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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, we will obtain initial effect sizes for short-term and long-term smoking cessation outcomes and perform an initial test of putative mechanisms.

1. Introduction

Panic attacks are common (7–10% of the general population regularly experience panic attacks; [32]) and co-occur with smoking at rates that exceed those found in the general non-psychiatric population [2,8,9,17,18,25,35]. For example, Lasser et al. [26] found that in an analysis of over 4000 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 et al. [34] recently reported that 30% of smokers seeking cessation treatment from the general community reported a history of panic attacks. Finally, Bakhshaie, Zvolensky, and Goodwin [4] 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 [34,48].

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 [31], has emerged as particularly promising. Indeed, anxiety sensitivity (a) is heightened among smokers with a history of panic attacks compared to those without [5], (b) is related to cognitive-affective reactivity and emotional regulatory deficits related to smoking cessation [49]; and (c) can be reduced with intervention [40]. Importantly, emerging evidence indicates that interventions that effectively reduce anxiety sensitivity facilitate the odds of smoking cessation in anxiety vulnerable adults [39,47,50].

Panic and Smoking Reduction Treatment (PSRT; [50]) 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 [19,38]. 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 subsequence relapse

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by helping patients change their relationship with internal cues (i.e., from signaling threat resulting in lapse and subsequent relapse to signaling 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 [50]. 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 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; [33]). For example, a meta-analysis of 9 trials showed a medium effect size in favor of DCS relative to placebo ($d = 0.46$; [7]). DCS, a FDA-approved drug for the treatment of tuberculosis (500-100 mg daily), facilitates N-methyl-D-aspartate receptor (NMDAR) functioning, which enhances fear extinction retention [33]. Research on the neural circuitry involved in extinction learning has led to the identification of core pathways and neurotransmitters involved in fear extinction [13]. 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 [27,28,36]. When given in small doses (50–250 mg), either before or immediately after a session that involves extinction training, DCS has been shown to facilitate fear reduction [24], particularly when these sessions are marked by low fear at the end of the session [41,42]. 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).

2. Methods

2.1. 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 h 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.

2.2. 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.

2.3. 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 [1]. 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.

2.4. 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.

2.4.1. 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 [21].

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