Enhancing Panic and Smoking Reduction Treatment with D-Cycloserine

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1. TITLE

Enhancing Panic and Smoking Reduction Treatment with D-Cycloserine

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3. PURPOSE

Approximately 9-15 million smokers in the U.S. meet criteria for at least one anxiety disorder during their lifetime (Kessler et al., 2005), and these individuals experience significant challenges quitting tobacco (Piper et al., 2010; Zvolensky et al., 2008). Yet, little attention has been given to the maintenance of tobacco use among persons with anxiety disorders, and in particular, smokers with a history of panic attacks. This group is especially important to study because research shows that they have significantly lower quit rates than smokers with no history of panic attacks, and that they respond the same to placebo, single cessation pharmacotherapy, and combination cessation pharmacotherapy (Piper et al., 2010a). Recent efforts from our group have led to the development of a cognitive-behavioral program, Panic and Smoking Reduction Treatment (PSRT), which integrates interoceptive exposure, cognitive restructuring, and psychoeducation exercises with standard smoking cessation strategies and nicotine replacement therapy. Early testing of this program indicates that this targeted smoking cessation treatment for smokers with panic attacks is efficacious, but leaves room for improvement. Specifically, a study examining the efficacy of PSRT revealed that individuals receiving PSRT evidenced significantly greater reductions in anxiety sensitivity and were more likely to be smoke free than those receiving standard smoking cessation treatment (Zvolensky et al., 2008). However, only 42.7% of the PSRT condition were smoke-free at 16 weeks post-quit.

The current study seeks to evaluate whether d-cycloserine (DCS) can augment the efficacy of PSRT. DCS is a partial NMDA agonist, which has shown to enhance the retention of fear extinction (Davis et al., 2005; Richardson et al., 2004; Ledgerwood et al., 2004; Ledgerwood et al., 2005), which is a key mechanism underlying the efficacy of PSRT (Zvolensky et al., 2008). Of note, DCS has shown to be an effective and safe augmentative strategy in panic disorder (Otto et al., 2010), which may make it a particularly effective strategy for smokers with panic attacks.

Our study consists of three aims: to compare, in a randomized clinical trial, (1) the effects of PSRT+DCS versus PSRT+PBO on smoking cessation outcomes and (2) the effect of PSRT+DCS vs. PSRT+PBO on the frequency and intensity of panic attacks, withdrawal symptoms, negative affect, anxiety sensitivity, and distress intolerance; and (3) to explore the

mechanisms by which PSRT+DCS improves smoking cessation outcomes. We hypothesize that individuals in the PSRT+DCS condition will evidence superior smoking cessation outcomes (i.e., longer time to first smoking lapse and relapse and lower PPA) and reduced anxiety and panic symptomatology compared to those in the PSRT+PBO condition.

To achieve our aims, adult smokers with panic attacks from the Austin community will be randomly assigned to either: (1) PSRT+DCS or (2) PSRT+PBO. Primary outcome measures will be point prevalence abstinence (PPA), time to first smoking lapse, and time to smoking relapse. Proposed mediators include panic attacks, distress intolerance, anxiety sensitivity, nicotine withdrawal symptoms, and negative affect. These variables will be assessed at baseline, weekly during the treatment phase, and at 2, 4, 8, 10, 16, and 24 weeks after quit date.

The proposed study represents a crucial and important stage in translating basic research to strategies for treating nicotine dependence. The investigation addresses an important public health issue by testing an integrated intervention - informed by basic research - that may lead to a more effective and efficient treatment for at-risk smokers while simultaneously isolating explanatory mechanisms. The expected findings should: (1) guide advances in the theoretical conceptualization of the mechanisms involved in panic- and anxiety-smoking relations; and (2) provide initial effect size data for the addition of DCS to an integrated psychosocial/behavioral and pharmacological smoking cessation intervention for smokers with panic attacks, and thus provide the necessary data for a large-scale follow-up trial.

Participants will also complete a computerized facial recognition task that examines generalization of memory to emotional stimuli. In the context of learning about threats, generalization can be adaptive; however, when the threat response is overgeneralized, it can be impairing. Recent research has focused on fear overgeneralization as a potential transdiagnostic mechanism of anxiety disorders (for review see Dymond et al., 2015; Lissek & Grillon, 2015). This research utilizes Pavlovian conditioning paradigms that pair one stimulus (CS+) with an aversive event (e.g., shock), and subsequently examines how defensive responses (e.g., startle, risk assessment) are generalized to stimuli that resemble the CS+. This line of research finds some degree of generalization in healthy participants (Lissek et al., 2008), but overgeneralization in patients with panic disorder (Lissek et al., 2010), generalized anxiety disorder (Lissek et al., 2014), posttraumatic stress disorder (Levy-Gigi et al., 2015), and obsessive compulsive disorder (Kaczkurkin et al., 2013). Thus, overgeneralization represents a potential treatment target (Kheirbek et al., 2012). This task aims to expand the understanding of stimulus generalization by focusing on *recognition* (i.e., no use of shock or Pavlovian conditioning) of socially relevant stimuli (i.e., faces), which may underlie the generalization of emotional responses observed in conditioning paradigms.

4. PROCEDURES

The proposed study will utilize a prospective, experimental research design. We will recruit adult daily smokers with a history of panic attacks in the last year and they will be randomly assigned to either: (1) Panic and Smoking Reduction Treatment plus d-cycloserine (PSRT+DCS) or Panic and Smoking Reduction Treatment plus placebo (PSRT+PBO). Participants will be adults between the ages of 18-65 who have smoked daily for at least a year, currently smoke an average of at least 8 cigarettes per day, and report a motivation to quit smoking in the next month of at least 5 on a 10-point scale. Moreover, participants will have elevated fears of withdrawal and anxiety related bodily sensations and a tendency to regulate these feelings with smoking, as indexed by meeting or exceeding established cut-off scores on the Smoking Abstinence Expectancies Questionnaire ($\geq$78), respectively. Eligible participants will be randomly assigned to either condition by the project biostatistician (David Rosenfield, Ph.D. – Consultant at Southern Methodist University). Primary outcome measures will be point prevalence abstinence (PPA), time to first smoking lapse, and time to smoking

relapse. Proposed mediators include panic attacks, distress intolerance, anxiety sensitivity, nicotine withdrawal symptoms, and negative affect. These variables will be assessed at baseline, weekly during the treatment phase, and at 2, 4, 8, 10, 16, and 24 weeks after quit date.

Eligibility Screening

Internet and Telephone Prescreen & In-person or Telephone Screening. Individuals interested in participating in the study will be directed via various recruitment strategies to an Internet prescreen using REDCap. The first page of the prescreen survey will include the consent form for the prescreen survey, telephone screening, and demographic and medical history questionnaire procedures where participants will be able to give informed consent through REDCap. This online prescreen will assess basic eligibility criteria and individuals who appear potentially eligible will be further assessed via a telephone prescreen. The prescreen procedure is the first point of contact for participants, and it will allow us to ask critical information about the potential participant's willingness and ability to commit to the frequency of clinic visits as well as the assessment of inclusion criteria. Participants will also be asked during the phone screen whether they have sufficient command of the English language, as visits will be conducted in English and all self-report measures are in English. If a participant passes the Internet and Telephone Prescreen, they will complete the Screening assessment either over the phone or asked to come into the lab for an in-person screening. The screening will include a psychiatric evaluation process through the Structured Clinical Interview for DSM-IV (SCID) and the Panic Disorder Severity Scale (PDSS) to evaluate the presence of panic attack history and psychiatric exclusion criteria. The interview will also allow for assessment of primary and secondary diagnoses if applicable. Suicidality will also be assessed at this time using the Columbia-Suicide Severity Rating Scale (C-SSRS). Demographic and general medical health history information will also be captured during the screening assessment. If a participant is assessed over the phone, the demographic and general medical health history survey will be sent to them via REDCap.

In-Person Screening Assessment. If a participant comes into the lab for their screening assessment, they will first read and give signed, informed consent. The researcher will answer any questions they may have and complete the screening. Participants' blood pressure, heart rate, and CO2 will be measured at this visit.

***Medical Screening*.** A study physician (Dr. Carlos Tirado) will review the patient's medical history to determine if it will be safe for them to take the study medication. The physician will schedule appointments and order lab tests if he deems it necessary should the patient be present with any of the following conditions: 1. Urinary complaints (flank pain, pyuria, dysuria) 2. Fever greater than 101.4 F/38.5 C within the last 24 hours 3. Diabetes 4. History of hypo/hyper thyroidism 5. Known hepatic disease (viral hepatitis, alcoholism) 6. Known or suspected substance abuse 7. Fatigue (acute) 8. Weight loss greater than 10 pounds in last 30 days 9. Other physical exam and medical history finding that in the physician's judgment requires further laboratory assessment to rule out a significant medical condition. If deemed necessary by Dr. Tirado, safety evaluations will also include laboratory tests (CBC, chemistry profile, thyroid function test, and urinalysis). A urine pregnancy test will be performed on all female participants of childbearing potential at intake and monthly following randomization. Research personnel will also discuss the potential side effects of DCS with potential participants. Any positive pregnancy tests resulting in exclusion from the study will be handled by having the PI or physician meet with the participant to provide a feedback session.

Baseline Visit for participants that completed the Screening Assessment over the phone

The consent form will be sent to participants via REDCap before the appointment so that they have time to read through the form and give their informed consent. Upon arrival, if the participant has not signed the consent form, they will receive an informed consent form explaining the details of the study, potential benefits and risks of participation, and the procedures they will undergo if they choose to participate. After reading the informed consent document, a study coordinator will discuss these issues with the potential participant and will answer any questions he or she may have about the study and participation. If the individual chooses to sign the informed consent, he or she will have their blood pressure, heart rate, and CO2 measured. Those who have readings outside of the safe range (ranges are provided by our study physician: 85mmHg < Systolic BP < 160mmHg and 55mmHg < Diastolic BP < 100mmHg) will have their measurements sent to our study physician for further safety assessments. If the physician deems it is unsafe for the participant to take the study medication, they will be notified, thanked for their time, and dropped from the study. All participants will continue with the rest of the baseline visit which includes introduction to the research study, goals of the treatment, explanation of data collection documents, and assignments including surveys to be completed before coming to the lab. Participants will also be asked to provide contact information of two significant others we can reach out to if we loose contact with them. If we need to contact these significant others, we will let them know the participant gave us their information, if they can provide us with the participant's new contact information (if it has changed, and/or leave them a message asking to contact us.

Randomization

The project Biostatistician, Dr. David Rosenfield, will oversee the randomization to either PSRT+DCS or PSRT+PBO conditions. Both participants and study personnel will be blind to study condition, and study medication will be labeled by either "A" or "B" by the pharmacy in order to blind the medication administration. A random number generator will be used to assign individuals to either condition. Only Dr. Rosenfield will have the information necessary to break the blind. Prior to data analyses, Dr. Rosenfield will check the balance of randomization and control for any factors that are imbalanced.

Intervention Modules

Panic Smoking Reduction Treatment (PSRT). Table 1 provides a session-by-session outline and illustrates the integrated nature of this hybrid treatment as well the nature of the experimental manipulation (i.e., DCS vs. PBO). PSRT incorporates elements of standard smoking cessation treatment (i.e., counseling plus NRT) with procedures for reducing panic and enhancing tolerance to withdrawal sensations. Written therapist and patient manuals will be used and followed at all times to ensure standardized delivery of the treatment (7-weeks of individual therapy). Interventions that uniquely focus on addressing panic, fears and intolerance of anxiety, bodily-related sensations, and affect-relevant withdrawal symptoms include: (1) interoceptive exposure; (2) corrective information about anxiety and cognitive interventions designed to teach patients alternatives to catastrophic misinterpretations of the sensations and their

feared consequences; and (3) situational exposure. Particularly novel here is that we are asking patients to remain cigarette-free prior to certain sessions before to the quit date. Indeed, this allows for direct extinction training during the session (where emotional cues are induced and no smoking occurs), and because patients can remain smoke-free for hours after the session (i.e., 2 to 12 hours after PSRT; Zvolensky et al., 2008), this training can ensure absence of a contingency between emotional induction and cigarette use, and during the time of DCS use. Lastly, the therapist will schedule with the participant a regular time each week between quit date (week 5) and the end of the protocol (week 29) to meet via telephone. During these brief telephone meetings, the therapist will address any barriers that may arise and to ensure that participants abstain from smoking. The therapist will provide social support, trouble shoot for high-risk situations, and develop a plan to keep the participant on track with study goals.

1. Table Session-by-session outline of intervention procedures			**DCS/PBO Administration**
Week	Standard Smoking Cessation Procedures	Panic Reduction Procedures	
1	• Provide quit support and reinforcement • Discuss past experiences • Set quit date (Monday of Week 5) • Initiate self-monitoring (tracking smoking and noting cues for smoking)	• Integrated treatment (PSRT) rationale • Education on panic-smoking link • Interoceptive exposure introduction • Interoceptive exposure practice • IE homework practice assigned	• No
2	• Help identify high-risk for relapse situations • Discuss abstinence violation effect • Develop coping strategies • Encourage enlisting social support • Provide self-help materials	• Review education on panic-smoking link • Review interoceptive exposure rationale • Cognitive restructuring • IE practice • IE homework practice assigned • Instruction to refrain from smoking 4 hours prior to Session 3	• No
3	• Review elements discussed in Session 2 and isolate any areas of question/concern for patients	• Interoceptive exposure practice • Cognitive restructuring • IE homework practice assigned • Instruction to refrain from smoking 4 hours prior to Session 4	• Yes
4	• Discussion of upcoming quit day • Instruct on proper use of NRT	• Homework practice review • Interoceptive exposure practice • Cognitive restructuring • IE homework practice assigned	• Yes
5	QUIT WEEK • Initiate NRT • Discussion of quitting experiences • Provide support	• Encourage self-awareness of the role of panic-related experiences in smoking behavior and urge to smoke.	• Yes

	• Anticipate high-risk situations	• Underscore importance of integrating exposure, non-catastrophic thinking, and education to maintain abstinence. • Cognitive restructuring • Interoceptive exposure	
6-7	• Continue NRT • Provide support • Anticipate high-risk situations • Develop social support for nonsmoking • Lifestyle changes (e.g., stress management, healthy diet, exercise, and increasing pleasant nonsmoking activities)	• Cognitive restructuring • Interoceptive exposure • Situational exposure (i.e., avoided situations)	• No

Nicotine Replacement Therapy (NRT). All participants will receive Nicoderm CQ®, 24-hour transdermal nicotine patches and will be educated about the use of the patch at the session immediately prior to quit date. They will be instructed to apply one patch daily, beginning on quit date (week 5). Participants will use the 3-step tapering Nicoderm process (21-mg, 14-mg, and 7-mg). This regimen has been used in previous trials with a similar formulation of the patch (Fiore, 2000). A meta-analysis found no differences in outcome between 16- or 24-hour patches (Fiore et al., 1994). Participants who continue to smoke or lapse after quit day will not be instructed to discontinue the patch until their smoking level reaches 4 cigarettes/day for 4 days. Smokers who lapse during treatment will be encouraged to set a new quit date and continue their cessation attempt.

***D-cycloserine or Placebo Treatment*.** All capsules will be identical in appearance to maintain the blind design of the study. Study capsules will be prepared containing: (a) 250mg d-cycloserine or (b) pill placebo. Individual doses of study medications, prescribed by Dr. Tirado, will to be dispensed to patients by study personnel 1 hour prior to sessions 3-5 and patients will be asked to remain in the clinic until session time. Because all pill taking is observed, no pill counts are necessary to help ensure adherence to the randomized drug condition. All medications will be stored in a locked refrigerator.

A. LOCATION

All data will be collected at the University of Texas at Austin. Upon completion of data collection, data analysis will take place at UT, Southern Methodist University (PI: David Rosenfield), the University of Houston (PI: Michael Zvolensky), and Boston University (PI: Michael Otto). All data will be encrypted with numeric codes so that no identifying information will be included in analyses. Drs. Rosenfield, Zvolensky and Otto will obtain IRB approval from their respective instructions prior to accessing the data.

B. RESOURCES

The project is funded through the National Institute on Drug Abuse (NIDA) grant number R34DA034658.

C. STUDY TIMELINE

Data collection will begin upon IRB approval (tentatively, November of 2013) and has an anticipated end date of August 2017. Data will be analyzed soon after data collection ends and the project will end once the findings has been published. We anticipate to keep the study open until December 2018.

5. MEASURES

Assessment Instruments

Screening Measures

Eligibility Screen. This prescreen questionnaire and telephone-screening will assess inclusion and exclusion criteria.

Motivation to Quit Smoking. This 10-item measure will be used to determine participants' pre-cessation motivation to quit smoking (Rundmo et al., 1997).

Demographics. Participants will be asked to provide standard demographic information (i.e. age, gender, race/ethnicity, level of education, etc.) as well as history of medical problems.

Psychiatric History. Diagnostic exclusions and lifetime prevalence of Axis I diagnoses will be determined by the Structured Clinical Interview for DSM-IV (SCID-NP; First et al., 2007) during the screening. The diagnostic interview will be administered by trained research personnel and will be supervised by the PIs. This interview will serve to contextualize participants' psychiatric history at baseline. In addition, the SCID will be conducted at the final follow-up visit (week 29) in order to assess for changes in diagnoses. Anxiety sensitivity interventions have been shown to aid in the prevention of future mental health disorders, so assessing for changes in diagnostic status in this population will be a useful addition to the literature.

Suicide. The Columbia Suicide Severity Rating Scale (C-SSRS; Posner, Oquendo, Gould, et al. 2007) is a standardized measure of current and past self-injurious behavior, suicidal intent, and suicidal behaviors. The C-SSRS has demonstrated good reliability and validity (Hammad et al., 2006; Posner et al., 2007). The C-SSRS will be administered as part of the diagnostic interview in order to assess for a history of suicide attempts or current suicidal thoughts or plans.

Vital Signs. As part of their screening visit, participants' blood pressure will be assessed.

Laboratory Testing. A study physician will review the patient's medical history and conduct a complete physical examination if deemed necessary. Safety evaluations will also include laboratory tests (CBC, chemistry profile, and thyroid function test). A urine pregnancy test will be performed as part of the general physical medical evaluation of patients during the baseline visit and to assess for study exclusion criteria. In addition, a urine pregnancy test will be performed each month following randomization. Blood draws will be performed(if deemed necessary) in our laboratory

at the University of Texas by a certified phlebotomist and Clinical Pathology Laboratories in Austin will analyze the samples.

Measures of smoking behavior, nicotine dependence, and withdrawal symptoms

Smoking History Questionnaire (SHQ). Smoking history and pattern will be assessed with the SHQ, a 30-item measure that includes items pertaining to smoking rate, age of onset of initiation, years of being a regular smoker, etc. (Brown et al., 2002; Zvolensky et al., 2005). This measure will serve to contextualize the participants' smoking behavior and history at intake.

Fagerström Test for Nicotine Dependence (FTND). The FTND is a 6-item scale designed to assess gradations in tobacco dependence (Heatherton et al., 1991). This measure will serve to quantify nicotine dependence, which will be used as a covariate in the primary analyses.

Nicotine Withdrawal Symptoms. Given its potential relation to outcome, we will monitor withdrawal severity at baseline, weekly throughout treatment and at follow-up assessments, using the Minnesota Withdrawal Scale, a reliable and sensitive 10-item scale (Hughes & Hatsukami, 1986).

Questionnaire of Smoking Urges (QSU). The QSU is a 10-item measure that assesses urges and cravings for cigarettes (Cox et al., 2001). We will monitor craving at baseline, weekly throughout treatment, and at the follow-up assessments. This assessment of urges can be used to evaluate consistency (or lack thereof) with withdrawal symptoms in follow-up tests from the data set.

Smoking Abstinence Expectancies Questionnaire (SAEQ). The SAEQ is a 28-item measure that assesses short-term psychological and physiological consequences to (hypothetically) abstaining from smoking among those that smoke everyday. The measure has 4 internally consistent subscales: Negative Mood, Somatic Symptoms, Harmful Consequences, and Positive Consequences.

Smoking Cessation Self-Efficacy (SE). A participant's confidence that he or she can carry out a behavior such as quitting smoking will be measured at baseline using a well-established 9-item scale developed by Velicer, Diclemente, Rossi, and Prochaska (1990). This instrument includes a subscale regarding confidence in remaining abstinent in negative affect. In previous work, we have successfully used this negative affect subscale for smoking self-efficacy (alpha = .85; Zvolensky, Schmidt et al., 2003).

Smoking Cue Appeal Survey (SCAS). The Smoking Cue Appeal Survey (Murray, McHugh, Rowley, Sirota, & Otto, 2010) measures cue appeal to sensory smoking cues. An initial study demonstrated good psychometric properties associated with smoking status and craving (Murray et al., 2010).

Barriers to Cessation Scale (BCS). The Barriers to Cessation Scale (Macnee & Talsma, 1995) is a 19-item measure assessing barriers or specific stressors associated with smoking cessation. It has been found to have good internal consistency, good content, and predictive validity (Macnee & Talsma, 1995).

Smoking Consequences Questionnaire – Brief (SCQ-Brief). The SCQ-Brief is an abbreviated version combining both the Smoking Consequences Questionnaire (SCQ; Brandon & Baker, 1991), an 80-item measure assessing positive and negative smoking outcome expectancies, and the Smoking Consequences Questionnaire - Adult (SCQ-A; Copeland et al., 1995), a 55-item measure considered to be more suitable for adults. The brief version is a 25-item measure that has shown good internal consistency and convergent validity (Rash & Copeland, 2008).

Intolerance for Smoking Abstinence Discomfort (IDQ-Smoking). The IDQ-Smoking questionnaire is a 17-item measure that assesses the intolerance of discomfort associated with recent smoking cessation. The IDQ-S has three reliable components: withdrawal Intolerance, Lack of Cognitive Coping, and Pain Intolerance.

Smoking Status. Self-reports of smoking status will be collected from participants at baseline, weekly throughout treatment and at follow-up assessments. Participant reports of abstinence at all times will be verified by expired carbon monoxide, and additionally at the 8, 10, 16, and 24-week interviews with saliva cotinine (see Table 2). The main outcome analyses are based upon 7-day point prevalence abstinence (i.e., reported abstinence of at least 7 days prior to each scheduled follow-up). Self-report will be overridden by objective verification in the conservative direction (Proceedings of the National Working Conference on Smoking Relapse, 1986).

In addition to point-prevalence outcomes, we also will use the timeline follow-back (TLFB) procedure for assessing the time to first smoking lapse and the time to first relapse, defined as the 7th day on which smoking occurs. The TLFB procedure has demonstrated good reliability and validity (Sobell & Sobell, 1996). The TLFB will be administered at each follow-up to assess cigarette use since the previous assessment.

Biochemical Verification. Self-reported abstinence at the 8, 10, 16, and 24-week follow-ups will be verified by saliva cotinine (cutoff value of 10 mg/ml) for stated abstinence of 2 weeks or more (cotinine may be incompletely metabolized before this time), and carbon monoxide analysis of breath samples (8ppm cutoff) for stated abstinence of 24 hours to 2 weeks (Jarvis et al., 1987). Saliva samples will be frozen and analyzed by an outside laboratory for cotinine level using radioimmune assay. Expired air carbon monoxide levels will be assessed with a Vitalograph Breathco carbon monoxide monitor (Jarvis et al., 1987). Detected values above the stated cutoff scores will be considered indicative of smoking.

Mood, Emotion, and Cognition

Inventory of Depression and Anxiety Symptoms (IDAS). The IDAS is a 64-item measure assessing specific symptom dimensions of major depression and related anxiety disorders (Watson et al., 2007). The scales are internally consistent and show excellent convergent validity and good discriminant validity (Watson et al., 2007).

Difficulties with Emotion Regulation Scale (DERS). The DERS is a 36-item self-report measure of clinically-relevant difficulties in emotion regulation (Gratz & Roemer, 2004). The scale has been validated in cocaine dependent (Fox et al., 2007) and alcohol dependent (Fox, Hong, & Sinha, 2008) populations.

NEO Five-Factor Inventory (NEO-FFI). The NEO-FFI is a 60-item self-report measure of five basic personality factors (Costa & McCrae, 1989). The measure has been shown to have high test-retest reliability (Robins et al., 2001) and internal consistency (Costa & McCrae, 1992).

Regulatory Focus Questionnaire (RFQ). The Regulatory Focus Questionnaire (RFQ; Higgins et al., 2001) was derived from a factor analysis of items assessing the history of individuals' success at promotion and prevention tasks over the course of their lives.

Sleep, Financial Strain, Life Stressors

Financial Strain Questionnaire (FINSTR). The Financial Strain Questionnaire (Perlin et al., 1981) is a measure of financial strain with 8 items (e.g., "Do you have enough money for the kind of clothing you and your family should have?").

Impulsivity

Delay Discounting. The Delay Discounting Task adapted from Kirby and Marakovic (1996) evaluates the degree to which participants are willing to delay rewards. Participants answer questions that evaluate choice points relative to delaying cash rewards (e.g., Would you rather have $10 in 30 days or $2 at the end of the session). Participants will be informed to make their choice as if they were to receive the amount they chose, but that they will not receive additional compensation as part of the study.

UPPS. The UPPS Impulsive Behavior Scale is a 44-item self-report measure of four personality factors hypothesized to underlie impulsive behaviors: sensation seeking, (lack of) premeditation, (lack of) perseverance, and urgency. The measure has demonstrated strong internal consistency reliability for each of the four subscales and has been linked to self-report of risky behaviors (e.g., Whiteside & Lynam, 2003; Whiteside, Lynam, Miller, & Reynolds, 2005). We will use the UPPS-P, a variant of this measure that includes 15 additional items designed to assess positive urgency in addition to negative urgency (Cyders et al. 2007).

Measure of panic severity

Panic Attack Questionnaire (PAQ). The Panic Attack Questionnaire (PAQ) is a commonly-used self-report measure to assess panic attacks. It begins by providing respondents with a definition of panic attacks (according to DSM-III) to create a common understanding of the construct. From there, participants construct their self-assessment. It collects information about participant's frequency of panic attacks and the context in which they arose, as well as intensity of pain symptoms. The final section of the questionnaire consists of open-ended questions about medication use, stress, and treatment received for other illnesses or disorders.

Panic Disorder Severity Scale. The Panic Disorder Severity Scale (PDSS; Shear et al., 1997) is a 7-item, psychometrically-sound clinician-rated instrument for measuring indices of panic severity, including a) frequency of panic attacks, b) distress during panic attacks, c) anticipatory anxiety, d) agoraphobic fear and avoidance, e) interoceptive fear and avoidance, f) impairment of work functioning, and g) impairment of social functioning. Items are rated on a five-point

Likert scale (ranging from 0 [none] to 4 [extreme]) with a total possible score of 28. In the present study, we are employing the PDSS global composite as an index of panic attack severity. Individual items can theoretically be employed in follow-up tests from this same measure (Shear et al., 1997), making it an ideal choice for the current study.

Measures of anxiety sensitivity, distress intolerance, and negative affect

Anxiety Sensitivity Index-III (ASI-III). The ASI-III is a 18-item psychometrically-sound measure of AS whereby participants rate their fear of internal anxiety-related sensations (Taylor et al., 2007).

Distress Intolerance Index (DII). The DII (McHugh & Otto, 2010) is a 10-item self-report measure of an individual's perceived ability to tolerate distressing states. This measure was developed in the context of a factor analysis of the most commonly applied measures of distress intolerance, namely the Anxiety Sensitivity Index (Peterson & Reiss, 1992), Distress Tolerance Scale (Simons & Gaher, 2005), and Frustration Discomfort Scale (Harrington, 2005).

Positive and Negative Affect Schedule (PANAS). The PANAS is a 20-item psychometrically-sound mood measure that assesses two global dimensions of affect: positive and negative (Watson et al., 1988).

Brief Pain Inventory (BPI). The BPI short form is a 15-item measure often used in clinical trials. The BPI allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. Initially developed to assess pain related to cancer, the BPI has been shown to be an appropriate measure for pain caused by a wide range of clinical conditions. It is now one of the most widely used measurement tools for assessing clinical pain.

Measures of treatment integrity, safety, and acceptance

Vital Signs. As part of their screening visit, participants' blood pressure and heart rate will be assessed.

Treatment Credibility and Expectancy. The 18-item Treatment Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000) will be used to examine whether treatment expectancy or credibility varied between PSRT+DCS and PSRT+PBO and the relationship between these constructs and treatment response. We will administer the scale after the first treatment sessions of PSRT+DCS and PSRT+PBO protocols.

Patient Adherence. Patient adherence will be assessed by taking attendance at each session. Adherence to the nicotine patch usage will be assessed at Weeks 1-8 following the quit date.

Therapist Adherence. Each session (for those participants who give consent to be videotaped) will be videotaped and 10% will be rated shortly thereafter by independent raters to assess therapist adherence to, and competence with, the treatment protocol. Participants are not required to be videotaped and will indicate on their consent form whether or not they are willing to participate in the recording of sessions.

Concurrent Treatment. Use of medications other than nicotine patch or other aids to smoking cessation and participation in any concurrent psychotherapeutic treatment will be assessed at each assessment point.

Safety Monitoring and Concerns**.** At each visit, participants will be asked about side effects of the study medication, nicotine patches, and treatment. Adverse Events and Severe Adverse Events forms will be utilized to track any symptoms expressed during weekly check-ins. Forms will be reviewed each visit by the study PI, and participants who report significant symptoms or adverse reactions will be interviewed separately to determine whether the patch should be discontinued or the dose reduced. Participants who discontinue the patch or change the assigned dose will continue their treatment.

AlcoBreath Screening. At each of the three study visits during which participants are asked to take medication (sessions 3-5), participants will be asked to breathe into an AlcoBreath tube in order to assess for the presence of alcohol before they are administered the study medication.

Facial recognition task

At baseline and follow-up participants will complete a computerized task that takes approximately 5-8 minutes. The task is currently in use in our lab (IRB: 2016_02_0139). Facial stimuli depicting the same adult Caucasian male with either a fearful or a calm facial expression will be selected from the standardized and validated NimStim Faces Set (Tottenham et al., 2009). Morphing software for Windows (Version 3.1, M. Fujimiya) was used to nonlinearly morph the images in 10% increments from the extreme ends (0% to 100%) between two identities, or within the same identity between neutral and fearful facial expression. The fearfulness morphs are the same identity changing on expression of fear. The "target" is the facial stimulus that must be recognized, which is the fearful face (100% morph). The learning phase involves eight 2-second presentations of the target stimulus. Following each presentation, participants are shown another facial stimulus and asked to identify whether it is the same as the target. In the memory phase of the experiment, there are five blocks of 12 randomly presented facial stimuli (11 morphs and 1 completely different identity) and participants have to identify which are the same as the target from the previous phase. The purpose of the first phase is for participants to learn procedures and the target image. The purpose of the second phase is to test for generalization of recognition to the morphs that resemble the target images on a gradient of emotional expression or identity. Participants' responses and reaction times are recorded.

Assessment Schedule

Participants will receive thorough assessments prior to and over the course of this study. The schedule of assessment visits is such that it allows us to (1) compare smoking cessation outcomes in the present study to that observed in previous studies and (2) carefully examine the proposed therapeutic mechanisms of action. A tabular synopsis of the intervention and assessment data collected throughout the study is provided in the table below.

Table 2. Schedule of assessments

Protocol Weeks	>-3	-2	0	1-2	3	4	5	6	7	9	13-29
Measures	Pre-Screen	Screening Assessment	Baseline				WK 0 Quit Week	WK 1	WK 2	WK 4	WK 8, 10, 16, 24
Screening											
Demographics	X	X									
Smoking history*	X	X									
Motivation to quit smoking* (20 items)		X									
SCID		X									X (week 29)
Medical history		X									
Laboratory testing (blood draw, pregnancy test[6])		X	X[6]		X				X	X[6]	X[6]
C-SSRS		X									
Post-Cessation Smoking Outcomes											
Point Prevalence Abstinence			X	X	X	X	X	X	X	X	
Timeline Follow-Back											X
Carbon Monoxide			X	X	X	X	X	X	X	X	X

Saliva Cotinine										X	X
Nicotine Dependence and Withdrawal											
FTND* 6 items		X									
QSU* 10 items			X		X		X		X	X	X
MWS* 15 items			X	X	X	X	X	X	X	X	X
Smoking Abstinence Expectancies Questionnaire (SAEQ) 28 items	X	X	X		X		X		X	X	X
Smoking Cessation Self-Efficacy (SE) 43 items		X	X		X		X		X	X	X
Smoking Cue Appeal Survey (SCAS) 8 items			X								X
Barriers to Cessation Scale (BCS) 19 items		X									
Smoking Consequences Questionnaire-Brief (SCQ-Brief) 25 items		X									
Intolerance for Smoking Abstinence Discomfort (IDQ-Smoking) 17 items		X	X		X		X		X	X	X
Mood, Emotion, and Cognition											
Inventory of Depression and Anxiety Symptoms (IDAS) 64 items			X		X		X		X	X	X

Difficulties with Emotion Regulation Scale (DERS) 36 items			X		X		X		X	X	X
NEO-FFI 60 items		X									
Regulatory Focus Questionnaire (RFQ) 11 items		X									
Sleep, Financial Strain, Life Stressors											
Financial Strain Questionnaire (FINSTR) 8 items		X									
Impulsivity											

Delay Discount Questionnaire 27 items			X								X
UPPS 59 items			X								X
Panic Severity											
Panic Attack Questionnaire (PAQ)	X										
PDSS* 7 items		X	X	X	X	X	X	X	X	X	X
Anxiety Sensitivity, Distress Intolerance and Negative Affect											
ASI-III* 18 items		X	X	X	X	X	X	X	X	X	X
DII 10 items		X	X	X	X	X	X	X	X	X	X
PANAS*		X	X	X	X	X	X	X	X	X	X
Brief Pain Inventory			X								X
Treatment Integrity/Acceptance											
Credibility/Expectancy				X[4]							
Therapist Adherence[1]				X	X	X	X	X	X		
Patient Adherence[2]			X	X	X	X	X	X	X	X	X
Adverse Events[3]		X	X	X	X	X	X	X	X	X	X
Concurrent Treatment		X	X	X	X	X	X	X	X	X	X

AlcoBreath Screening[5]					X	X	X				
Vital Signs			X								
Face Task											
Facial Recognition Task			X							X	X

Note. Shaded areas refer to measures of mediator variables. *These measures are completed as online questionnaires. [1,2] Patient adherence and therapist competence will be monitored separately and the schedule will vary. [3]Adverse events will be assessed for DCS/PBO and NRT. [4]Administered at the end of session 1. [5]Alcohol screening will be completed prior to each of the three sessions which include DCS/PBO administration. [6]The pregnancy test is the only one that will be completed at intake and monthly following randomization(SV2, 7, 13, 21, and 29). The remaining lab testing will only occur should the physician see fit.

6. PARTICIPANTS

A. TARGET POPULATION

Our target enrollment is 80 participants who complete all study procedures. However, we will recruit 4,000 participants between the ages of 18 and 65 to account for dropouts and ineligible participants. We have chosen to study adult daily smokers who have had a panic attack within the past year and use nicotine to regulate their emotions. Although subjects will be excluded at intake for use of certain psychotropic medications, we believe it would be unethical to prevent them from starting these medications once the study has begun. Thus, we will assess for the initiation of psychotropic medications throughout treatment and utilize this information when analyzing the study results. Participants evidencing suicidal ideation at screening will be referred to treatment and excluded from the study.

Inclusion of Women and Minorities

Those who do not have adequate command of the English language will not be included in the study. All materials for the study including the measures are written in English and developing psychometrics for non-English speaking populations is beyond the scope of this project. If eligible, participants will be enrolled without regard to ethnic background. To increase minority participation, we will utilize a multimedia campaign with the following strategies: flyers in information booths at community and church functions, and placement of flyers in retail outlets and organizations known to serve minorities. We will use the aforementioned recruitment strategies in a sustained manner in the hope of boosting minority enrollment to 40%; we have achieved this level of minority recruitment in recent studies using these methods (Hofmann, Meuret, Smits et al., 2006; Zvolensky, Feldner et al., 2005).

Inclusion of Children

Participants below the age of 18 (and adults above 65 years old) will not be included in the proposed research

study for several reasons. First, the study hypotheses are not directly relevant to children or older adults without significant modification to take into account differing cognitive and developmental issues as well as issues related to smoking metabolism. These different issues could manifest in behavior, affect, psychophysiology, and/or neurobiology. If children and older adults were to be included, the study design would, at a minimum, have to take these factors into account and hypotheses would have to be added. To do so, the sample size would have to be increased considerably to yield adequate power to test these additional hypotheses. The budget allocation for an individual project simply does not allow for this possibility without seriously compromising other aspects of the study. Second, we elected not to include individuals below the age of 18 for two significant reasons. One reason is that individuals below the age of 18 experience markedly lower rates of smoking and anxiety-related problems than do adults (Fiore et al., 2000, 2008; Ollendick, Mattis, & King, 1994). Given these findings, it is most parsimonious to sample adults at this stage of treatment development. A second reason is that it has been repeatedly hypothesized that panic problems are rare among children due to their limited cognitive capacities (Nelles & Barlow, 1988; Vasey & Daleiden, 1994). Specifically, youths have a limited ability to attribute anxiety to internal cues or associating the sensations of anxiety with mental or physical catastrophe, a process central to the AS construct. Thus, restricting this initial investigation of AS and smoking to adult participants will help eliminate concerns regarding the cognitive capacities of children. Additionally, if children were to be included, the study design would, at a minimum, have to take these factors into account and additional hypotheses would need to be added. To do so, the sample size would have to be increased considerably to provide for adequate power to test these new hypotheses. Therefore, to focus on individuals below the age of 18 years does not make practical or clinical sense or offer help in developing more generalizable data.

B. INCLUSION/EXCLUSION

Inclusion Criteria:

- Male and female patients ages 18-65 capable of providing informed consent
- Willing and able to provide informed consent, attend all study visits and comply with the protocol
- Daily smoker for at least one year
- Currently smoke an average of at least 8 cigarettes per day
- Report a motivation to quit smoking in the next month of at least 5 on a 10-point scale
- Evidence of panic attack within the past year and endorsement of smoking as an emotion regulation strategy (i.e., score at least a 78 on the SAEQ).

Exclusion Criteria:

- Subjects who do not use smoking as an emotion regulation strategy
- Current diagnosis of a psychotic, eating, developmental or bipolar disorder
- Significant suicide risk as determined by structured interview
- Pregnant women, lactating women, and women of childbearing potential who are not using medically accepted

forms of contraception (e.g., IUD, oral contraceptives, barrier devices, condoms and foam, or implanted progesterone rods stabilized for at least 3 months).

- Psychoactive substance abuse or dependence (excluding nicotine dependence) within the past 6 months
- Current use of isoniazid or ethionamide compounds
- A history of significant medical condition and/or be deemed as currently unhealthy by the study physician
- Limited mental competency and the inability to give informed, voluntary, written consent to participate
- Current use of any pharmacotherapy or psychotherapy for smoking cessation not provided by the researchers during the quit attempt
- Concurrent psychotherapy initiated within three months of baseline, or ongoing psychotherapy of any duration directed specifically toward treatment of anxiety or mood disorder other than general supportive therapy initiated at least 3 months prior to the study
- Use of other tobacco products
- Plans to move outside of the immediate area in the next six months
- Insufficient command of the English language

C. BENEFITS

Participants will have opportunity for direct benefit in the care and treatment of cigarette smoking. The population of adult smokers in general has a great opportunity for benefit since the results of the study may be valuable in the treatment of smoking. If we find that DCS augments PSRT, then smokers could elect this augmentation strategy to improve their quality of life. Further, the proposed study (i.e., design, assessment schedule, and analyses) offers the potential to improve the understanding of the mechanisms that underlie these effects. Thus, the anticipated benefits of the study are twofold: the results will be used to advance understanding of the factors related to anxiety and relapse to smoking after attempts at smoking cessation, and significant knowledge about the combined effects of cognitive-behavioral treatment for anxiety related vulnerabilities and the nicotine patch will be obtained. Participants can potentially benefit from the smoking cessation and panic reduction treatment provided as part of the study. The results of the study will have implications for matching treatments to specific characteristics of smokers.

D. RISKS

The risks associated with participating in this study are minimal. Potential risks also include nicotine patch side effects. Common side effects include local skin irritation at the site of the patch, and mild nausea if the participant continues to smoke at a high level while using the patch, and temporary vivid dreams. Less common are allergic skin reactions.

The possible side effects for d-cycloserine include: headache, confusion, tremor, vertigo, memory difficulties, paresthesias (itching or tingling of the skin), seizure, drowsiness, confusion, dizziness, drowsiness, irritability, restlessness, depression, muscle twitching, trembling, nervousness, and speech problems. However, these side effects are most commonly related with doses greater than 500mg/day (i.e., chronic dosing), which is two times the amount that participants will receive in this study. DCS is a safe medication in the dosage provided; indeed

10-fold doses are safely administered in chronic doses in other applications. Participants will be asked not to use any alcohol prior to the sessions and prior to the assessments. They will also be asked to breathe into a tube so that members of the study team can perform a test for the presence of alcohol. It should be noted that patients have been given acute 250mg doses in a previous study of obsessive compulsive disorder and 1000mg doses in a previous study of depression, with no significant adverse side effects associated with the administration in either study (Heresco-Levy et al., 2013; Storch et al., 2007). This dose of 250mg was selected for the current study as accumulating evidence suggests that a dose of 250mg may be more likely than a lower dose to aid the type of therapeutic learning that is the focus of the smoking cessation intervention that we will employ in this protocol.

Other potential risks include temporary nicotine withdrawal symptoms after quitting. Discomfort related to smoking cessation may include such symptoms as increased anxiety, irritability, difficulty concentrating, headaches, nausea, decreased heart rate, fatigue, increased hunger, and tobacco cravings. These symptoms are typical of nicotine withdrawal and result from the addictive nature of nicotine. Although symptoms of nicotine withdrawal may be uncomfortable, they are not harmful. It should be noted that participants in this study have already had numerous experiences with these sensations and feelings throughout their day-to-day life.

There are no absolute contraindications to the use of d-cycloserine in combination with other antibiotics. There are potential interactions with isoniazid and ethionamide compounds; current use of isoniazid or ethionamide compounds is listed as an exclusion criterion (see page 17).

The nicotine withdrawal state is primarily mediated by central and peripheral nicotinic acetylcholine activity. In rodent models, d-cycloserine has been shown to decrease nicotine self-administration therefore suggesting it may have an ameliorative effect on craving and withdrawal states. As an NMDA partial agonist, it is unlikely it will exacerbate nicotine withdrawal and there is no animal or human evidence it would exacerbate nicotine withdrawal.

There are no known risks associated with saliva cotinine and carbon monoxide analyses. The procedures for obtaining these samples are brief, safe, and minimally uncomfortable. Some participants may experience minor, short-term discomfort with these procedures. For example, some individuals may find it slightly uncomfortable to hold their breath for 15 seconds, as required for the carbon monoxide analysis. In addition, some individuals may report brief dry mouth following the saliva cotinine procedure.

The exposure-based treatment offered may make some patients anxious during the exposure procedures, but these procedures are generally very well accepted and are associated with treatment benefit (Gould et al., 1997). The assessment instruments may cause mild distress because of their focus on emotional topics associated with mental health.

Protection of Human Subjects from Research Risk

Adequacy of Protection Against Risks

The therapists are advanced doctoral students who are trained to identify a panic attack, and to help the patient recover. Specifically, the therapist will remind the patient that he/she is experiencing a false alarm, instruct the patient to breathe through the nose in order to reduce hyperventilation, and encourage the patient to allow the panic attack to run its course. Immediately following a panic attack, the therapist and patient will discuss the panic attack experience. This discussion is aimed to help the patient correct false beliefs regarding the consequences of panic attacks. The PI, Jasper Smits, Ph.D., is available for intervention as needed and back-up plans are established including involvement of the study physicians and referral to a hospital emergency department. These safety procedures have been effective in dealing with adverse physical and mental health events in previous and ongoing studies. Upon study completion, all participants will be referred to follow-up care if needed.

If the person is in imminent danger of harming him/herself, the interview will be stopped and 911 will be called. If the person is not in imminent danger, but seems to be in need of psychological services for suicidality, they will be encouraged to call the counseling center if he/she is a student or a local community agency if he/she is a community participant, to set up an appointment. The interviewer will make one follow-up call to the participant in the week following the assessment to ascertain whether he/she made the appointment and to get the name of the counselor he/she has been assigned to in order to inform the counselor of the participant's suicidality. If the participant decides not to make an appointment, no further action will be taken by Dr. Smits. If the participant makes the appointment and gives the name of the counselor, Dr. Smits will call the counselor within 24 hours to inform the counselor of the participant's suicidality (accompanied by the release of information form). If the participant is currently in therapy, Dr. Smits will call his/her therapist within 24 hours of the assessment if possible (accompanied by a release of information form) in order to inform the therapist of the participant's suicidality.

To minimize skin reactions due to nicotine patch, smokers will be instructed to move the site of patch placement each day and not repeat site use for at least one week. Smokers who smoke 4 cigs/day for 4 days will be asked to discontinue the patch until they are able to cut down or quit smoking again. The initial mg/day dose may be adjusted downward to 14 mg or 7 mg if there is significant nausea or other adverse reactions. Smokers will be instructed to remove the patch before bed if it significantly interferes with sleep. The patch will be discontinued entirely if severe skin reactions develop. Additionally, at each visit, participants will be administered a side effect and symptom profile. The most common side effects from using the nicotine patch are local skin irritation, nausea if the dose is too high (or if the patient continues to smoke at a high level while using the nicotine patch), and disturbed sleep and vivid dreams. Instructing the participant to rotate the site where the patch is applied and to remove the patch at night if sleep disturbance is impairing function will minimize these side effects. Participants will indicate on a checklist their incidence and severity of side effects. Checklists will be reviewed each visit by study personnel, and participants who report significant symptoms or adverse reactions will be interviewed separately to determine whether the patch should be discontinued or the dose reduced. Likewise, study staff will be available at all times to answer questions and concerns regarding symptoms. Participants who

discontinue the patch or change the assigned dose will be kept in the remaining treatment. We will track such changes to determine whether they affect outcomes. As noted in our previous trials, we have had little to no emergence of side effects with the patch (Zvolensky et al., 2008). Nonetheless, we will specifically query for potential side effects at each visit.

In regard to withdrawal symptoms, there is a strong likelihood that most study participants will experience some nicotine withdrawal symptoms, including anxiety, restlessness, anger, irritability, sadness, problems concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Because all participants will use the nicotine patch, this should diminish the overall severity of withdrawal discomfort, although the patch will not necessarily eliminate withdrawal discomfort entirely. Moreover, withdrawal symptoms are usually short-lived, with most symptoms abating within 1-2 weeks. During treatment, research team staff will monitor patients for development of severe psychological problems (e.g., depression) during each of our sessions and follow-up visits. Using the study instruments and clinical interviews, therapists will determine whether treatment or additional treatment for a specific psychological problem is needed and work with the patient to refer them to appropriate service centers.

Regarding the administration of DCS, the prescribing psychiatrist will be Carlos Tirado, M.D., M.P.H., F.A.S.A.M. Dr. Tirado will review the medical history of patients (for exclusion factors), and will prescribe the three doses of study medication (DCS vs. PBO) to be taken during assessment weeks (weeks 3-5). Patients will be encouraged to call the study physician should they experience any side effects or have any questions regarding the medication.

To deal with the potential risk of loss of privacy (judged to be minimal), we will maintain confidentiality by numerically coding all data, by disguising identifying information, and by keeping all data in locked file drawers. Video recordings will be coded by participant ID and will be deleted after therapist adherence ratings. Participant information will be accessible only to research staff. Identifying information will not be reported.

Functions of the Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support those purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality. Members of the DSMB include the PI (Jasper Smits, Ph.D.), the Co-PIs (Michael Otto, Ph.D., and Michael Zvolensky, Ph.D.); Conall O'Cleirigh, Ph.D. (Chair), Mark Pollack, M.D.; Carl Lejuez, Ph.D.; and Norman Schmidt, Ph.D.

As in any clinical trial, it is not possible to anticipate all possible adverse events. We do extensive training with our staff on ascertaining, monitoring, and documenting adverse events. The study investigators have extensive experience in clinical trials organization and management, including data safety monitoring for single site and multi-site trials. We have established procedures for rendering first aid and life threatening emergencies. Dr. Smits will oversee these procedures.

Reporting Mechanisms of AEs/SAEs to the IRB and NIDA

Unblinded Reporting. Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.

Range of Safety Reporting to the DSMB. It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates, and reasons for drop-out.

Serious Adverse Events. Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. *For purposes of this study, all SAEs will be required to be reported to the DSMB, regardless of any judgment of their relatedness to the study treatment.* All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail, and FAX transmittal of all related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study. Additional reporting to the IRBs will be done within 24 hours of the SAE; reporting to NIDA will be made according to the regulations governing SAE reporting.

Non-Serious Adverse Events. At periodic intervals, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

*Other Safety-Related Reports. T*hroughout the course of the study, the DSMB will receive unblinded summary reports of treatment retention and reasons for drop-out.

Collection and Reporting of AEs and SAEs

Information regarding AEs is to be obtained by questioning or examining the subject. At each visit all new complaints and symptoms (i.e., those not existing prior to signing of informed consent) must be recorded on the AE Form. Pre-existing complaints or symptoms that increased in intensity or frequency after having signed the Informed Consent Form must be entered on the AE Form also. All AEs must be characterized in terms of their start and stop dates, start and stop times, intensity, action taken on Intervention, relationship to Intervention, subject outcome and whether or not the AE led to a Serious Adverse Event (SAE). Any clinically relevant increase or decrease to the intensity or frequency of a reported AE requires a separate entry on the AE Form. If the event meets the definition of an SAE, the procedure for reporting SAEs must be followed; the event should not be reported on the AE Form also incase the start and stop dates are equal to the start and stop dates of the SAE.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious too.

All serious events occurring between signing of the Informed Consent Form by the subject and signing of the End of Trial Form by the investigator, except those pre-specified in the protocol, must be reported as soon as practical (within 24 hours of awareness) to the IRB and the DSMB. This includes serious events, which could be associated with the trial procedures, even if occurring outside the treatment period.

Follow-up of SAEs, which occurred during the trial, should in principle take place until resolution of the SAE. Under this protocol, the following event(s) will not be considered as (an) SAE(s) and should not be entered on the SAE form:

- Pre-planned hospitalizations for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of a clinical trial. These pre-planned hospitalizations must be entered on the medical history form, including the condition requiring hospitalization.
- Hospitalizations for uncomplicated delivery.

All SAEs (i.e. including serious events occurring outside the treatment period) must be reported as soon as practical (within 24 hours of awareness) to the IRB and DSMB. Reporting of an SAE must be done by means of

the SAE form. For each SAE, the investigator fills out this SAE form (as complete as possible) and sends the form and all available supporting documentation by fax.

Suicidality Plan

Endorsement of suicidal ideation will be assessed for level of risk. Low risk ideation (i.e. have thoughts or wishes to be dead with no plan or intent to hurt themselves) will be assessed at every session for changes to the risk level. Those with high risk ideation (i.e. has a plan and date in mind) will be sent a referral list that includes a 24/7 national hotline that they can call if necessary. Research personnel will communicate with the PI right away for supervision and will assess for appropriate procedures as necessary. Procedures include referral to counsellors, plans to get them to the hospital, and/or calling the police.

E. RECRUITMENT

Subjects will be recruited from the community and from physician referrals. Any subjects meeting the entrance inclusion criteria will be provided the opportunity to participate in this study. Recruitment sources include: 1) posting newspaper and Craigslist advertisements; 2) utilizing fliers, pamphlets, and handouts in community-based organizations, bulletin boards, stores, and handing them out at events and various other sites; 3) utilizing social media sites (e.g., Facebook, Twitter, LinkedIn) to post status updates with links to our online prescreen; 4) utilizing ResearchMatch; and 5) seeking organizations (eg. Live Tobacco Free Austin). It is noteworthy that these recruitment strategies have been, and are currently being, used to recruit smokers from the community for previous studies run in the Anxiety and Health Research Laboratory at the University of Houston (PI: Dr. Zvolensky) and have been used effectively at the Anxiety Research and Treatment Program at Southern Methodist University (PI: Dr. Smits).

F. OBTAINING INFORMED CONSENT

Any subjects meeting the entrance inclusion criteria will be provided the opportunity to participate in this study. The consent form will be sent to participants via REDCap before the baseline appointment so that they have time to read through the form and give their informed consent. If a participant has not yet signed the consent form before the baseline session, we will give them the consent form to read over and sign. Research associates obtaining consent will explain the study procedures and answer any questions the potential participant might have. Informed consent will be obtained from all participants prior to undergoing any screening procedures. Participants may be asked to give signed consent on an electronic device such as an iPad using REDCap. Participants will read the consent form on the device, print their name, and sign using their finger or stylus directly onto the iPad. We will either provide them with a paper copy, or email them a copy of the consent form

for their records, depending on their preference. All paper consent forms will be kept in locked cabinets with ID numbers to assure each participant has signed a consent form for at least 3 years. All electronic consent forms will be housed in REDCap, which will be password protected and only accessible by the PI and study personnel. The Institutional Review Board at the University of Texas (UT) consists of independent bodies of reviewers. Research associates and physicians will receive training regarding procedures required to obtain informed consent, and training is completed yearly in order to continually reinforce such procedures.

The Prescreen Survey informed consent will detail procedures about the prescreen survey and screening assessment. Participants will read and give informed consent by clicking "I Agree" before continuing on with the survey. A waiver of documentation is requested for the prescreen survey informed consent procedures. All eligible participants will give signed, informed consent for the rest of the study procedures once they come into the lab for their first visit.

7. PRIVACY AND CONFIDENTIALITY

Data and Safety Monitoring Plan

Data Entry Methods

Our general policy for data management is that research assistants copy all data files and these files are brought to Dr. Smits on a weekly basis. Data forms and accompanying narrative summaries will undergo a systematic and rigorous editing process before they are keyed into the database. The research assistants routinely evaluate the data and discuss any problems and questions with the study staff and Dr. Smits at regular weekly team meetings. Accuracy of data entry will be ensured by a standard double-entry procedure. Data management formal reports on record status across the three following domains will be employed: entered, verified, and edited. These reports of data records will be evaluated one time a month during the final team meeting of the month. To help ensure data protection, backup copies, automatically generated by our computer systems, will be available. Additionally, our hard copy record systems, as described previously, will be maintained in fire-resistant locked cabinets.

This study will utilize a web page-internet data collection and management system used in previous work. All data for the current study including demographic information, diagnoses, laboratory values, medication counts, and participant and clinician rated measures will be directly entered into an electronic case report form (eCRF). The eCRF will be entered into a dedicated computer at the University of Texas maintained by Dr. Smits in his capacity as chief study data manager.

The eCRF will consist of a series of separate web pages for study personnel and participants. A series of passwords will be programmed to ensure that participants are unable to access pages reserved for study personnel. The eCRF will be constructed so that all requested information must be entered into each page in the fields provided, or the system will not permit access to the next page. The system is designed so that only completed eCRFs can be transmitted. If information for a field is either not available or not applicable, the system will require that it be documented as such in

the eCRF. Field parameters will be specified such that suspect values are either disallowed or flagged for the immediate attention of the study directors and Principal Investigators.

At each visit a hard copy of the eCRF will be printed and promptly reviewed, signed, and dated by the investigator for clinician rated measures and by the participant for participant rated measures. A print out of the data will then be made, authenticated (with signature and date) by the investigator and participant and kept in the participant's study file.

Some study data (eCRF) will be collected and managed using Qualtrics and REDCap. Qualtrics and REDCap are high-end web survey tools that have been used in experimental research and is designed in a way that ensures the security of data transmission and protection. Qualtrics and REDCap offers Transport Layer Security (TLS) encryption (HTTPS) and survey security options like password protection and HTTP referrer checking. Qualtrics and REDCap are HIPAA compliant, and servers are stored in a tier one data storage facility that includes adequate security measures.

CONFIDENTIALITY OF THE DATA OR SAMPLES

a. Describe how data or samples (i.e., blood, salvia, tissue, etc.) will be collected.

- Saliva samples will be collected using salivettes (Sarstedt, Rommelsdorf, Germany), which are plastic vials with cotton dental rolls inside.

b. Describe how the data or samples will be securely stored and how you will achieve this.

- Once the samples are collected, they will be frozen and stored (-80 degrees C) for future processing. To extract saliva, the samples will be centrifuged at 4 degrees C for 5 minutes at 2000 xg. They will be assayed with an enzyme immunoassay at Salimetrics, LLC, located in State College, PA, using a commercial kit (Diagnostic Products Corporation, Los Angeles, CA).

c. Provide the length of time the data or samples will be kept.

- Salimetrics, LLC will immediately dispose of the cotinine samples once the information needed is collected.

d. Describe whether data or samples will be kept confidential (i.e., data can potentially be linked to participants) or anonymous (i.e., impossible to link data and participants). You must include if the data or samples will be shared by other researchers for research purposes not detailed in this study.

- The results of cotinine analyses will be kept confidential and will not be returned to participants in this study. Further, tubes will be identified by participant identification numbers only. Staff processing the cotinine samples will not have access to any identifying information of the participants.

e. If the data or samples will be destroyed, describe when and how the destruction will occur.

- Salimetrics, LLC will take all precautions and dispose of the cotinine samples in a biohazard disposal.

8. COMPENSATION

Participants will be paid $25 for the baseline visit, $10 for weeks 1, 2, 4, 5, 6, and 7, $15 for week 3, and $20

each follow-up (Weeks 9, 13, 15, 21, 29). Thus, participants can receive up to $200 for their participation in the study. These payments are not contingent upon smoking status at the time of assessment or follow-up. We feel this amount is appropriate in order to assure that all participants involved with the study have the means to attend assessment visits, thus aiding our goal of evaluating treatment efficacy at various time points.