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Enhancing Panic and Smoking Reduction Treatment with D-Cycloserine: Study Protocol for a Randomized Controlled Trial

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Abstract

There has been relatively little attention focused on treatment strategies for smokers with panic attacks despite their increased risk of relapse. Panic and Smoking Reduction Treatment (PSRT) integrates standard smoking cessation treatment with an exposure-based intervention targeting the mechanisms underlying panic-smoking relations. Building upon emerging evidence supporting the efficacy of d-cycloserine (DCS) for augmenting exposure-based therapy, we are conducting an initial test of the efficacy of DCS for enhancing PSRT outcomes. Utilizing a randomized, double-blind trial comparing PSRT+DCS to PSRT+placebo ($N=80$), we will obtain initial effect sizes for short-term and long-term smoking cessation outcomes and perform an initial test of putative mechanisms.

Keywords

Smoking Cessation; panic; d-cycloserine; behavioral intervention; clinical trial; augmentation

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Introduction

Panic attacks are common (7–10% of the general population regularly experience panic attacks; Norton, Cox, & Malan, 1992) and co-occur with smoking at rates that exceed those found in the general non-psychiatric population (Amering et al., 1999; Breslau & Klein, 1999; Breslau et al., 1991; Glassman et al., 1990; Goodwin & Hamilton, 2002; Hughes et al., 1986; Pohl et al., 1992). For example, Lasser et al. (2000) found that in an analysis of over 4,000 respondents from the National Comorbidity Survey (NCS), current smoking rates for respondents with panic attacks in the past month or lifetime were significantly greater than smoking rates among respondents with no mental illness. Similarly, Piper and colleagues (2010) recently reported that 30% of smokers seeking cessation treatment from the general community reported a history of panic attacks. Finally, Bakhshaie, Zvolensky, and Goodwin (2016) found that smoking prospectively predicted later panic attacks and that quitting smoking helped reduce such risk. In summary, smokers who experience panic attacks are common and are an at-risk group for smoking cessation failure (Piper et al., 2010; Zvolensky, Schmidt, et al., 2005).

One effective approach to enhancing smoking cessation success rates in this group may be to target the mechanisms that underlie the panic-smoking relation prior to making a quit attempt. Among such intervention targets, anxiety sensitivity, or the fear of anxiety and related sensations (McNally, 2002), has emerged as particularly promising. Indeed, anxiety sensitivity (a) is heightened among smokers with a history of panic attacks compared to those without (Bernstein, Zvolensky, Vujanovic, & Moos, 2009), (b) is related to cognitive-affective reactivity and emotional regulatory deficits related to smoking cessation (Zvolensky, Vujanovic, Bernstein, & Leyro, 2010); and (c) can be reduced with intervention (Smits, Berry, Tart, & Powers, 2008). Importantly, emerging evidence indicates that interventions that effectively reduce anxiety sensitivity facilitate the odds of smoking cessation in anxiety vulnerable adults (Smits et al., 2015; Zvolensky, Bogiaizian, Salazar, Farris, & Bakhshaie, 2014; Zvolensky, Yartz, Gregor, Gonzalez, & Bernstein, 2008).

Panic and Smoking Reduction Treatment (PSRT; Zvolensky et al., 2008) is a treatment protocol that integrates elements of standard smoking cessation treatment with exposure-based strategies for reducing anxiety sensitivity. These exposure-based strategies, which aim to help individuals reestablish a sense of safety around feared bodily sensations (i.e., safety learning), have been successfully applied to the treatment of panic disorder (Gould, Otto, & Pollack, 1995; Smits, Powers, Cho, & Telch, 2004). Applied to help smokers who experience panic attacks, exposure in PSRT is specifically employed to extinguish fears of sensations experienced during smoking discontinuation (i.e., withdrawal). Hence, the goal is to reduce the likelihood of lapse and subsequent relapse by helping patients change their relationship with internal cues (i.e., from signalling threat resulting in lapse and subsequent relapse to signalling relative safety/absence of threat, resulting in resilience to these cues for lapse). An initial pilot randomized trial of this integrated treatment was completed with 25 participants randomly assigned to either an 8-session standard smoking cessation treatment with nicotine replacement treatment (NRT) or 8-sessions or PSRT with NRT (Zvolensky et al., 2008). Results indicated that from 2 to 16 weeks post quit, abstinence rates dropped from an initial 81.0% to 42.7% of participants in the active condition, while abstinence in the

control condition dropped from an initial 48.1% to 29.7% of participants from week 2 to the 16 week post quit time point. Although the results are in line with theory and basic research findings, there is important room for improvement in smoking cessation outcome among this high-risk smoking population (i.e., by 16 weeks post-quit only 42.7% of the participants in the active condition were smoke-free, and abstinence was declining).

Aiming to optimize the efficacy of PSRT, the present study draws from recent evidence suggesting that the extinction learning achieved with exposure-based interventions can be strengthened by the acute administration of d-cycloserine (DCS; Otto et al., 2015). For example, a meta-analysis of 9 trials showed a medium effect size in favor of DCS relative to placebo ($d = 0.46$; Bontempo, Panza, & Bloch, 2012). DCS, a FDA-approved drug for the treatment of tuberculosis (500-100mg daily), facilitates N-methyl-D-aspartate receptor (NMDAR) functioning, which enhances fear extinction retention (Otto et al., 2015). Research on the neural circuitry involved in extinction learning has led to the identification of core pathways and neurotransmitters involved in fear extinction (Davis et al., 2002). Animal studies indicate that both fear learning and extinction are blocked by antagonists at the glutamatergic NMDA receptor. D-cycloserine (DCS), a partial NMDA agonist, appears to augment the process of extinction of conditioned fear in animals (Richardson et al., 2004; Ledgerwood et al., 2004; Ledgerwood et al., 2005). When given in small doses (50–250mg), either before or immediately after a session that involves extinction training, DCS has been shown to facilitate fear reduction (Hofmann, Otto, Pollack, & Smits, 2015), particularly when these sessions are marked by low fear at the end of the session (Smits, Rosenfield, Otto, Marques, et al., 2013; Smits, Rosenfield, Otto, Powers, et al., 2013). Accordingly, in this treatment development study, we aim to test whether PSRT augmented by DCS would yield better smoking cessation outcomes relative to PSRT augmented by pill placebo (PBO) up to 24 weeks after the quit date by producing an enhanced response to the exposure training (e.g. greater reduction in anxiety sensitivity).

Methods

Study Design

Eighty adult smokers with panic attacks will be enrolled in a 7-week PSRT protocol and asked to make a quit attempt at week 5. At week 3, participants will be randomly assigned to receive 250 mg of DCS (PSRT+DCS) or pill placebo (PSRT+PBO) 1 hour prior to each of sessions 3, 4, and 5, which focus on extinction training. Smoking will be assessed at baseline, during the treatment period and at 2, 4, 8, 10, 16, and 24 weeks after quit date.

Specific Aims

1. To evaluate, in a randomized clinical trial, the effects of PSRT+DCS vs. PSRT+PBO on abstinence. We hypothesize that abstinence will be higher, both in the short term and long term, for those in the PSRT+DCS condition than for those in the PSRT+PBO condition.
2. To explore the mechanisms by which PSRT+DCS improves smoking cessation outcomes. We will examine whether PSRT+DCS engages putative targets (e.g., panic attack reduction, anxiety sensitivity reduction, negative affect reduction) and

whether target engagement accounts for improved abstinence rates seen with the intervention.

Participants

Participants will be 80 males and females between the ages of 18 and 65, with a history of at least one panic attack within the last year as determined via structured clinical interview, who have been daily smokers for at least one year and are currently smoking an average of eight or more cigarettes per day. Participants must also exhibit psychological and physiological consequences to abstaining from smoking as assessed by a score of 78 or above on the 28-item Smoking Abstinence Expectancy Questionnaire (Abrams, Zvolensky, Dorman, Gonzalez, & Mayer, 2011). This criterion is used to indicate that the participant uses smoking as an emotion regulation strategy. Participants must also report a motivation to quit smoking of at least 5 on a 10-point scale. In addition, participants will be evaluated by a study physician to rule out safety concerns. Participants must also be capable and willing to provide informed consent, attend all study sessions, and adhere to the study protocol.

To preserve high internal validity and reduce risk of adverse events, we will employ the following exclusion criteria: (1) current diagnosis of a psychotic, development or bipolar disorder; (2) significant suicide risk as determined by structured interview; (3) psychoactive substance abuse or dependence (excluding nicotine dependence) or eating disorder within the past 6 months; (4) current use of isoniazid, ethionamide, nortriptyline, bupropion, or prn use of benzodiazepines; (5) a history of significant medical condition and/or be deemed as currently unhealthy in the context of a complete physical examination; (6) limited mental competency and the inability to give informed, voluntary, written consent to participate; (7) current use of any pharmacotherapy or psychotherapy for smoking cessation not provided by the researchers during the quit attempt; (8) 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; (9) use of other tobacco products; (10) planning on moving outside of immediate area in the next six months; (11) insufficient command of the English language; and (12) currently pregnant, planning on becoming pregnant in the next year, current breastfeeding, or women of childbearing potential who are not using medically accepted forms of contraception.

Procedures

The study is funded by the National Institute on Drug Abuse (NIDA; R34DA034658) and is registered on clinicaltrials.gov (ID: NCT01944423). The Institutional Review Board of the University of Texas at Austin approved the study and a Data Safety and Monitoring Board provides ongoing oversight. The study is currently in the recruitment phase.

Screening—Potential participants are recruited via various strategies (e.g., flyers, newspaper ads, social media) and instructed to visit a study website. An Internet prescreen is conducted to determine eligibility for all potential participants. The prescreen survey is the first point of contact for participants. The prescreen is utilized to obtain critical information about the potential participant to determine initial eligibility including motivation to quit,

smoking history and initial cutoff score via the smoking abstinence expectancy questionnaire. All online data, including the prescreen is collected through, REDCap (Research Electronic Data Capture), an electronic data capture tool hosted at University of Texas at Austin (Harris et al., 2008).

Individuals who appear eligible based on the initial prescreen receive a follow-up telephone call to further verify eligibility criteria. Those deemed eligible via telephone screen are then either invited to the university to receive an in person psychiatric diagnostic intake or a remote intake conducted over the phone. Previous studies show the comparable validity of diagnostic interviews conducted over the telephone versus face-to-face (Aziz & Kenford, 2004; Crippa, de Lima Osorio, Del-Ben, Filho, da Silva Freitas, & Loureiro, 2008; Lynneham & Rapee, 2005). Providing participants with the option of completing the screening session in person, or over the phone, increases our retention efforts for the eligibility screening portion of the study. Before starting the psychiatric diagnostic intake, a trained staff member will go over the informed consent with all participants. Informed consent procedures include details of the study including treatment procedures, potential risks and benefits of the study, and study timeline.

The diagnostic interview will be administered by trained graduate student-level therapists and will be supervised by the principal investigators. The psychiatric diagnostic screening begins with the Structured Clinical Interview for DSM-IV Diagnosis of Axis I Disorders Non-Patient Version (SCID-NP; First, Spitzer, Gibbon, & Williams, 2007) to evaluate the presence of psychiatric exclusion criteria and primary and secondary diagnoses. A urine pregnancy test will be performed on all female participants of childbearing potential prior to enrollment. Additionally, medical screening information will be obtained from all participants to evaluate past medical and health history. Once the initial intake is complete, individual's unidentified medical screening information will be sent to the study physician for study enrollment approval. The medical screening by study physician is used to evaluate potential eligibility to receive study medication and participate in interoceptive exposure activities. After reviewing medical screening information, if deemed necessary, the study physician may order laboratory testing and complete physical examination before providing approval for study participation.

Baseline/Enrollment—If eligible after the psychiatric diagnostic and medical screening, participants are invited to study baseline/enrollment visit. Participants are provided with a brief treatment orientation by a graduate-level staff member and are asked to complete a number of assessments. Baseline assessments include evaluation of motivation to quit and expectancy to complete study intervention, breath holding task, reading of expired air carbon monoxide levels (assessed with a carbon monoxide monitor; Smokerlyzer® by coVita), timeline follow-back procedure (assessing previous seven days of smoking; Brown et al., 1998), and a battery of online assessments.

Panic Smoking Reduction Treatment (PSRT)—All participants receive PSRT (Zvolensky et al. 2008) that combines intensive standard cognitive-behavioral smoking cessation counseling and the nicotine patch (Fiore, Bailey, Cohen, Dofman, Goldstein, Gritz, et al. 2000), with procedures for reducing panic (Gould, Otto, & Pollack, 1995; Smits,

Powers, Cho, & Telch, 2004) and tolerance to withdrawal sensations (see Table 1). This standard treatment is delivered through manualized once-weekly 90-minute sessions over a 7-week period by trained staff supervised by the first author. Treatment components include: (1) interoceptive exposure; (2) cognitive restructuring; (3) and psychoeducation exercises developed for panic intervention programs. Subjective units of distress (SUDs) are collected during exposures to guide the intervention and to be used for later analysis. Uniquely, participants will also be asked to refrain from smoking before sessions 3–5 prior to their quit day in order to provide training on tolerating symptoms of nicotine withdrawal. Week 5 of the protocol is designated as the “quit day,” at which participants are suggested to make their quit attempt. All participants will be offered Nicoderm CQ®, 24-hour transdermal nicotine patches and educated about the use of the patch at the Week 4 session, immediately prior to quit date. The patch will be provided to participants for up to 8 weeks of treatment. While using the patch, the study therapist will assess for any current side effects they may experience. Participants may also elect to not use the patch. Table 1 provides a summary of intervention procedures.

Randomization and Study Medication—The project Biostatistician will generate the randomization schedule for all 80 participants prior to study inception, using variable sized permuted block-randomization (block sizes will vary from 2 to 8). An independent pharmacy will produce a pill box for each of the 80 participants, one box per participant, labeled with their participant number (1–80) and containing the appropriate 3 capsules for that participant based on the randomization schedule for that participant number (all 3 pills will be either DCS or PBO). Participants will be assigned their participant number at week 3, and given 1 capsule from their pill box at each of sessions 3–5. Study capsules containing DCS and placebo will be identical in appearance, and will be administered by study staff blind to study condition. Unblinding will not occur until the study is completed and the data is cleaned. Study medication will be given to the participant 1 hour prior to sessions 3–5. At this time, participants are asked to remain in the clinic. Participants are asked to remain smoke-free for a period of 3 hours before the pill administration and 3 hours after the session.

Assessment

The assessment battery takes approximately 15 to 30 minutes to complete

Screening and Baseline

Demographics: Participants will be asked to provide standard demographic information including gender, age, race/ethnicity, level of education, etc. during the screening session.

Motivation to Quit Smoking: Participants will be asked to report their motivation to quit on a 10-point scale at prescreen.

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, Lejuez, Kahler, & Strong, 2002;

Zvolensky & Bernstein, 2005). This measure will serve to contextualize the participants' smoking behavior and history at screen.

Fagerström Test for Nicotine Dependence (FTND): The FTND is a 6-item scale designed to assess gradations in tobacco dependence at baseline (Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

Smoking Abstinence Expectancy Questionnaire (SAEQ): Smoking Abstinence Expectancies Questionnaire (Abrams et al., 2011) is a psychometrically-sound, 28-item self-report measure of expected consequences as a result of 24-hours of smoking abstinence.

Psychiatric Diagnosis: Diagnostic exclusions, history of panic attacks within the last year, 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 visit by a trained study therapist. All diagnostic interviews will be supervised by the first author.

Primary Outcome

Abstinence: We will use the timeline follow-back (TLFB) procedure to assess cigarette consumption at each day following the previous assessment. We have previously used the TLFB to assess cigarette use among high anxiety sensitivity smokers (McLeish, Zvolensky, & Bucossi, 2007) and the assessment has demonstrated good reliability and validity (Brown et al., 1998). Self-reported abstinence at every assessment will be verified by expired carbon monoxide (CO). Abstinence at 16 and 24 weeks following the quit day will additionally verified with saliva cotinine. Self-reported abstinence will be overridden by a positive carbon monoxide (>8ppm) or saliva cotinine verification (>10 ng/mL) (Smits et al., 2015). If neither CO nor cotinine levels were available to verify abstinence at an assessment, abstinence will be considered missing data (Blankers et al., 2015). As in past work (Smits et al., 2015), we will employ 7-day point prevalence abstinence (PPA) and prolonged abstinence (PA) as the primary outcomes. PPA will be defined as no smoking, not even a puff, in the 7 days prior to any assessment. Failure to maintain PA at any assessment will be defined by 7 or more consecutive days of smoking or smoking at least 1 cigarette over the 2 consecutive weeks prior to the assessment. Because some participants will quit before the target quit day (week 5), the starting point for measuring abstinence will be at baseline.

Mechanisms of Action

Panic Disorder Severity Scale (PDSS): The PDSS 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 (Shear et al., 1997).

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

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, Clark, & Tellegen, 1988).

Minnesota Withdrawal Scale (MWS): The MWS is a reliable and sensitive 10-item scale to monitor withdrawal severity at baseline, weekly throughout treatment and at follow-up assessments (Hughes & Hatsukami, 1986).

Measures of Treatment Integrity and Acceptance

Treatment Credibility and Expectancy: The 6-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. 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: All sessions will be videotaped and 10% will be rated shortly thereafter by independent raters to assess therapist adherence to, and competence with, the treatment protocol.

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: At each visit, participants will be assessed for adverse events using standard reporting forms. Participants who report significant symptoms or adverse reactions to the nicotine patch will be assessed 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 psychosocial treatment.

Data Analysis

Because of the nature of this R34 project (i.e., treatment development), the primary focus is to obtain initial effect sizes for the intervention, which will guide a future efficacy study. Effect size analyses will be complemented by significance testing as follows. The effects of treatment on abstinence (PPA and PA; Aim 1) will be examined using Generalized Linear Mixed Models (GLMM), employing the logistic linking function, as recommended by the Society of Research on Nicotine and Tobacco (Hall et al., 2001). In our GLMM analyses, the repeated measures of abstinence will be nested within individuals. Our GLMM analysis will employ a 3-phase piecewise growth curve model to track abstinence over the course of the 29-week study. This is the model we used in our other smoking cessation research that followed a similar pattern of treatment (Smits et al., 2015). The first phase of the growth model will contain the first 5 weeks of the study (pre-quit treatment phase), the second phase will include weeks 6–8 (post-quit treatment phase), and the third phase will cover weeks 9–29 (post-treatment phase). We will model a discontinuity in the growth curve between the

first and second phase to reflect the jump in abstinence expected for the scheduled quit attempt. We will also model a discontinuity in the growth curve between the second and third phases to reflect a potential large drop in abstinence when treatment support ends and the follow-up phase begins.

Treatment condition will be included as a level-2 predictor of all the growth curve parameters. Non-significant terms in the growth curve model will be deleted to simplify the final model. Based on our previous smoking cessation research in which the quit day occurred after much of the treatment had been administered (Smits et al., 2015), we expect treatment condition differences in the discontinuity from the beginning of week 5, just before the quit attempt, to the beginning of week 6, after the quit attempt. This treatment condition difference reflects expected differences in the success of the participants' quit attempts. Treatment condition may also impact participants' ability to remain abstinent during phase 2 and their ability to remain abstinent immediately after treatment ends (as indicated by the discontinuity between phase 2 and 3). Treatment condition differences at any time point can be assessed by "centering" our growth curve parameters at that time point (Hayes, 2013).

We will use the mixed effects models to test target engagement and adjust the the GLMM model predicting abstinence (used in Aim 1) to examine the relation between the putative mediators and abstinence. Tests of the mediated pathways will be conducted using the distribution of products (Tofighi & MacKinnon, 2011). Pattern mixture modeling will be used to assess the effect of missing data on all our analyses. To determine both if missing data impacts our findings and how the differences between PSRT+DCS and PSRT+PBO depend on the missing data pattern, we will rerun all analyses coding for various missing data patterns (no missing data, sporadic missing data, dropouts, etc.). If results differ between participants with different missing data profiles, each result will be evaluated for each of the different missing data profiles.

Power Analyses

We performed a Monte Carlo study to calculate the minimum PRST+DCS PPA rate detectable by our GLMM analysis (Aim 1). We assumed that we would obtain data from participants at 9 of the 13 assessments (69%) and that we would have 15% abstinence in PSRT+PBO at 24 weeks postquit. We examined numerous PSRT+DCS abstinence rates to determine the lowest rate detectable with a .80 power by our analysis, performing 1000 simulations for each PPA rate. The results indicated that we would have .80 power to detect a significant treatment effect if the abstinence rate in PSRT+DCS at the last follow-up was 32% or greater.

Discussion

Smoking significantly increases the risk for developing and maintaining panic attacks. Further, panic disorder, and panic psychopathology, is related to a significantly increased risk of smoking cessation failure. Although targeted smoking cessation treatments for smokers with panic attacks exist, they leave room for substantial improvement. The goal of the current research is to evaluate the potential efficacy of the addition of DCS versus

placebo to a specialized cognitive-behavioral program targeting the role of anxiety sensitivity and panic attacks in relapse.

This 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.

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Table 1

Overview of Intervention Procedures

Intervention/Session	Session 1	Session 2	Session 3	Session 4	Session 5 Quit Day	Session 6-7
Standard Smoking Cessation Procedures	<ul style="list-style-type: none"> • Provide quit support and reinforcement • Discuss past experiences • Set quit date (First day of Week 5) • Initiate self-monitoring (tracking smoking and noting cues for smoking) 	<ul style="list-style-type: none"> • Help identify high-risk for relapse situations • Discuss abstinence violation effect • Develop coping strategies • Encourage enlisting social support • Provide self-help materials 	<ul style="list-style-type: none"> • Review elements discussed in Session 2 and isolate any areas of concern for patients 	<ul style="list-style-type: none"> • Discussion of upcoming quit day • Instruct on proper use of NRT 	<ul style="list-style-type: none"> • Initiate NRT • Discussion of quitting experiences • Provide support • Anticipate high-risk situations 	<ul style="list-style-type: none"> • Continue NRT • Provide support • Anticipate high-risk situations • Develop social support for nonsmoking
Panic Reduction Procedures	<ul style="list-style-type: none"> • Integrated treatment (PSKI) rationale • Education on panic-smoking link • Interceptive exposure introduction • Interceptive exposure practice • Homework practice assigned 	<ul style="list-style-type: none"> • Review education on panic-smoking link • Review interceptive exposure rationale • Cognitive restructuring • Interceptive exposure practice • Homework practice assigned • Instruction to refrain from smoking 4 hours prior to Session 3 	<ul style="list-style-type: none"> • Interceptive exposure practice • Cognitive restructuring • Homework practice assigned • Instruction to refrain from smoking 4 hours prior to Session 4 	<ul style="list-style-type: none"> • Homework practice review • Interceptive exposure practice • Cognitive restructuring • Homework practice assigned 	<ul style="list-style-type: none"> • Encourage self-awareness of the role of panic-related experiences in smoking behavior and urge to smoke. • Underscore importance of integrating exposure, non-catastrophic thinking, and education to maintain abstinence. • Cognitive restructuring 	<ul style="list-style-type: none"> • Cognitive restructuring • Interceptive exposure • Situational exposure (i.e., avoided situations)

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Intervention/Session	Session 1	Session 2	Session 3	Session 4	Session 5 Quit Day • Interoceptive exposure	Session 6–7
Asked to Abstain Prior to the Session?	No	No	Yes	Yes	Yes	Yes
DCS/PBO Administration?	No	No	Yes	Yes	Yes	No