a relapse vulnerability (32); drinking alcohol – drinking alcohol reduces inhibition and often leads to relapse to cigarette smoking (9). Thus, additional measures will be acquired in this protocol that will provide data towards these potential mitigating factors.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population:
Patients will be 100 randomized physically healthy and mentally stable male and non-pregnant female patients between the ages of 18 and 60 who smoke 6 or more cigarettes per day for at least 6 months. Subjects will not be excluded based on gender, religion, race, or socioeconomic status. The subject population of previous smoking studies in our lab was 54% female, 62% Caucasian and averaged 15 years of education. This is representative of the urban population in the northeast region of the United States who seek help for nicotine dependence. We expect our current population to have similar characteristics. Thus, women and minorities will be well represented in our study. No special subject groups are included in the protocol.

2. Accrual: *100 randomized* (we expect 15 subjects to be lost to attrition)

3. Inclusion Criteria:

1) Physically healthy, as determined by a comprehensive physical examination and approval of the study physician males or females who smoke cigarettes, ages 18-60.
2) Smoke ≥ 6 cigarettes per day for at least 6 months prior to study start date.
3) Females must be non-pregnant, non-lactating and either be of non-childbearing potential (i.e. sterilized via hysterectomy or bilateral tubal ligation or at least 1 year post-menopausal) or of child bearing potential but practicing a medically acceptable method of birth control. Examples of medically acceptable methods for this protocol include barrier (diaphragm or condom) with spermicide, an intrauterine device (IUD), the Nuvaring, oral contraceptives, levonorgestrel implant, hormonal injection or complete abstinence.
4) Provide voluntary informed consent.
5) Must be able to read. [Subjects are required to be able to read because there are several self-administered measures that they must read, understand and provide written answers.]
6) Intelligence quotient of ≥ 80.

4. Exclusion Criteria:

1) Current DSM-IV Axis I diagnoses other than nicotine, alcohol, and marijuana dependence and ADHD
2) Presence of magnetically active irremovable prosthetics, plates, pins, permanent retainer, bullets, *etc*. (unless a radiologist confirms that it's presence is unproblematic). An x-ray may be obtained to determine eligibility given the possibility of a foreign body.
3) History of psychosis.
4) Claustrophobia or other medical condition preventing subject from lying in the MRI for approximately one (1) hour.
5) Positive urine toxicology report, except for marijuana, at the physical evaluation visit.
6) Current or past 3 month treatment for alcohol dependence.
7) Current use of any smoking cessation treatments such as Zyban, Chantix, Wellbutrin, patch, gum, inhaler, electronic cigarettes, herbal preparations.
8) Vision problems that cannot be corrected with glasses.

9) Weight exceeding 300 pounds, body girth > 52 inches and a head girth > 25 inches. [Imaging data acquisition is impaired with high weight individuals].
10) Individuals suffering from stroke and/or stroke related spasticity.

5. Eligibility Determined Case by Case by the PI and/or Study Physician:

1) HIV positive on medication for symptoms. This will be determined on an individual basis by results from the physical examination and final approval by our study physician; all results from the physical within normal range for study inclusion.
2) Use of medications or natural herbs that cause sedation or affect the brain systems that are being studied. Medication use will be evaluated by our study physician on a case-by-case basis. For example, if the subject takes Benadryl but can safely refrain from use 24 hours prior to scanning sessions, they will not be excluded.
3) History of seizures. This will be determined on an individual basis by results from the physical examination and final approval by our study physician. For example, if seizure history is resolved and all results from the physical evaluation (blood/urine labs) are within normal range, s/he will not be excluded. Additionally, subjects should be seizure-free for a period of one year.
4) History of stroke more than 10 years ago.
5) History of head or neck injury causing loss of consciousness, lasting more than ten (10) minutes with post-concussive symptoms (e.g., headaches, loss of memory for the injury, sleep disturbances) or associated with skull fracture or inter-cranial bleeding or abnormal MRI.

6. Vulnerable Populations: None

7. Populations vulnerable to undue influence or coercion: None

8. Subject Recruitment:

Subjects will be recruited from those who respond to our advertisements. Advertisements will be in the form of IRB-approved radio ads, flyers, billboards, e-lists, Facebook page, and word of mouth. An initial telephone interview covering recent medical status, substance use, treatment history, medication, and general psychiatric history will be conducted. The potential subject will be provided with an overview of the study and will be informed that all information obtained will be used to determine his/her eligibility for study participation. If the individual satisfies preliminary criteria and shows continued interest in participating in the study, an appointment will be made for further screening at the Center for Studies on Addiction (CSA). The CSA initial screening process will be described, and the individual will also be informed that s/he must be available for at least two separate appointments during the screening week (unless the two appointments are combined). If the individual does not qualify for the study, s/he will be provided with appropriate community smoking cessation referrals.

STUDY DESIGN

1. Phase II

This is a low risk, single-site, Phase II study, involving a medication that has been FDA-approved for other indications for over forty years, is well-tolerated and has been used extensively in our hands both in neuroimaging and also in a Smoking Reduction Clinical Trial. Currently we hold an IRB-approved protocol to examine baclofen's effects on brain and behavior in marijuana dependence (CURE, IRB # 813953, CoPI, Franklin).

2. Design

Non-abstinent subjects will be randomized by sex and DAT genotype. We will use our perfusion fMRI/cue paradigm to acquire resting baseline (RB) and SC data to confirm and extend our finding of a DAT-mediated SC-vulnerable endophenotype; 9-repeat carriers will exhibit enhanced brain activity in the interconnected VS/mOFC (regions involved in conditioned drug reward) compared to 10/10-repeats. Behavioral responses, including craving and cigarette consumption, will be significantly greater in 9-repeat carriers compared to 10/10-repeats following SC exposure.

Within the 2 x 2 design (9-repeat carriers vs 10/10-repeats) X (baclofen vs placebo), treatment-seeking subjects will participate in an 8-week medication regimen. Baclofen or placebo will be prescribed to non-abstinent subjects at the same doses that have been demonstrated to be clinically effective in our Smoking Reduction Trial. The importance of subjects being non-abstinent is twofold. First, our goal is to determine if and how baclofen affects SC reactivity independent of WD to disentangle these two major motivators underlying relapse. Second, differences in smoking behavior modulate brain activity, so it is important that baclofen- and placebo-treated groups have similar smoking characteristics.

3. Study Duration

This study requires a one-week screening phase and 8 weeks of monitoring and medication. All subjects will complete 2 MRI sessions (one before starting medication, one following 3 weeks of medication) and 5 weeks of additional treatment. Each subject will be enrolled in the study for approximately 10 weeks.

The entire study will commence 12/01/2012 and will run until 08/31/2017, approximately. 20 to 25 subjects will be randomized each year.

DRUGS OR DEVICES

Baclofen and matching placebo

STUDY PROCEDURES

General Procedures

*Interested potential subjects will be screened with a structured interview. Individuals who may qualify are scheduled for the consenting visit. If the consent is successful, individuals will be scheduled to come in for physical and psychological examinations and to provide a genetics sample.
*After the results of the examinations are reviewed, the subject will be contacted to inform them whether or not they qualify. If the examinations reveal any health problems that require medical attention, the subject will be referred to their family physician.
*Subjects will then participate in the 1st fMRI session and will complete a Cognitive Bias session described in detail below. At this appointment, subjects will be asked to set a Quit Date to occur one week after the second scanning session.
*Subjects will be randomized as described in detail below and participate in several study procedures over the course of the study.
*After 3 weeks, subjects will participate in the 2nd fMRI session (on treatment condition).
*Subjects will be called and reminded of their Quit Date prior to their next weekly appointment. At this appointment they will receive a "You can quit smoking booklet" and participate in a counseling session aimed at helping them recognize their relapse triggers, find alternative behaviors to engage in and get support from friends and family. They will make an attempt to quit smoking at this time.
*Subjects will continue treatment for a total treatment time of 8 weeks (i.e., 1st fMRI session followed by 3 weeks of medication treatment; 2nd fMRI session and 5 additional weeks of medication treatment).

***Specific Procedures* (Overview Table provided below description)**

1. Initial Telephone Screening Procedures (approximately 30 min) Subjects will be recruited from the Center for the Studies of Addiction (CSA; UPenn), at 3900 Chestnut St., through local advertisement, social media (Facebook), and "word of mouth". Subjects who express interest by responding to advertising are contacted by phone and participate in a telephone screening interview. The nature of the study, including the number of visits to the center, an fMRI description, subject protections and confidentiality, are described. If the caller is still interested, questions on general health are asked. If the applicant is determined to be eligible based on this screening, s/he is asked

whether they accept or decline to participate. If the caller is still interested, they will be scheduled for an initial consenting appointment.

2. Informed Consent Procedures Visit (approximately 1 to 1.5 hr)
Subjects fill out a subject information sheet, which provides contact information. Subjects are then escorted into a private room in which study staff use a structured confirmatory screen that verifies information acquired during the phone screening and elicits study-specific information. Subjects are provided a standard HIPAA form that contains privacy laws. Potential subjects are provided a 1-paragraph study description that they read out loud. This reminds them of general study procedures and provides an opportunity for us to observe their reading ability. The subject is then provided with a copy of the consent form. The technician reads the study consent aloud as the prospective subjects read along silently and is given the opportunity to ask questions at any time during this process. If the subject decides to participate, s/he signs the consent in the presence of the research technician. After signing, subjects are given a study-specific quiz to ensure study comprehension and must score 100% on the quiz to participate in the study. Incorrect answers are reviewed until the 100% criterion is met. S/he is also reminded that the consent expresses willingness to participate but that the subsequent screening process will determine final eligibility. Further, s/he is reminded that participation is voluntary, and at any time, s/he may withdraw from the study. The subject then watches an fMRI video that simulates the experience of undergoing an MRI. During this visit, the study technician will administer the Addiction Severity Index measure, obtain a breath sample to measure the subject's carbon monoxide level, and acquire a urine sample to be immediately tested for the presence of illicit substances.

Demographics: After a subject consents, they will be asking to fill out the Treatment Research Center Participant Information Form containing subject contact information, general information and demographics, including sexual orientation and gender identity.

Addiction Severity Index (ASI): The ASI is a 35-minute structured interview yielding composite scores reflecting the patient's functioning in seven areas: drug use, alcohol use, medical, employment, psychiatric, legal, and family-social problems. Composite scores are computed in each of the areas to provide an indication of recent problem severity (0.00-1.00). This instrument has been shown to have good reliability and its concurrent and predictive validity have been demonstrated. A research technician trained and certified to administer this instrument conducts the interview.

Carbon Monoxide (CO): A meter will be used that measure CO, which provides information on recent smoking.

Urinalysis: The research technician will ask the subject to provide a urine sample which will be tested immediately for the presence of psychoactive substances. If a urine sample tests positive for psychoactive substance, other than marijuana, the subject will be given the opportunity to provide a drug free urine sample before being eligible to proceed with the physical and psychological examinations. We offer this 'second chance' because sometimes a subject might test positive for a drug that they take infrequently and that they did not know would come up on a drug screen (sleeping pill, anti-anxiety medication). If a subject returns to provide a second urine sample more that 30 days after their consent, they will need to be re-consented.

3. Physical Examination Visit (approximately 1 to 1.5 hr) A complete physical examination and laboratory evaluation are conducted by a certified nurse practitioner. Baseline laboratory measures include: 1) Blood count 2) Blood chemistries 3) EKG 4) Urine Toxicology (presence of psychoactive drugs) and 5) Urine pregnancy test for females; any contraindications will be reviewed by the study physician. A total of approximately 2 tablespoons of blood will be taken. A portion (approximately 1 tablespoon) of this blood sample will also be used to acquire DNA samples from each subject. This portion will be stored for later extraction and analyses.

LABCORP Standard Blood work tests include:
LP+13AC+CBC/Plt
Chemistries: Glucose, Serum
Uric Acid, Serum
BUN
Creatinine, Serum

eGFR If NonAfricn Am OR eGFR If Africn Am
BUN/Creatinine Ratio
Sodium, Serum
Potassium, Serum
Albumin, Serum
Bilirubin, Total
Alkaline Phosphatase, S
LDH
AST (SGOT)
ALT (SGPT)
GGT

Lipids:
Cholesterol, Total
Triglycerides
HDL Cholesterol

CBC and Platelet Ct:
WBC
RBC
Hemoglobin
Hematocrit
MCV
MCH
MCHC
RDW
Platelets

Measures acquired at the Physical Examination Visit

Smoking History Assessment Demographics, family history, smoking topography and severity of nicotine dependence is determined from a laboratory-developed Smoking History Questionnaire (SHQ) that includes the **Fagerstrom Test for Nicotine Dependence (FTND).** The FTND is a 6 item, self-report measure of nicotine dependence derived from the Fagerstrom Tolerance Questionnaire. Internal consistency of the FTND scale is satisfactory (Cronbach's alpha - .64), and it has a high test-retest reliability (re = .88). Demographics and smoking history assessments are necessary for characterizing the population and publication. (administration time: approximately 5 min)

Reasons for Smoking Questionnaire (RSQ), is a 34 item, 4-point likert-scale, self-report measure probing the underlying motivations for smoking. Individual reasons underlying smoking behavior (e.g., to reduce WD symptoms, SC exposure, stress) will be used in conjunction with brain and genetic data to learn more about individual smoking behavior that will eventually be helpful in planning personalized smoking cessation strategies. (administration time: approximately 4 mins)

Toronto Alexithymia Scale (TAS-20) is a widely used and psychometrically valid instrument to measure alexithymia. It is a self-report questionnaire containing 20 items (e.g., I am often confused about what emotion I am feeling) rated on a 5-point scale from strongly agree (1) to strongly disagree (5). A high score (>62) indicates a high degree of alexithymia. Scoring on this questionnaire is interpreted using a three-factor solution: factor 1 items reflect difficulty identifying feelings, factor 2 items reflect difficulty describing feelings, factor 3 items reflect externally-oriented thinking. This measure is being acquired because we have found that symptoms of alexithymia may be modulated by DAT genotype and higher symptoms may be found in 9-VNTR smokers. We are collecting this measure to test this hypothesis. (administration time: approximately 3 min)

Menstrual Cycle Questionnairre (MCQ) This questionnaire will be administered by the Nursing Staff to all female prospective subjects during the physical evaluation. It elicits information on menses status, menstrual cycle length, and premenstrual symptoms (PMS). This measure is acquired because we have found that menstruating females

who are in the luteal phase of the cycle crave more during smoking cue exposure (101), do poorly in treatment (6, 102), and have greater brain responses to smoking cues (103) compared to follicular phase females. Further, it is acquired because symptoms of PMS and withdrawal are poorly distinguished (104). The questionnaire is designed to distinguish symptoms that are clearly PMS from those that are clearly withdrawal. In this way, we will have information that will help us determine whether potential symptoms are related to withdrawal or PMS. Further, we have observed that the brain responses of females who are post-menopausal differ during smoking cue exposure compared to menstruating females, perhaps revealing different underlying relapse vulnerabilities. This questionnaire (and progesterone/estrogen levels) will help us determine if females are pre-, peri- or post-menopausal [administration time: 1-3 min (this varies depending on whether subject menstruates)].

4. Psychological Evaluation Visit (1 to 1.5 hours)
The following evaluations will be completed by a trained clinician:
MINI International Neuropsychiatric Interview (MINI): This is a short and accurate structured diagnostic psychiatric interview. It will be used to determine current DSM-IV diagnosis of any psychoactive substance dependence other than nicotine. Nicotine dependence is often accompanied by other drug dependencies. It will also be used to diagnose current severe psychiatric symptoms, e.g., psychosis, dementia, acute suicidal ideation, mania or depression requiring antidepressant therapy, or which would make it unsafe for the subject to participate in the opinion of the primary investigators. The MINI has excellent inter-rater reliability and very good test-retest reliability. Prior to completion of the MINI, the administering clinician will review the subject's reported history, in addition to any prohibited medications. Since the MINI does not evaluate for acute homicidal ideation, we have referenced such a question from another study within our center and have included it in our procedures. (administration time is approximately 30 minutes).

Wechsler Abbreviated Scale of Intelligence (WASI) is a brief and reliable measure of intelligence that provides an estimate of an individual's IQ scores. We will use the two subtest form (vocabulary and matrix reasoning) that offers an estimate of an individual's cognitive functioning. Individuals with an intelligence quotient of ≤ 80 are excluded because they do not have the cognitive skills necessary to participate in several of the study components. (administration time: approximately 15 mins).

Following these procedures, Dr. Franklin will meet with the assessing clinician to discuss any subject reservations. For subjects who we feel may need additional eligibility verification, we would like to have the option to view their medical records. In these instances, we will first check EPIC to see if the subject has an EMR. If they do not, we will work with the subject and their PCP to obtain the appropriate medical releases to obtain information on their recent medication use and diagnoses, when available.

Prospective subjects will be notified of their eligibility by telephone within 5 business days after the physical and psychological evaluations. This waiting period is necessary to examine results from laboratory and psychological tests to determine whether the subject meets eligibility requirements (i.e., if all values and scores fall within normal limits).

1st MRI session Visit (approximately 3 hours)
Stimuli used will be audio-visual video clips consisting of either smoking-related cues: individuals differing in race, age and sex who are smoking and using explicit language designed to induce appetitive desire for a cigarette; or non-smoking-related cues that are similar in content, but individuals relate interesting short stories that do not portray cigarette smoking or smoking reminders. Two similarly-valenced cue sets will be employed (counterbalanced) to control for habituation that may occur at Time 2. In prior studies, our SCs elicited robust reward-related neuroactivity and subjective craving responses, in conjunction with strong brain/behavioral correlates.

MRI scanning will be conducted on a Siemens 3.0 Tesla Trio whole-body scanner (Siemens AG, Erlangen, Germany), using a standard Transmit/Receive head coil. A 30-second localizer scan and a 5-minute T1-weighted high-resolution scan are acquired before the functional scanning. These scans are used for subsequent normalization and anatomical co-registration of the images, and they provide subjects with a habituation period to the MRI environment. The 3-plane localizer scan (sagittal, axial and coronal) is acquired with FOV = 280 mm, TR/TE = 20/5ms, 192x144 matrix, and slice thickness 5mm. Acquisition parameters for the 3D High-Resolution MPRAGE

structural in the axial plane are: FOV = 250 mm, TR/TE = 1620/3ms, 192x256 matrix, slice thickness 1 mm. The CASL technique will be used to acquire images during functional MRI (RB and SC exposure). Interleaved images with and without labeling will be acquired using a gradient echo echo-planar imaging sequence. A delay of 1000 ms will be inserted between the end of the labeling pulse and image acquisition to reduce transit artifact. Acquisition parameters are: FOV=22cm, matrix=64x64, TR/TE = 3000/17ms, flip angle=90°. Fourteen slices (8mm thickness with 1.5mm gap) will be acquired from inferior to superior in a sequential order. Each cue CASL scan with 200 acquisitions will be 10 minutes in length. The RB CASL scan will be 5 minutes with 100 acquisitions.

Cognitive Bias Computer Tasks: It is documented that individuals with emotional or dependence disorders exhibit biased attention toward stimuli associated with their disorder. This bias appears to diminish following successful treatment. Several tasks will be administered: the dot-probe attention task, the primed attention task, the implicit association task, a go/nogo inhibition task, and a Balloon Analog Risk Taking (BART) task. Generally, subjects will be told that the purpose of the task is to see how quickly and accurately they can detect targets presented on a display terminal. During the tasks, the subject will be seated in front of an eye level computer screen. Smoking, nonsmoking, pleasant and unpleasant pictures will be presented on the screen. Subjects will be given specific instructions for each task and will be asked to respond appropriately by pressing a button. (administration time is approximately 60 minutes)

The Hamilton Depression Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A): Fourteen-item standardized Clinician-administered scales that have been the benchmarks for clinical studies worldwide for almost 30 years. Baclofen is an anxiolytic. It's properties to reduce anxiety may be a mechanism underlying it's potential effectiveness in smoking cessation. Here we will collect data to test that hypothesis. These measures provide total scores and a psychic and somatic cluster of depression and anxiety, respectively. (administration time: approximately 10 - 20 minutes for both measures)

ADHD Battery: Brown Attention Deficit Disorder Scale for Adults [BADDS], a 40-item self-report questionnaire/interview conducted orally by a clinician, and the self-report measures Patient Behavior Checklist [PBC], the Wender Utah Rating Scale [WURS]. (administration time approximately 10 - 20 minutes)

A pulse oximeter probe (attached to finger) and blood pressure cuff will be used to measure blood oxygen level, HR/pulse, galvanic skin response, and blood pressure during imaging. Subjects with high or erratic HR are suspected of experiencing anxiety/claustrophobia will be escorted out of the scanner to meet with a clinician.

Craving and WD Questionnaire (CWQ): A brief, easy to use, self-report measure used in our nicotine studies. The CWQ consists of items that are designed to measure WD and craving. The CWQ is administered immediately prior to and following each SC and non-SC exposure to examine subjective measures of craving induced by cues. (administration time: approximately 1 min)

Shiffman-Jarvik Smoking WD questionnaire (SJ): A widely used standardized self-report 17-item questionnaire developed to assess WD symptomatology. This will be administered pre-and post cue exposure(s) to determine whether WD has accrued over the time in the scanner. (administration time: approximately 3 mins)

Modified Cigarette Evaluation Questionnaire (mCEQ): Assesses the degree to which subjects experience the reinforcing effects of smoking. It is a standardized, validated and reliable measure with multi-item domains on smoking satisfaction, psychological reward and aversion and craving reduction. Confirmatory factor analysis exceeds 0.90. Baclofen has been shown to modify how one assesses smoking (105). This might be one mechanism underlying its potential efficacy. The mCEQ will be administered to assess the effects of baclofen on the evaluation of subject's last cigarette. (administration time: approximately 3 mins)

Blood: On scan days, all females will provide a blood sample (approx.. 2 tablespoons) for biochemical verification of cycle phase. Bloods will be tested for levels of progesterone and estradiol.

Urine Pregnancy Test: All females of childbearing potential will be assessed for pregnancy with a urine test prior to being allowed to participate in the MRI.

Urinalysis: Urines are analyzed for cotinine, the primary metabolite of nicotine, at this visit, Scan Day 2 and also at the Week 8 visit. Cotinine levels correlate with nicotine intake, which will aid in determining changes in smoking behavior. In addition, the urine sample from Scan Day 1 and 2 will be tested on-site for the presence of illicit substances. A positive result will lead to the cancellation of the scan and the exclusion of the subject from further study participation.

Cigarette filters for solanesol testing: Cigarette filters will be collected and analyzed for solanesol, a naturally occurring substance present in tobacco that provides a precise measurement of smoke exposure.

Alcohol Craving Measures –. It has been shown (see Background and Significance section above) that baclofen reduces craving and relapse in alcohol dependence. Subjects in this study are not alcohol dependent, but they have varying amounts of use. Since drinking alcohol and smoking often go hand in hand, we have added the following two measures to examine whether baclofen reduces alcohol urges and/or drinking.

The Alcohol Urge Questionnaire (AUQ) (Bohn et al., 1995) is an 8-item, self-administered state measure assessing the urge for an alcoholic drink at the time the questionnaire is completed and provides an index of acute craving. The AUQ contains four items pertaining to the desire for a drink: two items regarding expectations of positive effects from drinking, and two items relating to the inability to avoid drinking if alcohol were present. This measure has strong correlations with measures of alcohol dependence and severity.

Timeline Follow Back (TLFB): The TLFB will be used to measure subjects' alcohol use. Baseline 30-day TLFB is administered at the pre-treatment scan (week 1). At the on-treatment scan TLFB is acquired to measure use between baseline and present. Finally, at the follow-up visit the TLFB will cover the last month.

Randomization: Subjects will be unequally randomized at a rate of 2 baclofen to 1 placebo. Study medication, supplied by Watson Pharmaceuticials, will be packaged in blister packs for individual subjects and supplied by the HUP Investigational Drug Service to the study medical staff who will monitor and dispense the medication. The randomization schedule will be available in the hospital pharmacy 24 hours a day in the event of an emergency. Baclofen will be prescribed at 20 mg 4 times per day. Each baclofen pill will be 10 mg. Thus, 2 pills will be taken at each scheduled dose for a total of 8 pills a day. In this way, the titration schedule, taper and potential dose reductions can be managed. Placebo-treated subjects will follow the identical schedule. This dose was chosen based on the results from our *Baclofen for Smoking Reduction Study* wherein we found this dose to be effective at reducing the number of cigarettes smoked per day(72).

As with any study in which subjects are asked to take a medication, compliance is an issue. Once a week, the number of pills returned in the blister pack will be subtracted from the number of units dispensed to obtain a measure of the amount of medication consumed by the subject throughout the week. To improve tolerance and thereby compliance, baclofen will be introduced slowly to minimize the possibility of undesirable side effects, such as sedation. The study physician or the nurses under the physician's supervision will monitor administration of study medication. See Dispensation Schedule (below). The key describes how the medication will be administered. P = placebo, O = 10 mg baclofen, X = 20 mg baclofen. There are two pills in every blister. These are packaged by IDS to accommodate the titration and taper. Once the full dose is reached (Day 4) and if a subject experiences discomfort or adverse events that may be related to the medication the dose will be decreased until symptoms remit. This will be accomplished by consultation with the Medication monitoring team (Study Physician and Nurses), who will determine if the adverse events might be medication-related. The subject will then be instructed to only take one of the two pills within each blister and disregard the other pill. This lower dose may be maintained throughout the study if the subject so desires. In our ten years experience with this medication and our ongoing protocol (CURE Protocol # 813953) we have had a few subjects request a reduction in dose so we are prepared for this possibility.

Baclofen Dosing Schedule

Study Day	8 AM	12 Noon	4 PM	8 PM
Day 1	Placebo	10 mg Baclofen	Placebo	10 mg Baclofen

Day 2	Placebo	10 mg Baclofen	10 mg Baclofen	10 mg Baclofen
Day 3	Placebo	20 mg Baclofen	20 mg Baclofen	20 mg Baclofen
Day 4-7	20 mg Baclofen	20 mg Baclofen	20 mg Baclofen	20 mg Baclofen
Week 2 - 7	20 mg Baclofen	20 mg Baclofen	20 mg Baclofen	20 mg Baclofen
Week 8 Day 1-2	Placebo	20 mg Baclofen	20 mg Baclofen	20 mg Baclofen
Week 8 Day 3-4	Placebo	20 mg Baclofen	Placebo	20 mg Baclofen
Week 8 Day 5-6	Placebo	10 mg Baclofen	Placebo	10 mg Baclofen
Week 8 Day 7	Placebo	Placebo	Placebo	Placebo

2nd MRI session Visit (approximately 2 hours)
The 2nd MRI session takes place after a subject has been on the medication for 3 weeks. At this session, the subject will be asked to take their medication in the presence of Study Staff [Baclofen has a short life with maximum effects at 2 hours and waning thereafter. Thus ingesting the medication in front of study staff will ensure that the medication was ingested and that its effects will be observable during the MRI as well as standardize time since dose]. Otherwise, this visit will be exactly the same as the first MRI session described above except cognitive bias testing will not be conducted.

At the weekly appointment following the second scan the subject will make a quit smoking attempt. To assist the subject in meeting this goal, study staff will meet with the subject to go through the "You can quit smoking' pamphlet during this appointment which is an interactive tool designed to help people recognize relapse triggers, provide alternative strategies when craving occurs, and how to acquire support from friends and family. Explicit instructions for how to conduct this session are included with the uploaded IRB documents (Titled: Smoking Booklet Script). Monitoring of smoking behavior is accomplished with subject Daily Diaries, weekly phone calls with study staff, weekly meetings with study staff, CO measurements and urine cotinines.

Measures collected at Weekly Study Visits

- **Adverse Events Questionnaire** is used to monitor adverse events during the administration of study medication and is administered and maintained by the study physician or nurse. Information about the onset, severity, and possible relationship to study medication, and outcome of action taken is recorded at each study visit. All locally relevant Internal Review Board (IRB) regulations and practices concerning adverse event reporting are followed. Serious adverse events will be reported to the UPenn SOM IRB within 24 hours.
- **Daily Diary:** Subjects are provided a Daily Diary in which they record medication adherence and smoking behavior (e.g., cigarettes per day, craving, pleasure received from smoking). These forms are filled out daily and collected at each visit.
- **Carbon Monoxide (CO):** A meter will be used that measure CO, which provides information on recent smoking.
- **Modified Cigarette Evaluation Questionnaire (mCEQ):** Assesses the degree to which subjects experience the reinforcing effects of smoking. It is a standardized, validated and reliable measure with multi-item domains on smoking satisfaction, psychological reward and aversion and craving reduction. Confirmatory factor analysis exceeds 0.90. Baclofen has been shown to modify how one assesses smoking (105). This might be one mechanism underlying its potential efficacy. The mCEQ will be administered to assess the effects of baclofen on the evaluation of subject's last cigarette. (administration time: approximately 3 mins)

Measure collected at Follow-up Visit

- Subject Treatment Opinion Form (TOS): During their Follow-up Visit with the Nurse, the subject will be asked to fill out a 4 item questionnaire, assessing whether or not the subject feels that they were receiving the study medication, Baclofen, or the placebo. If the subject feels they were receiving the active

medication, this measure then further assesses the subject's thoughts on the medications level of effectiveness and in what specific areas the subject saw improvement.

Table of Measures	**Consent Visit**	**Eval Visit**	**Scan Visit 1**	**Scan Visit 2**	**Quit Wk**	**Sub-Study Scan+**	**Wkly Visits**	**Wk 8 Visit**	**FU**
Patient Information Sheet	X								
Confirmatory Screen	X								
Consenting Process	X								
ASI	X								
MRI video	X								
Breath sample (CO)	X	X	X	X	X	X	X	X	
Record handedness	X								
Daily Diary			X	X	X	X	X	X	
mCEQ			X	X	X	X	X	X	
SHQ		X							
RSQ		X							
TAS		X							
Smoke and collect filter			X***						
MRI safety sheet			X	X		X			
Pulse Oximeter			X	X					
HAM-A and HAM-D			X	X					
Physical Evaluation		X							
Blood sample (2 Tbsp)		X	Females	Females					
Urine sample	X	X	X	X		X		X	
Pregnancy Test (Females)		X	X	X		X			
MCQ		X							
EKG		X							
Psychological Eval (Clinician)		X		X					
Computer Tasks			X						
Medication Monitoring (Nurse)		X	X	X		X	X	X	X
Return Medication Card and Daily Diary Receive and discuss medication issues AEs recorded									
Attempt to Quit					X				
Receive Quit Counseling				X					
S-J			XX***	XX***					
CWQ			XX***	XX***					
WSRS-Alcohol						XX***			
AUQ			X	X		X		X	
TLFB			X	X		X		X	
TOS									X
Completer certificate, resource packet									X
		Between weekly visit phone call to discuss medication issues and smoking behavior (between appointments)							

*Part of the physical ** Part of the Psych Eval *** Collected pre- and post scan + Occurs the same day as the Quit Wk appt

2. Analyses

Imaging Data Processing: Prior to performing analyses, brain data are examined for gross movement and full image acquisition. An SPM-based ASL data processing toolbox is used for data analyses. ASL image pairs are realigned to the mean of all control images and spatially smoothed with a 3D isotropic Gaussian kernel with FWHM of 10mm. CBF image series are generated using a simplified two-compartment model with the sinc interpolation method for CBF calculations. The mean control image of each subject's data is co-registered to a HR 3D T1 structural image using the mutual information based co-registration algorithm provided by SPM8. The same co-registration parameters are used to co-register the CBF maps to the structural image. The structural image is then spatially normalized to the MNI standard brain. The same parameters are used to normalize the CBF images to the MNI standard space. Each subject's normalized mean control images are segmented using SPM8. The segmented gray matter masks are averaged and the overlap of subject's gray matter is extracted. This final mask is used for calculating global CBF for each session.

Imaging Data Analyses: Voxel-wise analyses of the CBF data are conducted on each subject using a general linear model (GLM). Global CBF time course is included in the model as a covariate to examine the effects of baclofen. Analyses are conducted on absolute (RB) and relative (during SC exposure) CBF. No temporal smoothing is applied. Contrasts between conditions (Time 1 versus Time 2) are defined in the GLM model to assess the voxel by voxel CBF difference. Using the corresponding parametric maps of this contrast (maps), random effects analysis is employed to test for a significant main effect of condition with a SPM map of the T statistic at each voxel for population inference for each session for the placebo and baclofen groups (second-level analysis). A 2x2 factorial design matrix is used to assess the effects of the pharmacological manipulation by including the group (baclofen vs placebo) and condition (Time 1 vs Time 2) as the two factors. This two-stage analysis is theoretically equivalent to a 2 way ANOVA.

We have recently gained expertise in connectivity analysis, which we will utilize here as in our previous studies. This approach determines the degree to which the time course of each voxel correlates with the averaged time course from a specific region of interest (e.g., the VS/mOFC). In this approach, the time course of all voxels within this region of interest will be extracted, and the averaged time course will be used as the regressor to check the correlation between the seed region and the rest of brain. As an alternative, we can repeat the same correlation analysis but using the principal component of all time courses extracted from the ROI as the reference function. For each subject, the ß map of the voxel wise connectivity analysis (correlation analysis) will be collected, and group analysis through random effects using one-sample t-tests will be performed to assess the across-subject effects of the brain connectivity to the seed region of interest. Neuropsychological and behavioral scores can be used as simple regressors to examine their relationship to connectivity for a brain target. Though our focus for the project is VS/mOFC connectivity due to its role in emotional arousal, the same analyses can be performed for other regions of interest (e.g., lateral OFC).

Behavioral Analyses: Statistical significance tests use an alpha of .05 unless otherwise noted. Continuous demographic variables (e.g., age, education, FTND, CPD, pack years, TAS, RSQ, SJ, mCEQ and the CWQ composite scores, latency to smoke, and cigarette consumption) are checked for normality, transformed if necessary, and summarized by calculating means, standard deviations and ranges. Scores on each factor will be included as covariates of interest with respect to perfusion fMRI SC data and genetic variance in DA-ergic components. Analysis of variance will be used to assess demographic differences across groups. Nominal demographic variables (e.g., race, sex, genotype) are summarized by calculating proportions and compared across groups using chi square analyses. Demographic (age, years education, monthly income) and clinical (depression, anxiety and psychiatric symptom scores) will also be summarized and compared across the treatment groups.

Genetics Analysis: Genomic DNA will be extracted from anticoagulated venous blood samples using a standard salting out method. Genotyping of the DRD4 and DAT VNTR will be performed using standard methods as described previously. DRD2 and COMT genotypes will be determined using the Applied Biosystems Inc. (ABI) Assays-on-demand (ABI, Foster City, CA, USA) SNP genotyping assay as per manufacturers protocol. Genotyping quality control steps for all markers will include Hardy-Weinberg equilibrium determination and genotyping of 20% duplicates for each marker.

Solanesol Assay: Cigarette filters from cigarettes smoked at specific study time points will be collected and stored for future analysis.

Sample Size Determination and Power: Using our published findings examining the effects of the DAT polymorphism on SC reactivity, we calculated an effect size of 0.78 in the VS and 0.98 in the OFC. These effect sizes will allow us to determine between group differences at greater than 0.80 power with group sizes ranging from 18-24. Importantly, in other studies ongoing in our lab, none of the genotypes examined deviated from those expected from Hardy Weinberg Equilibrium. The proposed number of subjects should be adequate to acquire data on the effects of the several brain, behavioral and genetic endpoints. We are also encouraged that we will find between group differences by results of studies that have utilized similar sample sizes. With these sample sizes it should be possible to generate groups large enough to explore gene-gene interactions. Smolka et al was one of the first studies to demonstrate that functional brain imaging can be used to assess the interaction of multiple genes on the function of neuronal networks. They observed an additive effect of COMT and 5-HTT polymorphisms (N=48), accounting for 40% of the inter-individual variance in the averaged BOLD response of amygdala, hippocampal and limbic cortical regions elicited by unpleasant stimuli. We will examine the interaction between COMT and DAT genotypes first as we have preliminary data suggesting a gene-gene interaction on cue reactivity (not presented here). We expect that we will have 15-20 subjects per group (9-repeat carriers / Val carriers, 9-repeat carriers / Met homozygotes, 10/10-repeats Val carriers, 10/10-repeats / Val carriers. Groups will not be large enough to examine the contribution of more than one gene on medication response.

3. Confidentiality

There is the risk of breach of confidentiality of subject information.

Protection: All medical and research records are accessed only by staff engaged in the project or clinical care of the subjects, or by representatives of NIDA, the FDA, or other government agencies as required and permitted by law. Subjects are identified by a code, not by name, on the computerized database. As part of consent procedures, subjects are advised of the precautions taken to preserve confidentiality.

How will confidentiality of data be maintained? Check all that apply.

☒ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
☒ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
☒ Whenever feasible, identifiers will be removed from study-related information.
☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☒ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
☐ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
☐ Other *(specify):* _____

4. Subject Privacy/Protected Health Information

Please see above.

5. Tissue Specimens

Blood and urine will be collected at the initial physical evaluation to assess general health. On scanning days, an additional blood sample will be collected from females to assess menstrual cycle phase and/or stage.

Genotyping: DNA for genotyping will be extracted from the blood sample collected during the initial physical from all participants,, which will be done by using standard methods. Subjects who decide to participate in the study will provide a genetics sample. Samples will be stored in a lab located within The Center for Neurobiology at the University of Pennsylvania.

Only study staff will have access to the sample. The genetic testing laboratory will not have access identifiers and information will be stored in restricted locked rooms within locked cabinets. Stored DNA will be used only with the permission of the principal investigator for studies relating to the identification and treatment of subjects with substance abuse disorders.

RISK/BENEFIT ASSESSMENT

1. Risks and Protections

Risks associated with Magnetic Fields and the MRI environment: There are no known negative health effects of the magnetic field on the body. However, the magnetic field may move or cause dysfunction of magnetic objects in or on the body such as surgically placed steel clips, cardiac pacemakers, pumps, prostheses or bullets.

Protection: Subjects having metal in their bodies are excluded from participation in the study. Pregnant women or those not using an acceptable form of birth control will be excluded from the study. Subjects who have been metalworkers will not be eligible to participate in the study (unless a radiologist confirms that there is no danger), because they may have small metallic particles in their eyes. Patients are told that to communicate any discomfort with any of the stimuli or with the MR environment immediately. All metal must be removed from subject's clothing and pockets. No metal is allowed in the magnet room at any time. The study will be discontinued at any time and immediately at the subject's request. They will be told not to attempt to exit by themselves and will be assisted in leaving the MRI machine.

All the software used to run the fMRI sessions conforms to Specific Absorption Rate and Gradient Slew Rate limits defined by the FDA (8 watts/kg). All of the hardware used for these studies has been approved by the University of Pennsylvania Center for Advanced MRI and Spectroscopy (CAMRIS). Some of the imaging sequences and/or radio frequency coils are experimental and are not FDA approved but are considered non-significant risk investigational devices.

Regardless of whether or not the subject has requested an MRI report, if study personnel determine a subject's MRI images are unusual, those images will be forwarded to the Hospital of University of Pennsylvania for examination by a certified neuroradiologist. The neuroradiologist will inform study personnel of any potential problems. The P.I. and/or other appropriate study staff will meet with the subject to discuss his/her MRI and the neuroradiologist's recommendations, if any. If necessary, the subject will be strongly encouraged to follow up with his/her primary care physician.

Risks associated with Baclofen Administration: Baclofen has been used safely as an anti-spastic for many years, but it can be associated with some sedation or drowsiness (particularly in the early dosing). Its effects are often transient and can be alleviated or eliminated by decreasing the dosage. Effects are seldom severe enough to warrant withdrawal of the medication. Baclofen should not be stopped abruptly after chronic use (the body adjusts to the muscle relaxant effects and abrupt cessation can result in muscle spasm). The most common adverse reactions associated with baclofen are transient drowsiness, daytime sedation, dizziness, weakness, and fatigue. Less common side effects include skin rash and itching, shortness of breath, problems in urinating, constipation or diarrhea, dizziness, headache, nausea, irregular heartbeat or chest pain. Ovarian cysts have been found in about 4% of patients with multiple sclerosis that were treated with baclofen for up to one year. In most cases, these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1% to 5% of the normal female population.

Protection: Good clinical practice will be followed in terms of regularly monitoring patients for any side effects of the medication. Pregnant women or those not using an acceptable form of birth control will be excluded from the study. A physician will meet with the subject to prescribe baclofen and discuss its possible side effects. Subjects will be cautioned not to drive or operate machinery during the first few days, and will be instructed not to combine the use of baclofen with alcohol or other sedating drugs or medications. Subjects will be carefully monitored by the physician throughout the study for both common and uncommon side effects of baclofen.

Stopping Procedures: If the patient is experiencing discomfort due to side effects, reducing the dose and/or early termination will be recommended. Significant side effects (chest pain, irregular heartbeat) would occasion breaking of the blind, removal from the protocol, and provision of appropriate clinical care as indicated. Baclofen will be

tapered according to a pre-determined, conservative schedule following the cue/fMRI session. Subjects will continue to be monitored by the physician until s/he is weaned off of the medication and is not experiencing any discomfort.

Risks associated with Blood Drawing: There is a slight risk associated with the drawing of blood. Bleeding, bruising (only 1-2% significant enough to last more than 24 hrs) or infection (has not been observed due to appropriate sterilization and proficient phlebotomy techniques of staff) may occur at the site of venipuncture.
Protection: Only experienced medical staff will draw bloods under sterile conditions, minimizing any risk. The amount of blood drawn (55 cc) will not pose a risk. Standard policies for safe handling of blood samples will be followed to protect subjects and staff. All individuals who will be handling blood are required to participate in specialized Biohazard training through the University of Pennsylvania.

Risks associated with Confidentiality: Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential unless a subject says he/she intends to harm himself or another or that he/she has abused a child or an elderly person. However, authorized representatives of the Sponsor(s) (if any), the University of Pennsylvania, as well as the Food and Drug Administration (FDA), will have access to and may copy, both medical records and records from participation in this study. This access is necessary to insure the accuracy of the findings and subject safety and welfare. If any publication or presentations result from this research, subjects will not be identified by name. The data are kept in secure, locked areas and access to these areas is possible only through the investigator or research technician.
Protection: All possible measures will be taken to ensure the protection of subject privacy. Study procedures will be conducted in environments that are only accessible by study personnel (e.g. private offices or interview rooms). Subjects will only be asked questions that directly relate to study participation. Subjects will be reminded that they do not have to answer any questions that make them feel uncomfortable, although not answering certain questions may disqualify them if their safety cannot be ensured. Please refer to the HIPPA section for more information. All of the study staff who will have access to collected data are listed in the study delegation log. If a new technician is hired for this study, they will be trained and have access to the data. In addition, the following individuals and University of Pennsylvania organizations may use or disclose subjects personal health information for this research project: - The Principal Investigator and the Investigators study team (other University staff associated with the study) - The University of Pennsylvania Institutional Review Boards (the committees charged with overseeing research on human subjects) and University of Pennsylvania Office of Regulatory Affairs - The University of Pennsylvania Office of Human Research (the office which monitors research studies) - Authorized members of the University of Pennsylvania and the University of Pennsylvania Health System and School of Medicine workforce who may need to access subjects information in the performance of their duties (e.g., to provide treatment, to ensure integrity of the research, accounting or billing matters).

Specific to Genetics protections: No one other than study staff will have access to the blood. Blood samples will be coded with no subject identifiers according to the procedures of the Center for the Studies of Addiction. The genetic testing laboratory will not have access to your name, and all information will be stored in restricted areas and locked cabinets. Subjects will be identified by number only on the computerized database. As part of consent procedures, subjects will be advised of the precautions taken to preserve confidentiality. DNA samples will be stored in a laboratory at The Center for Neurobiology at the University of Pennsylvania. Access to stored samples will be limited to approval by Dr. Franklin (215-222-3200) or her designee. Future studies involving stored DNA samples must receive University of Pennsylvania approval and will be limited to studies related to addictions. DNA samples will not become part of the clinical record and will not be made available for commercial use.

2. Potential Study Benefits

Subjects may benefit from the close medical monitoring, which may assist in quitting smoking In comparison, the benefits to society in gaining knowledge about the brain substrates involved in tobacco dependence are great. The studies are well grounded in pre-clinical research literature, hypothesis-driven, and employ state-of-the-art instruments and expertise. Important and significant contributions to drug addiction research are substantial and outweigh the few (well-managed) risks in the study.

3. Alternatives to Participation

Regardless of the reason, if an individual interested in smoking reduction/cessation help does not participate in this study, he or she may be informed of non-research smoking reduction/cessation programs available within the Penn Health System or around Philadelphia. These individuals may also be informed of other available smoking help options (e.g. NRT, American Cancer Society programs, etc.).

4. Management of Information for Multi-center Research where a Penn Investigator is the Lead Investigator of a multi- center study, or Penn is the lead site in a multi-site study.
N/A

5. Risk/Benefit Assessment
Risks associated with this project are minimal because of the described protections that will be implemented. Subjects may benefit from the close medical monitoring, which may assist in quitting smoking In comparison, the benefits to society in gaining knowledge about the brain substrates involved in tobacco dependence are great. The studies are well grounded in pre-clinical research literature, hypothesis-driven, and employ state-of-the-art instruments and expertise. Important and significant contributions to drug addiction research are substantial and outweigh the few (well-managed) risks in the study.

6. SUBJECT COMPENSATION
- $6 for travel for each scheduled appointment (all visits, even if subject does not pass the consent/screening
- $25 for the consenting appointment (Consent Visit)
- $25 for a DNA sample (Physical Visit)
- $25 if the physical and psychological evaluations are completed on different.
- $75 for first scanning session (Scan Day 1 Visit)
- $25 if subject is double-booked and not scanned. A participant is only eligible to be double-booked once.
- $100 for second scanning session (Scan Day 2 Visit)
- $100 for third scanning session (Optional Sub-study Scan Day 3 Visit)
- $5 for each returned medication card
- $30 additional compensation of treatment subjects for study completion (Follow up Visit).

Payments will be made with either cash or GreenPhire Clincards. Clincards are reloadable prepaid cards that may be used for in-store purchases (by selecting either the “credit” or “debit” option), online purchases, ATM, and cash advances at a bank. Funds added to the card should be available immediately, however, in some cases it may take 1 business day. If a subject loses their card, it will be replaced at no charge. However, if a subject is repeatedly losing their card, they may incur a small fee to replace it, to be determined by the Comptroller’s Office at the University of Pennsylvania whom is monitoring Clincard registration/subject activity.

7. Subject Monitoring

Overview: Subjects will be examined and monitored by the certified nursing staff and physicians at the CSA. Psychological testing will be administered by certified therapists. Subjects will be consented and monitored by trained research technicians. The study will be overseen by the PI who will regularly examine medical and research charts.

All study personnel are required to be familiar with the study protocol. Meetings will be held weekly with the PI and study staff to ensure that all procedures are being followed correctly and that data is collected according to the IRB-approved protocol and HIPAA regulations. Research technicians are trained by the PI with the assistance of an explicit set of written study procedures that must be followed by each subject. Research technicians are required to initial and date each study procedure as it is carried out.

Technician Monitoring of Subject: Subjects will meet with the Research technician at each visit to discuss issues, monitor study progress, collect Daily Diaries, answer any questions the subjects may have, and schedule appointments. Subjects will be called in between weekly appointments by the Research Technician to discuss any potential side effects.

Medical Staff Monitoring of Subject: The study medical doctor reviews all physical examination results to determine whether the subject meets general good health requirements. The nurse will meet with the subjects at

all visits to discuss study medication, discuss side effects, review any concomitant medications, collect previous weeks' pill packs and take note of any medical concerns the patient expresses with regard to the medication. The nurse will measure vital signs and go over the Adverse Events sheet with the subject.

8. Data and Safety Monitoring

Who will monitor this study? Check all that apply.

This is a low risk, single-site, Phase II study, involving a medication already FDA approved and marketed for the treatment of other illnesses. The study design is straightforward and familiar to the research staff at the CSA. Therefore, one monitor should be sufficient to complete the monitoring process.

√ Principal Investigator
Sponsor or contract research organization
NCI sponsored cooperative group
Cancer Center (if mandated by CTSMRC)
Medical monitor
Safety monitoring committee
√Center for the Studies of Addiction Coordinator: A study monitor who is knowledgeable in the protocol, regulations, and university approved procedures for conducting and monitoring clinical investigations will be assigned to monitor the study. The monitor will be selected from one of the Study Coordinators working at the University of Pennsylvania Center for the Studies of Addictions.

Written monitoring procedures for monitoring clinical investigations, proposed by the OHR and previously established at the CSA will be implemented to assure the quality of the study and to assure that each person involved in the monitoring process carries out his or her duties.
The Principal Investigator will maintain a record of the findings, conclusions, and action taken to correct errors noted by the monitor for each visit.
Monitoring Responsibilities (conducted by the Study Coordinator). The monitor, in accordance with local and NIH requirements, should ensure that the study is conducted and documented properly by carrying out the following activities:

a. Verifying that the investigator has adequate qualification and resources and these remain adequate throughout the study period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the study and these remain adequate throughout the study period.
b. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
c. Verifying that written informed consent was obtained before each subject's participation in the study.
d. Verifying that the investigator is enrolling only eligible subjects.
e. Reporting the subject recruitment rate.
f. Verifying that source data/documents and other study records are accurate, complete, kept up to date, and maintained.
g. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated and identify the study.
h. Checking the accuracy and completeness of the CRF entries, source data/documents, and other study related records against each other.
i. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained, and initialed by the investigator or by a member of the study staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.
j. Determining whether all adverse events (AE's) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the applicable regulatory requirement(s).
k. Determining whether the investigator is maintaining the essential documents.
l. Communicating deviations from the protocol, SOP's, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.
m. Follow the University SOP's, GCP, and the applicable regulatory requirements.

Study Monitoring

The study Principal Investigator and research staff will prepare a case record form (CRF) that is designed to reduce coding errors and promote data quality. Each page of the CRF will contain a header that includes the title of the protocol, the protocol number, the subject randomization number, subject screening number, and visit number. The technicians are responsible for data entry. The research charts will be maintained separately from the CRF and will contain subject information that is not entered in the study CRF database.

Regulatory Binder: A detailed Regulatory Binder will be assembled by the research team. Any changes to procedures are documented in this section. This binder is the backbone of quality assurance. We use this binder to train any new study personnel and for reference so that our policies and procedures are standard throughout all phases of the protocol. The 'Measures' section of the binder addresses, specifically all forms and instruments that comprise the CRF. A Table of Contents has been prepared that contains all the forms used in the study.

The study manual will include

- study protocol research team names, titles, roles and responsibilities, work and home phone numbers
- purpose of study, study intent and rationale
- all study procedures for each team member (PIs, technicians, study coordinator, pharmacists, nurses, physicians, etc.)
- recruitment and S screening procedures
- intake procedures
- study phase procedures
- completion/discontinuation procedures

Data Collection Training

The CSA provides comprehensive data collection training for all research technicians (RTs). RTs receive training on how to proceed with problematic Subjects. RTs are extensively trained on all MRI procedures. RTs are trained to follow the general data collection guidelines listed below.

- RTs should be present when subject is completing instruments.
- Research interviews and evaluations should be administered in a private, quiet office or area.
- Instruments are introduced and explained the same way each time to each subject.
- Order of research assessments should be maintained, as much as possible.
- Order of specimens obtained should be maintained as much as possible.
- RTs should show an interested, polite, appropriate, and helpful demeanor.

Quality assurance (QA) procedures

Changes to the CRF and the study database are strictly monitored. After a single line is drawn through the corrected data point, the RT documents the change by placing his or her initials and the date of the change adjacent to the correction. Typical QA responsibilities of the RT include:

- Checking all data during or immediately after study visits.
- Checking charts at predetermined points during the study (initials and date of checker are required on each form checked).
- Performing the initial data check after a few charts have been entered.
- Performing a 10% data check when all data have been entered.

Typical responsibilities of the PI include:

- Monitoring and reporting on RT interviewing and data collection proficiency at subject study visits.
- Checking charts at predetermined points during the study (initials and date of PI are required on each form checked).
- Supervising study database checks.
- When databases, in Filemaker Pro or other applications, are developed by the research staff, only the data checked by the RT are entered. Data sets are double checked in pairs by technicians. The PI supervises any corrections to the data set and reviews the completed database before the information is used in any reports or analyses.
- The PI holds meetings with the RTs to report and review the project and data entry status.
- PI reviews lab results and screening information (inclusion/exclusion checklist) for potential subjects.
- PI reviews adverse events on at least a weekly basis

Study Logs and Reports
Study logs are routinely maintained in order to keep computerized back up records of S identifying and socio-demographic characteristics and experimental group status. The study subject log usually includes subjects' initials, study number, CRF number, date of birth, race, medication start dates, subject status (active, drop-out, completer, follow-up) and relevant dates and comments.

Data Storage on Site
The CRFs and research charts are stored in file rooms specifically designed for data storage. All study data are housed in locked file cabinets. Only designated members of the research team have access to the file cabinets containing research data. Data are kept on site for not less than three years after the subject has completed the final assessment. Data are then eligible for archiving.

9. APPENDIX 1: (Sub-study) Baclofen effects on brain and behavior in treatment-seeking cigarette smokers who drink heavily

9.1 Background
Epidemiological studies have suggested a strong correlation between smoking and alcohol use (106). Specifically, it has been estimated that 20–25% of smokers are also heavy alcohol users (107), and this co-occurrence has been associated with poorer outcomes in terms of physical health and smoking cessation quit rates (107, 108). In the context of a quit attempt, alcohol use has been associated with increased risk for a smoking lapse, such that heavy drinking smokers are 4 times more likely to experience a smoking lapse in the context of a drinking episode and 8 times more likely to lapse in the context of a heavy drinking episode (108).

Several theories have been proposed to explain the strong co-occurrence of alcohol and cigarette use. For example, participants with a past history of alcohol dependence have reported greater reinforcement from nicotine administration as compared to those who were never alcohol dependent (109). Given that baclofen is a GABAergic agent that has been shown to reduce cue-induced craving and brain activity in reward-related regions, baclofen may have a similar effect on alcohol cue-induced craving. To date, however, there are no studies examining the effects of baclofen on brain and behavioral responses to both smoking and alcohol cue reminders in cigarette smokers seeking smoking cessation treatment who drink heavily. As such, this sub-study will yield novel findings on baclofen's effects on brain and behavioral responses associated with co-occurring alcohol and tobacco use.

9.2 Risk/Benefits
Potential Risks
This sub-study is part of a larger, ongoing study described above. As such, the potential risks are the same as the larger study.

Potential Benefits
In addition to the benefits described in the larger, ongoing study, this sub-study benefits society by providing information and a potential improvement in the effectiveness of treatment for problem drinking in cigarette smokers, which may reduce the personal and societal costs associated with these problems.

Risk Benefit Ratio
The potential benefits of this study far outweigh the potential risks. Co-occurring alcohol and tobacco use is a serious concern with only mildly effective pharmacotherapy. Even in the best programs, relapse rates are high. Individuals accepted into this study will receive close medical and psychiatric monitoring. Subjects will be screened prior to admission into the study and those at risk for adverse reactions will be excluded.

10. Sub-Study Objectives
Objective 1: Examine the effects of baclofen on brain responses to alcohol cues (compared to non-alcohol cues) and drinking behavior compared to placebo following 4 weeks of baclofen or placebo in individuals actively seeking smoking cessation treatment and drink heavily.

Hypothesis 1: Baclofen will modulate resting brain activity—specifically, activity in the lateral orbitofrontal cortex. Baclofen will also modulate alcohol cue reactivity: activity in reward-related regions will be blunted in subjects receiving baclofen, while those receiving placebo will display the original signature of craving. Baclofen will correct vulnerabilities by modulating neural activity in the amygdala and ventral striatum, regions known to respond to reward and in the insula, which is considered an autonomic signaling relay station and plays a role in drug craving.

11. Sub-study Design

11.1 General Design

This optional sub-study involves adding one additional MRI scanning session to the larger, ongoing main study (described above). Twenty (20) individuals who are seeking smoking cessation treatment and drink heavily (drinking five or more alcoholic drinks on the same occasion on five or more days in the past 30 days). The additional scan will occur after 4 weeks of baclofen or placebo and will follow most of the same procedures as the previous two scan sessions; however, instead of viewing smoking cues, subjects will view alcohol cues.

11.2 Primary Study Endpoints

The primary endpoints to be measured include:

- Self-report ratings of cues, subjective ratings of craving during/following cue exposure, and neuroimaging data on cerebral blood flow when the brain is at rest and when exposed to alcohol cues.

12. Sub-study Subject Selection

12.1 Inclusion Criteria

1) Subjects have consented to main study protocol and are eligible to randomize to study drug.
2) Provide voluntary informed consent.
3) Consume five or more alcoholic drinks on the same occasion on five or more days in the past 30 days.

12.2 Exclusion Criteria

1) See exclusion criteria for main study

12.3 Subject Recruitment and Screening

Subjects will be recruited from those who respond to our advertisements for the main study. Following the consent of the main study, potential subjects will provide information on recent substance use through administration of the Addiction Severity Index (ASI). If the potential subject reports consuming five or more alcoholic drinks on the same occasion on five or more days in the past 30 days, s/he will be flagged as a potential participant for the sub-study. If the individual shows continued interest in participating in the study, an appointment will be made for further screening at the Center for Studies on Addiction (CSA). The CSA initial screening process will be described, and the individual will also be informed that s/he must be available for at least two separate appointments during the screening week (unless the two appointments are combined) (see the Physical Examination Visit and Psychological Evaluation Visit sections pg 10-11 for more information). Potential subjects will be informed that all information obtained will be used to determine his/her final eligibility for main and sub-study participation. If the individual does not qualify for the study, s/he will be provided with appropriate community smoking cessation referrals.

12.4 Informed Consent Visit

Subjects will undergo the informed consent process for the sub-study once their 1st MRI session imaging data is able to be reviewed. Once their eligibility is confirmed, an in depth explanation of the study procedures, its risks, potential benefits, and alternatives to treatment will be discussed with the subject, given their interest in participation. Following resolution of any questions, subjects who appear to understand the nature of the study and consent will be asked to sign the study consent form. A copy of the sub-study informed consent form will be given to each subject. S/he is also reminded that participation is voluntary, and at any time, s/he may withdraw from the main study or sub-study. **Measures and procedures described for the MRI sessions of the main study will be mostly the same for the sub-study's 3rd MRI session visit. The major differences will be the use of alcohol imaging cues, a different craving scale measure pre/post scan (Within-Session Rating Scale-Alcohol (WSRS-Alcohol) and no cotinine testing.**

13 3rd MRI session visit (2 hours)

The 3rd MRI session takes place after a subject has been on the medication for 4 weeks. At this session, the subject will be asked to take their medication in the presence of Study Staff [Baclofen has a short life with maximum effects at 2 hours and waning thereafter. Thus, ingesting the medication in front of study staff will ensure that the medication was ingested and that its effects will be observable during the MRI as well as standardize time since dose]. Stimuli for the 3rd scan will be audio-visual video clips consisting of either alcohol-related or non-alcohol-related cues instead of smoking-related and non-smoking-related cues presented during scans 1 and 2. In addition, subjects will be asked about their craving pre- and post-alcohol cue exposure using the WSRS-Alcohol. Otherwise, this visit will be exactly the same as the previous MRI sessions described above.

At this appointment, the subject will make a quit smoking attempt. To assist the subject in meeting this goal, study staff will meet with the subject to go through the "You can quit smoking" pamphlet during this appointment which is an interactive tool designed to help people recognize relapse triggers, provide alternative strategies when craving occurs, and how to acquire support from friends and family. Explicit instructions for how to conduct this session are included with the uploaded IRB documents (Titled: Smoking Booklet Script). Monitoring of smoking behavior is accomplished with completion and collection of subject Daily Diaries, weekly phone calls with study staff, weekly meetings with study staff, and CO measurements.

14 Sub-study Subject Stipends or Payments

In addition to the payments received as part of the main study, sub-study subjects will receive $6 for travel expenses and will be paid $100 for completing the 3rd scan session visit.

*** ALL REMAINING ASPECTS OF THE SUB-STUDY ARE DESCRIBED ABOVE IN SECTIONS 1-8.**

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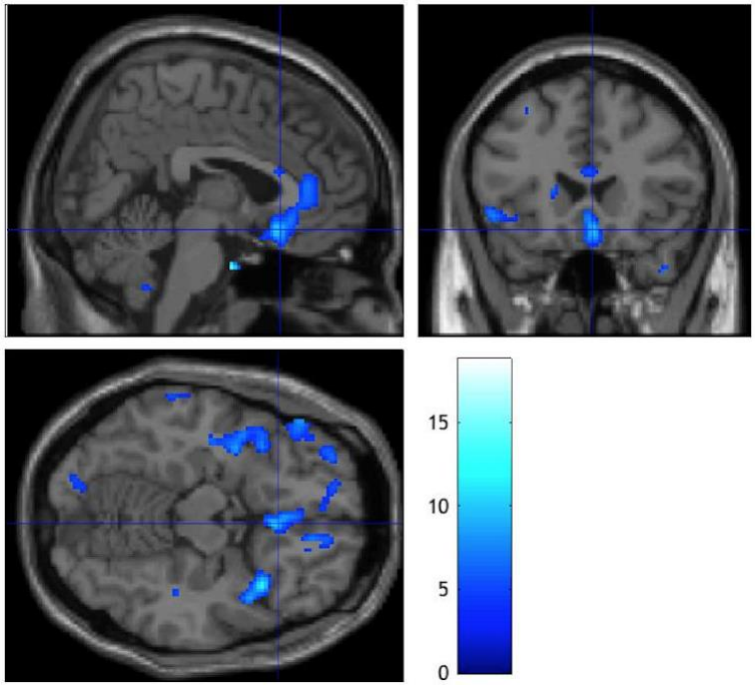
Brain Response to Baclofen versus Placebo during Smoking Cue Exposure



The phenomenon of brain and behavioral drug cue reactivity is complex and multifaceted. As we have shown previously, genetic variance, sex, hormones, and many other variables affect smoking cue reactivity. As such, we cannot expect that one medication will be helpful in every individual, which is why one goal of our GABA B R01 grant was to identify a cue-vulnerable baclofen-responsive endophenotype. In spite of the multitude of inter-individual differences that can provide protection or confer vulnerability to smoking reminders, we were able to show an overall reduction in smoking cue reactivity in baclofen-treated subjects that was not observed in placebo-treated subjects (N = 22 per group). The figure (right) shows reduced brain activity during smoking cue versus nonsmoking cue exposure in individuals receiving 20 mg baclofen, q.i.d. Similar to our study in cocaine patients during cocaine cue exposure (Young et al, *J. Neuroscience*, 2014), baclofen blunted smoking cue responses in the medial orbitofrontal cortex, ventral medial prefrontal cortex and bilateral anterior ventral insula (i.e., mesolimbic circuitry). This study adds to the literature by comparing brain activity before and during treatment, and by examining baclofen's effects in nicotine use disorder (NUD). There were no differences in smoking cue neural reactivity between pre- and during treatment comparisons in the placebo group. This data is currently being prepared for dissemination to the scientific community.