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EFFECTS OF D-CYCLOSERINE ON CUE-INDUCED CRAVING AND CIGARETTE SMOKING AMONG CONCURRENT COCAINE- AND NICOTINE-DEPENDENT VOLUNTEERS

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Abstract

Rates of cigarette smoking are 3- to 4-fold greater among those with cocaine-dependence, and compared to non-users, cocaine users are at greater risk of incurring smoking-related negative health effects and death. The current study examined D-cycloserine's (0 or 50 mg once weekly) 2) effects on 1) extinction of cue-induced craving for cigarettes, 2) cigarette smoking in conjunction with cognitive-behavioral therapy, and 3) safety and tolerability in cocaine-dependent smokers. This was a double-blind, placebo-controlled, between groups, outpatient study. Participants (N=29) were concurrent cocaine- and nicotine-dependent volunteers seeking treatment for their cigarette smoking. Study visits were 3 times per week for 4 consecutive weeks. At each visit, participants received cognitive-behavioral therapy for smoking, were exposed to smoking cues. A subset of participants (N=22) returned for 6-month follow-up visits. While craving decreased, no significant effects of D-cycloserine treatment were observed. Likewise, significant decreases in smoking were observed at study days 6 ($p < 0.002$) and 12 ($p < 0.0001$) relative to baseline, although no participants achieved complete abstinence. However, there was no effect of D-cycloserine on cigarette smoking during treatment or at 6-mos follow-up. The treatment was safe and tolerable, with nearly 90% of treatment sessions attended based on an intent-to-treat analysis. While no effects of D-cycloserine on craving or smoking were observed in the current study, the results do suggest smoking treatment is well accepted and may be effective for cocaine-dependent individuals.

Keywords

D-cycloserine; cocaine; nicotine; cognitive-behavioral therapy; cues; craving; treatment

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Author Disclosures

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1. Introduction

Cigarette smoking is a substantial public health concern and is particularly concerning among cocaine-dependent individuals. Among cocaine-dependent individuals, rates of smoking are 3- to 4-fold greater than that of the general population (Budney, Higgins, Hughes, & Bickel, 1993; Gorelick, Simmons, Carriero, & Tashkin, 1997; Kalman, Morissette, & George, 2005; Lasser et al., 2000; Patkar et al., 2002; Patkar et al., 2006; Patkar, Sterling, Leone, Lundy, & Weinstein, 2002). Compared to non-drug using cigarette smokers, cocaine-dependent cigarette smokers have greater risk of incurring death (Hser, McCarthy, & Anglin, 1994; Hurt et al., 1996) and other negative smoking-related health consequences (Patkar et al., 2005; Patkar, Lundy, et al., 2002). Unfortunately, little research has focused on developing smoking treatments for those with cocaine-dependence (Morisano, Bacher, Audrain-McGovern, & George, 2009; Weinberger & Sofuoglu, 2009).

Among cigarette smokers in general, millions attempt to quit smoking each year, yet most relapse within the first 8 days of the quit attempt (Hughes, Keely, & Naud, 2004). Even with the aid of first line smoking-cessation medications such as nicotine replacement therapy (NRT), bupropion, or varenicline, rates of smoking abstinence are only 20–33% at 6 months after the initial quit attempt (Fiore, Jaén, Bailey, Benowitz, & Et al., 2008). These results suggest that non-nicotinic factors (e.g., cue-induced craving for cigarettes) may also play an important role in maintaining cigarette smoking (Caggiula et al., 2002; Rose, 2006). For example, previously neutral smoking-related cues (e.g., sight & smell of cigarettes, emotional states, particular environments, etc) may become potent conditioned-reinforcers through pairings with nicotine. In turn, presentation of these cues alone may induce cravings for cigarettes and precipitate relapse (Ferguson & Shiffman, 2009). Also, when asked why they relapsed, participants enrolled in cessation treatment often point to irresistible cravings following exposure to smoking cues (Bliss, Garvey, Heinold, & Hitchcock, 1989; Shiffman, 1982; Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). Similarly, *in vivo* studies using portable electronic diaries have observed a reliable and temporally proximal relationship between recent exposure to smoking cues and relapse (Shiffman et al., 1997; Shiffman, et al., 1996). Taken together, the available data support that addressing cue-induced cravings is integral for decreasing the likelihood of relapse.

Cue exposure therapy (CET) extinguishes cue-induced cravings by presenting cues in the absence of any drug effect (Ferguson & Shiffman, 2009; Perkins, 2009). Previously developed CET paradigms utilized stimuli that only partially modeled the complexity of real-life smoking cues (e.g., pictures, videos, *in vivo* cues), and consequently failed to translate outside of the laboratory (Bordnick et al., 2004a). Recently, researchers have developed virtual-reality (VR) cues that produce greater levels of craving when compared to traditional methods of cue exposure (Bordnick et al., 2004b; Bordnick et al., 2008; Kuntze et al., 2001; Lee, Kwon, Choi, & Yang, 2007; Traylor, Bordnick, & Carter, 2008, 2009). VR cues have been utilized for treatment for addiction (Lee, et al., 2007) and phobias (Heldt, Green, & Ressler, 2004), and successfully produce cue-induced craving in smoking studies (Baumann & Sayette, 2006; Bordnick, et al., 2004a; Bordnick, Graap, Copp, Brooks, & Ferrer, 2005; Bordnick, Traylor, Graap, Copp, & Brooks, 2005; Carter, Bordnick, Traylor, Day, & Paris, 2008; Lee et al., 2003; Lee, Lim, Wiederhold, & Graham, 2005; Traylor, et al., 2008).

D-cycloserine is an N-methyl-D-aspartate (NMDA) partial agonist demonstrated to enhance CET. Activation of the NMDA receptor has been associated with extinction and induces long-term potentiation, which is thought to play a key role in associative learning (Martina et al., 2004). D-cycloserine (50 mg/week) in conjunction with CET enhanced extinction of

acrophobia (Ressler et al., 2004) and social phobia (Hofmann et al., 2006). Note that in the Ressler et al. study, acrophobia was induced using a VR elevator.

The current study had three primary goals: 1) to examine the effects of D-cycloserine (50 mg/week) on enhancing CET to virtual smoking cues, and 2) to examine the effects of D-cycloserine in conjunction with cognitive-behavioral therapy (CBT) and CET on cigarette smoking among concurrent cocaine- and nicotine-dependent volunteers seeking treatment for their cigarette smoking, and 3) to assess the safety and feasibility of administering D-cycloserine over the course of a 4-week treatment for cigarette smoking in cocaine-dependent individuals

2. Methods

2.1 Participants

Participants were recruited from the Houston metropolitan area through newspaper and radio advertisements. The study was approved by the Baylor College of Medicine and Michael E. DeBakey Veterans Association Medical Center (MEDVAMC) Internal Review Boards. All participants completed an initial telephone screen in order to assess basic eligibility. Eligible candidates were invited to complete an in-person assessment at the MEDVAMC Research Commons. During the in-person interview, candidates received an explanation of the study purpose and requirements and were allowed to review, inquire about, and sign the informed consent form. Eligible individuals were required to be between 18–55 years of age, speak English, report a history of smoking 10 cigarettes/day for the last year, and reported that their motivation to quit cigarette smoking was >50 on a 1 to 100 scale, provide a baseline breath CO level 10 ppm, meet DSM-IV criteria for cocaine and nicotine dependence, and report that they were seeking treatment for their cigarette smoking (but not for their cocaine dependence). Participants were excluded for any psychiatric or medical illness, serious neurological or seizure disorder, use of any psychoactive medication (especially medications for smoking cessation), drug or alcohol dependence excluding cocaine and nicotine, known allergies to D-cycloserine, or current use of smokeless tobacco, pipes, or cigars. Women were not eligible for the study if they were pregnant, breast feeding, or not using a reliable form of birth control. Participants were compensated with a \$40 gift certificate for completing the in-person screen.

2.2 Procedure

All study visits took place at the MEDVAMC Research Commons. Initial screening measures were assessed at the in-person screen interview and included a medical and drug use history, EKG, and vital signs, which were conducted by trained research staff. Eligible participants were randomized to D-cycloserine or placebo conditions by the Research Pharmacy in order to maintain the double-blind. Participants were informed that they would have to provide an initial breath CO 10 ppm on the first visit in order to initiate the study. This 1st day contingency was put in place in order to increase the likelihood that only participants that were motivated to quit smoking were enrolled into the study. Participants were informed that they should stop smoking by 5 pm the day prior to the first visit in order to meet the 1st visit breath CO criterion.

The study was 4-weeks in duration and study visits were scheduled three times per week (Monday, Wednesday, & Friday) for a total of 12 study visits. Participants could initiate the study on any of those three days. At each study visit, participants were administered study forms, provided breath, urine, and saliva samples in order to assess recent drug use and cigarette smoking, participated in a brief (~30 min) CBT session; and completed the 20 min

CET session. At the beginning of each study week (visits 1, 4, 7, & 10), participants were administered 50 mg D-cycloserine or placebo. Participants were compensated \$50 per visit.

Follow-up visits were conducted to assess potential long-term changes in behavior. To this end, completers were asked to visit the laboratory 3 times over a 1-week period in order to get a representative sample of their smoking behavior. Participants' recent drug use and smoking status were assessed at each of these visits. Participants were compensated \$10 per follow-up visit.

2.3 Treatments

2.3.1 Virtual Cue-Exposure Therapy Session—The exposure apparatus was created based on a previously validated virtual cue environment based in Second Life® (Culbertson et al., 2010). Virtual cues were presented on a 32" LCD, flat-panel HDTV monitor, which was connected to a desktop computer running the Microsoft Windows® Vista operating system. The monitor and computer were housed in a sensory attenuated environment in order to isolate participants from external, irrelevant stimuli (Culbertson, et al., 2010). Participants navigated the online environment using a standard computer mouse, which was only set to accept input commands for movement but not mouse-key presses. Sessions were conducted by research staff via a second mirrored monitor, mouse, and keyboard placed outside of the chamber.

Second Life® is a persistent, online virtual world and served as the exposure platform. Two distinct 3-D, virtual apartments with either smoking cues or neutral (non-smoking) cues were created within Second Life® and used photorealistic cues and 3D graphics to enhance the overall realism of the online environments. An orientation environment to familiarize participants with the environment was created as well. Prior to entering the other environments, participants were first exposed to the orientation environment, where they learned how to alter their avatar's view using a standard computer mouse. Once participants were comfortable with how to alter their avatar's perspective, CET sessions were initiated.

CET sessions consisted of two cue sessions (smoking and neutral) that were each 5 minutes in duration. Pictures of the neutral-cue apartment have been previously published (Culbertson, et al., 2010). The smoking-cue apartment was similar, but with addition of various smoking cues (packs of cigarette on the table, ashtray, beer bottle, etc). During both sessions, the participant's avatar was situated on a sofa in a living room. Several other avatars were also present in the room. During the smoking-cue session, all of the avatars, including the participant's, engaged in pre-programmed smoking animations with virtual cigarettes. A virtual television was also in the room. During the smoking-cue session, the television showed various real-life smoking scenarios (while reading a paper, while drinking coffee, waiting in line at a club, etc) from a 1st-person perspective. During the neutral-cue session, the video consisted of non-smoking scenarios (folding laundry, cooking, shopping, etc) from a 1st-person perspective. In addition to the virtual cues, participants were presented with physical cues during each cue session. During smoking-cue sessions, participants had access to their preferred brand of cigarettes and were asked to pull one out, manipulate it, and to smell the cigarette, though they were not allowed to smoke the cigarette during the session. During the neutral-cue session, participants were presented with a cue similar in shape (pack of crayons) and asked to manipulate and smell an individual crayon in a similar manner. Smoking- and neutral-cue sessions were presented in random order.

2.3.2 Brief Cognitive-Behavioral Therapy Session—CBT sessions were conducted at each visit for study days 1 through 12. CBT is an evidence-based treatment that helps participants engage in the treatment process, modify their attitudes and behaviors related to cigarette smoking, and increase healthy life skills (Carroll & Onken, 2005). Specifically,

CBT seeks to help participants recognize, avoid, and cope with situations in which they are most likely to smoke cigarettes. A previous meta-analysis has established the efficacy of CBT in over 24 randomized controlled trials among adults with substance dependence, and CBT appears to be particularly effective in treating nicotine dependence (Carroll, 1996). Recent studies have suggested that D-cycloserine may enhance the effectiveness of CBT (Ganassen, Ipser, & Stein, 2010).

CBT sessions were conducted by therapists (JY, CH, JM, RH, KL, and ER) with a minimum of a master's degree in a relevant field of study. Therapists received additional training in the form of relevant literature and role-playing prior to conducting sessions, and continued to engage in weekly meetings with a licensed psychotherapist (RF) specializing in CBT. CBT sessions for participants were 30 min in length. While some treatments have utilized much more intense schedules of CBT, previous studies have demonstrated that abbreviated versions of CBT are still effective for the treatment of amphetamine (Baker et al., 2005) and marijuana use (Copeland, Swift, Roffman, & Stephens, 2001). Note that CBT in the current study was aimed at cigarette smoking only and not cocaine use.

2.4 Measures

2.4.1 Assessment of Cigarette Smoking & Recent Drug Use—Cigarette smoking was assessed via self-report, breath CO (Vitalograph® Inc, Lenexa, KS), and salivary cotinine. For the purpose of the current study, the smoking abstinence criterion was defined as a breath CO $\leq$ 10 ppm, which is a commonly utilized indicator of recent smoking abstinence (Benowitz et al., 2002). Salivary cotinine levels were assessed via Salimetrics® salivary cotinine enzyme immunoassay kit. Saliva samples were collected according to company instructions, frozen, and shipped to Salimetrics® for analysis of cotinine levels. Individual samples were assessed in duplicate.

Recent alcohol use was evaluated via breath-alcohol monitor (Alco-Sensor FST®, Intoximeters, Inc, Saint Louis, MO), and illicit drug use was assessed at each visit via NIDA 5-Panel Drug Test Kits (Arham International, Inc., Greenville, SC), testing for cocaine, amphetamine, methamphetamine, THC, and opiate metabolites. The effect of D-cycloserine on other drug use was not the focus of this study, and these data are not reported here.

2.4.2 Assessment of Nicotine Dependence

Fagerström Test for Nicotine Dependence (FTND): The FTND is a 5-item questionnaire that has been previously demonstrated to be reliable and valid and is widely used to characterize nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The FTND was assessed during the in-person screen and at each study visit.

2.4.3 Self-Reported Cravings for Cigarettes

Urge to Smoke Questionnaire (UTS): The UTS consists of 10 items, with each item scored on a 7-pt scale, that measures nicotine withdrawal (Jarvik et al., 2000). Participants were administered the UTS prior to the CET session (−5 min) and immediately after each of the individual 5-min cue sessions (+5 min and +15 min).

2.4.4 Assessment of Cardiovascular Measures—Heart rate and systolic and diastolic blood pressure (GE Medical Systems Information Technologies, Inc., Milwaukee, WI) were assessed prior to the CET session (−5 min) and immediately after each of the 5-min cue sessions (+5 min and +15 min).

2.5 Study Medication

D-cycloserine (50 mg) or placebo was administered at the beginning of study days 1, 4, 7, and 10. Medication was administered 60 min prior to the CET session. The dosing regimen was based on previous clinical trials utilizing D-cycloserine in conjunction with CET for anxiety disorders (Hofmann, et al., 2006; Ressler, et al., 2004). In support of the 50 mg/week dose, Ressler et al., observed no differences in 50 vs. 500 mg of D-cycloserine, and it has been suggested that doses higher than 50 mg may be less effective (Rothbaum, 2008). As further support, nearly all positive studies following the seminal Ressler et al. study have utilized a 50 mg dose of D-cycloserine administered 1 hr prior to cue exposure, as done in the current study. Note that D-cycloserine was not paired with each CET session as CET was administered each session as part of our comprehensive treatment. Therefore, the goal was to examine if weekly administrations of D-cycloserine would enhance the ongoing CET. Additionally, there is evidence that more frequent administration of D-cycloserine can reduce its extinction enhancing effects (Davis, Ressler, Rothbaum, & Richardson, 2006).

D-cycloserine (250 mg) tablets produced by Eli Lilly and Company were obtained from the Chao Center (West Lafayette, IN). Greenpark Compounding Pharmacy & Gifts (Houston, TX) crushed the tablets and repackaged them into 50 mg capsules as well as matching placebo capsules.

2.6 Data Analysis

Data were analyzed using StatView 5.0 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were compiled for demographic and drug use variables and parametric (e.g., FTND scores, cigarettes/day) and non-parametric (e.g., gender, ethnicity) tests were used as appropriate.

Safety Data—Total number of adverse events (AEs) was summed from all study visits (1 to 12) for both experimental conditions (D-cycloserine: 0 vs. 50 mg). An ANOVA was conducted to evaluate the occurrence of AEs between the two conditions.

Cardiovascular data (heart rate and blood pressure) was compared using one-way ANOVA as a function of D-cycloserine treatment (0 or 50 mg) at baseline, day 6, or day 12. Repeated-measures ANOVA was used to evaluate changes in heart rate and blood pressure as a function of D-cycloserine treatment (0 or 50 mg) and time (baseline and study days 1 to 12). In order to control for individual baseline differences, a subtraction procedure was conducted in which cardiovascular scores from study days 1 to 12 were subtracted from observed baseline values for each participant.

Attendance Data—Total sessions attended were compared using one-way ANOVA as a function of D-cycloserine treatment (0 or 50 mg). Percent of individuals who attended all sessions was compared using Chi-Square as a function of D-cycloserine treatment (0 or 50 mg).

Physiological and Subjective Effects Data—These data included breath CO and salivary cotinine. Baseline data were compared using one-way ANOVA as a function of D-cycloserine treatment (0 or 50 mg). Data from baseline, day 6, or day 12 were compared using one-way ANOVA as a function of D-cycloserine treatment (0 or 50 mg). Repeated-measures ANOVA was used to evaluate conditions as a function of D-cycloserine treatment (0 or 50 mg) and time (sessions). A subtraction procedure was utilized to control for baseline values.

Self-reported cigarettes smoked per day were compared at baseline, day 6, and 12 using one-way ANOVA as a function of D-cycloserine treatment (0 or 50 mg). Repeated-measures ANOVA was used to evaluate changes in cigarettes smoker per day as a function of D-cycloserine treatment (0 or 50 mg) and time (days). A subtraction procedure was utilized to control for baseline values.

Urge to Smoke scores at day 1, day 6, and day 12 were compared individually using one-way ANOVA as a function of D-cycloserine treatment (0 or 50 mg). Repeated-measures ANOVA was used to evaluate craving during pre-CET, smoking-cue, and neutral-cue sessions as a function of D-cycloserine (0 or 50 mg) and time (study days 1–12).

An intent-to-treat (ITT) analysis was conducted on attendance data for all eligible participants that entered treatment, with study dropouts treated as missing any further sessions. For the sake of brevity, we did not conduct an ITT analysis on other outcome measures given the general lack of effects observed using conventional ANOVA tests. Inclusion of those individuals would likely further wash out group effects. Additionally, one of the primary measures of interest would be cigarette smoking, which is generally reported using 7-day point-prevalence measures of smoking abstinence. As no individuals completely quit smoking in this study such an analysis would not alter the overall negative findings.

All data, except time, were analyzed as between-subjects factors. Time (in days) was analyzed as a within-subjects factor. For all measures, test were two-tailed, and statistical significance was set at $p < 0.05$. All data are presented as mean $\pm$ standard error of the mean (S.E.M.).

3. Results

3.1 Participant Recruitment and Attendance

A total of 47 participants were consented for the study and randomized by the research pharmacy into one of the two experimental conditions. Of those randomized, 34 participants completed the study. Of the 13 non-completers, 4 failed to initiate the treatment portion of the study (did not meet the initial CO criterion), 8 terminated the study for personal reasons, and one was discharged from the study after missing 3 consecutive visits. Baseline characteristics in the 8 individuals that terminated the study and the 1 that was dropped were comparable to those that completed the study. Five participants' data were not included in the final data analyses after we determined that these participants did not accurately report their smoking history (as verified by salivary cotinine levels) and therefore did not meet the smoking inclusion criteria. Figure 1 shows the progress of participants in the study. Demographic and drug use characteristics of the 29 completers are presented in Table 1. Overall, participants were predominately male, African American, in their late 40s, and averaged a high-school level of education (Table 1). In terms of cigarette smoking, participants were relatively heavy smokers, and this was the first attempt to quit cigarette smoking for approximately half of them. In terms of cocaine use, all participants were crack-cocaine users and reported using cocaine approximately half of the days in the last month. The conditions did not differ for any basic demographic or drug use variables.

ITT analysis was conducted on session attendance. Results showed 88.2% and 89.0% of sessions were attended in the placebo and D-cycloserine conditions, respectively. One-way ANOVA revealed no significant differences in the percent of sessions attended according to treatment condition ($F_{1,36} = 0.93$, $p = 0.34$). ITT analyses were not conducted on other study outcomes. In regards to follow-up visits, 11 participants participated for each experimental condition. Average time between completing treatment and follow-up visits were 177.4 ± 20.6 days for the placebo condition and 187.0 ± 22.9 days for the D-cycloserine condition.

3.2 Safety

No serious AEs were reported during this study. Average numbers of AEs per participant in the D-cycloserine condition (0.69 ± 0.51) and placebo condition (0.23 ± 0.17) were not significantly different ($F_{1,27} = 1.31, p = .26$). The most common AEs were pains associated with arthritis (7 reports for one participant), cough (3 reports for 3 participants), and cold symptoms (2 reports for 2 participants), vomiting/diarrhea (1 report), and high blood pressure (1 report), but these were not likely related to D-cycloserine or placebo administration.

Results from cardiovascular measures are shown in Table 2. Overall, no differences in cardiovascular measures were observed at baseline, day 6, and day 12 between the experimental conditions with the exception of systolic blood pressure on day 12. Repeated-measures ANOVA revealed no significant effects of D-cycloserine, Time, or D-cycloserine X Time interaction for systolic blood pressure. Repeated-measures ANOVA revealed a significant increase in heart rate across Time, but these differences were not clinically significant (Table 2).

3.3 Effects on Craving

Overall, similar craving patterns (pre-CET, smoking-cue, neutral-cue) were observed across treatment days. Craving levels were highest on study day 1 and steadily decreased over the course of treatment. Figure 2 shows pre-CET craving scores across study days for participants in the placebo and D-cycloserine conditions. Similar patterns were observed for smoking-cue and neutral-cue sessions (data not shown). One-way ANOVA revealed no significant differences in craving at day 1, day 6, and day 12 in pre-CET, smoking-cue, and neutral-cue sessions between the placebo and D-cycloserine conditions (Table 2). Repeated-measures ANOVA revealed a significant decrease in craving across study days in pre-CET, smoking-cue, and neutral-cue craving scores. No significant effects of D-cycloserine or D-cycloserine X Time interaction for any of the craving scores were observed (Table 2).

Exposure to virtual smoking cues produced significantly greater craving relative to neutral cues, which subsequently extinguished over repeated exposures. Craving during smoking-cue sessions was significantly greater than during neutral-cue sessions on study day 1 ($t_{28} = 2.94, p = 0.007$). However, these differences were not statistically significant by study day 6 ($t_{28} = 1.10, p = 0.32$) and 12 ($t_{28} = 0.83, p = 0.41$), indicating extinction. Repeated-measures ANOVA revealed a significant decrease in relative craving across study days. However, no significant effects of D-cycloserine or D-cycloserine X Time interaction were observed (Table 2).

3.4 Effects on Cigarette Smoking

3.4.1 Breath Carbon Monoxide During Baseline Treatment Period—One-way ANOVA revealed no differences in breath CO levels at baseline, day 6, and day 12 (Table 2). Repeated-measures ANOVA revealed a significant effect of Time (Table 2) with breath CO increasing as function of study day during days 1 to 12 of treatment. Note that this effect was primarily due to the decreased CO levels observed on day 1, which had the additional contingency requiring participants to present breath CO levels ≤ 10 ppm to qualify for the study (Figure 3). Results of repeated measures ANOVA on days 2–12 revealed no significant effects of Time ($F_{1,10} = 1.2, p = .29$). During treatment, significant decreases in breath CO levels ($\sim 50\%$) were observed relative to baseline (Fig. 3). For example, breath CO levels were significantly lower on day 6 ($t_{28} = 3.35, p < 0.002$), and day 12 ($t_{28} = 6.00, p < 0.0001$) of treatment as compared to baseline. However, no participants achieved complete abstinence for the duration of treatment.

3.4.2 Salivary Cotinine During Baseline and Treatment Period—Due to initial problems with salivary cotinine vial labeling, baseline samples from 4 placebo and 8 D-cycloserine participants could not be analyzed. One-way ANOVA on salivary cotinine levels on available samples revealed no difference at baseline, day 6, and day 12 (Table 2). During 1-month treatment all salivary cotinine samples were available. Repeated-measures ANOVA were conducted on cotinine levels during days 1 to 12 of treatment, which did not reveal any significant effects (Table 2). Due to differences in the available samples, no comparison of cotinine levels between baseline and treatment were conducted.

3.4.3 Self-Reported Cigarettes Smoked—One participant's data from the D-cycloserine condition were not included in the final analysis as they reported smoking cigars for one week of the study. Also note that data represent the number of cigarettes smoked on the day prior to each visit in order to get an accurate representation of a full day's worth of smoking. One-way ANOVA revealed no differences in cigarettes smoked per day at baseline, day 6, and day 12 (Table 2). Repeated-measures ANOVA revealed no significant effects of D-cycloserine during days 1 to 12 of treatment as well (Table 2). During treatment, significant decreases in reported cigarettes smoked per day were observed relative to baseline. For example, cigarettes smoked per day were significantly lower on day 6 ($t_{27} = 4.7, p < 0.0001$), and day 12 ($t_{27} = 10.5, p < 0.0001$) of treatment as compared to baseline.

3.4.4 Follow-up of Smoking Status—Breath CO and salivary cotinine levels at baseline, day 6, day 12, and the average values observed during 3 follow-up visits for the subset of participants (11 for each condition) that attended these sessions are shown in Table 3. Data on cigarettes smoked per day was not collected at follow-up visits.

One-way ANOVA revealed no significant difference at any of time-points between the placebo and D-cycloserine conditions for either breath CO or salivary cotinine, (Table 3). While differences in follow-up breath CO levels seemed promising, they were not significant and similar results were not mirrored in salivary cotinine levels. Repeated measures ANOVA revealed an effect of Time for breath CO with breath CO decreasing as a function study day. Due to differences in baseline cotinine samples noted above, repeated measures ANOVA was not conducted for salivary cotinine.

4. Discussion

To summarize the main findings, no effect of D-cycloserine on the primary dependent measures (changes in craving during CET and smoking as measured by breath CO) was observed. Craving for cigarettes decreased across study days and cue-induced craving was extinguished following repeated sessions of CET using virtual smoking cues. Significant decreases in cigarette smoking were observed as measured by both breath CO and self-reported cigarettes smoked per day. D-cycloserine was found to be safe to administer among cocaine-dependent cigarette smokers and the smoking cessation treatment was well tolerated.

The goal of the current study was to simply examine whether once weekly administration of D-cycloserine would enhance CET and subsequently produce similar decreases in smoking. When the current study was designed, no studies had been published examining the effects of D-cycloserine on craving for cigarettes. Since then, studies have examined the effects of D-cycloserine on craving for alcohol (Kamboj, Massey-Chase, et al., 2011; Watson et al., 2011), cocaine (Price et al., 2009), and cigarettes (Kamboj, Joye, et al., 2011; Santa Ana et al., 2009). With the exception of the Santa Ana et al study, no D-cycloserine-dependent decreases in craving have been observed, and in the Price et al., study D-cycloserine increased cocaine cue reactivity. In the Santa Ana et al. study, non-treatment seeking

cigarette smokers were exposed to six CET trials during two separate sessions in week 1 and 3 of the study. Participants in the D-cycloserine condition exhibited significantly greater decreases in skin conductance across trials by session 2 and decreases in self-reported average urge-to-smoke during both sessions, compared to those that received placebo. However, no effects on overall cigarette smoking as measured by breath CO were detected. Whether an effect of D-cycloserine would have been observed in the current study using similar procedures as Santa Ana is unknown. However, Kamboj et al. utilized comparable procedures to the Santa Ana *et al.* study by presenting smoking cues repeatedly over the course of one day's session among non-treatment seekers and also did not observe an effect of D-cycloserine on craving.

The overall failure to observe enhanced extinction of craving for cigarettes and other drugs of abuse in humans is puzzling given previous reports showing D-cycloserine to be effective in enhancing extinction to fear-inducing cues in both human and non-human animal studies and to conditioned drug cues in non-human animal studies (Kantak & Nic Dhonnchadha, 2011). A critical variable that may explain these disparate findings is continued pairings between drug and drug cues that are likely occurring between CET sessions in human drug studies. In a study with rats, D-cycloserine-enhanced extinction of the fear response was disturbed following reacquisition of the fear response (Ledgerwood, Richardson, & Cranney, 2004). Additionally, another study with rats has shown that while D-cycloserine enhances initial fear extinction, subsequent extinction following reacquisition of the fear response is no longer influenced by NMDA-receptor mechanisms and therefore unaffected by D-cycloserine (Langton & Richardson, 2008). Similar reconditioning generally does not occur in non-human animal studies and are less likely to be an issue in human studies extinguishing fear as such participants generally avoid fear-inducing cues in their natural environment.

In the current report, we did not observe effects of D-cycloserine on cigarette smoking, which was also not observed in the Santa Ana et al. and Kamboj et al. studies. Such results in the current study are not surprising given that we assumed that any D-cycloserine-related decreases in smoking would be the result of decreased cue-induced craving for cigarettes following D-cycloserine treatment. As no effect of D-cycloserine was observed on cue-induced craving, the lack of any differences in smoking between the two treatment conditions is expected. However, we observed significant reductions of cigarette smoking among cocaine-dependent individuals during treatment relative to baseline. To our knowledge, this is the first report of any treatment, behavioral or pharmacological, to demonstrate such notable reductions in smoking in cocaine-dependent participants. High rates of cigarette smoking in this study population were first noted by Budney et al. (1993). Since then, more recent reviews have confirmed high rates of smoking among those with substance use disorders (Kalman, et al., 2005) and stimulant dependence (Weinberger & Sofuoglu, 2009). Previous studies have examined treatments for cigarette smoking among those with substance use disorders (Prochaska, Delucchi, & Hall, 2004) as well as cocaine-dependent participants maintained on methadone (Poling, Rounsaville, Gonsai, Severino, & Sofuoglu). To the best of our knowledge, only one other study has targeted cigarette smoking among cocaine-dependent participants (Burling, Salvio, Seidner, & Ramsey, 1996). In that report, cocaine-dependent participants in a residential treatment program received a treatment consisting of systematically decreasing the nicotine content of cigarettes, which resulted in increases in a variety of smoking behaviors. Although a randomized-controlled trial is necessary to show whether or our treatment was responsible for decreased smoking, the current results provide promising support for developing smoking interventions for cocaine-dependent individuals. Of importance, we achieved high attendance rates in both treatment condition, and that is a source of optimism for conducting similar studies in this population. Note that participants scheduled to attend study visit three times a week, study

visits generally lasted at least 1 hr and sometimes several times as long. Such results provide clear evidence that providing smoking cessation treatment is feasible in this population.

Another potential limitation noted above is that D-cycloserine was not provided prior to each CET session, nor were higher doses of D-cycloserine examined. In regards to the former, extinction is a robust phenomenon following CET, regardless of the presence of D-cycloserine. So therefore, the present study was designed to simply observe if 50 mg of D-cycloserine administered once per week enhanced the extinction process. In regards to the latter limitation, Ressler et al., observed no differences in 50 vs. 500 mg of D-cycloserine and it has also been suggested that doses higher than 50 mg may be less effective (Rothbaum, 2008). Furthermore, a recent publication has noted that nearly all positive studies following the seminal Ressler et al. study have utilized a 50 mg dose of D-cycloserine administered 1 hr prior to cue exposure, as done in the current study (Watson, et al., 2011).

Some additional limitations were that the current study may have been underpowered to observe any effects (N=29). However, we would like to point out that previous studies such as those conducted by Santa Ana et al. (N=25) and Ressler et al. (N=28) observed significant effects with comparable sample sizes. Additionally, the study by Kamboj et al., had a slightly larger sample of 32 participants and did not observe an effect of D-cycloserine on cue reactivity for cigarettes. A post-hoc power analysis based on the current study's sample size showed that the current design would be sensitive enough to detect an effect size f of 0.18 (small to medium effects) at a critical F of 2.37 with power set at 0.80 and $\alpha = 0.05$.

To summarize, daily craving and cigarette smoking decreased during the treatment period, but these changes were not affected by D-cycloserine. Both the treatment and study medication were well tolerated by participants, and the results provide evidence that smoking cessation treatments are feasible among those with cocaine dependence.

Highlights

- D-cycloserine did not affect cue-induced craving for cigarettes or cigarette smoking.
- The treatment program was feasible and well accepted by participants.
- Significant reductions were observed in cigarette smoking.

Acknowledgments

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Figure 1.
Outline of participant flow through the study.

Figure 2.

Average pre-CET UTS craving scores obtained at each of the 12 study visits for the placebo (black bar) and D-cycloserine (grey bar) conditions. Error bars represent +1 S.E.M.

Figure 3. Relative difference in average craving scores from smoking-cue and neutral-cue sessions for the placebo (black bar) and D-cycloserine (grey bar) conditions. Error bars represent +1 S.E.M.

Figure 4.

Average breath CO (ppm) observed at baseline and during the 12 study visits for the placebo (black bar) and D-cycloserine (grey bar) conditions. Error bars represent +1 S.E.M.

Table 1

Summary of participant socio-demographic characteristics and drug use history.

Participant Characteristics	Placebo (N = 13)	D-cycloserine (N = 16)
Demographics		
Females (%)	23.1	12.5
White (%)	15.4	25.0
African-American (%)	84.6	75.0
Hispanic (%)	7.7	6.3
Age (years)	48.2(1.7)	47.5 (1.4)
Education (years)	12.6(0.4)	12.5(0.4)
Drug Use Cigarettes		
BL CO (ppm)	25.8(3.6)	25.4(3.3)
Per Day	17.5(2.3)	19.4(1.8)
Years Use	26.7(2.5)	25.5(1.7)
FTND	5.6(2.3)	5.9(1.6)
1 st Quit Attempt (%)	53.8	50.0
Cocaine		
Route of use Smoke (%)	100.0	100.0
Use in Last 30 (days)	16.7(2.8)	13.0(2.8)
Use Lifetime (years)	18.3(1.8)	17.9(2.0)

Values in parentheses represent $\pm$ S.E.M.

Table 2

Cardiovascular, craving, and smoking measures at baseline (day 1 for craving measures), day 6 (mid-treatment), and day 12 (end of treatment) in the left 3 column of numbers. Right three column of numbers represent data from repeated measures ANOVA across study days 1 through 12.

Dependent Measures	Experimental Conditions		One-Way ANOVA	Effect-Size	Repeated-Measures ANOVA		
	Placebo Mean±SEM	D-cycloserine Mean±SEM	F (p)	r ² ****	D-cycloserine F (p)	Time F (p)	Interaction F (p)
Heart Rate (beats/min) *							
Baseline	71.9±2.6	75.9±3.6	.76(.39)				
Day 6	74.9±2.8	77.5±4.3	.23(.64)				
Day 12	76.3±9.6	74.9±2.8	.13(.72)		.08(.37)	2.23(.02)	.84(.60)
Systolic BP (mm Hg) *							
Baseline	137.9±3.9	129.2±4.2	2.24(.15)				
Day 6	132.1±5.0	124.0±3.0	2.06(.16)				
Day 12	139.3±3.7	126.0±2.9	8.16(.008)		.004(.95)	.91(.53)	1.09(.37)
Diastolic BP (mm Hg) *							
Baseline	82.5±3.1	75.0±3.4	2.62(.12)				
Day 6	79.9±2.8	73.6±2.6	2.70(.11)				
Day 12	82.5±3.9	76.1±2.2	2.28(.14)		.45(.51)	.56(.86)	.86(.57)
Craving (Pre CET)							
Day 1	5.1±0.6	4.6±0.5	.38(.54)				
Day 6	2.0±0.2	2.4±0.3	.95(.34)				
Day 12	1.7±0.3	1.9±0.3	.29(.59)		.09(.76)	26.12(<.0001)	.97(.47)
Craving (Post Smoking Cues)							
Day 1	4.9±0.4	4.8±0.5	.007(.94)				
Day 6	1.8±0.3	2.3±0.3	1.52(.23)				
Day 12	1.6±0.2	2.0±0.3	.86(.36)		.80(.38)	26.56(<.0001)	.97(.48)
Craving (Post Neutral Cues)							
Day 1	4.5±0.5	4.1±0.5	.23(.64)				
Day 6	1.8±0.2	2.1±0.3	.82(.37)				
Day 12	1.5±0.3	1.9±0.3	1.11(.30)		.38(.54)	20.46(<.0001)	1.00(.44)

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Dependent Measures	Experimental Conditions		One-Way ANOVA	Effect-Size		Repeated-Measures ANOVA		
	Placebo Mean±SEM	D-cycloserine Mean±SEM	F (p)	r ² ****		D-cycloserine F (p)	Time F (p)	Interaction F (p)
Craving (Smoking - Neutral)								
Day 1	.39±0.3	.71±0.2	.65(.43)					
Day 6	-.03±0.07	.13±0.08	1.94(.16)	-.27				
Day 12	.06±0.09	.04±0.09	.02(.89)	.03		1.88(.18)	2.10(.02)	.39(.96)
Breath CO (ppm) *								
Baseline	25.8±3.6	25.4±3.3	.005(.94)					
Day 6	15.9±3.0	15.4±3.5	.009(.93)	-.06				
Day 12	14.5±1.2	11.7±2.3	.99(.33)	.19		.12(.73)	2.36(.008)	.35(.97)
Salivary Cotinine (ng/ml)								
Baseline	337.8±60.5	413.1±89.3	.51(.49)					
Day 6	288.1±32.1	324.6±71.3	.14(.71)					
Day 12	198.9±55.2	295.2±58.3	.006(.94)			.003(.96)	.48(.91)	.44(.94)
Cigarettes/day ***								
Baseline	17.5±2.3	19.4±1.9	.41(.53)					
Day 6	4.3±1.5	6.1±3.9	.16(.70)					
Day 12	3.2±1.2	2.5±1.2	.17(.69)			.50(.49)	1.25(.19)	1.09(.36)

* Results of repeated measures ANOVA are based on data from days 1 through 12 after accounting for baseline levels utilizing a subtraction procedure.

** Samples were available for 9 placebo and 8 D-cycloserine participants at baseline.

*** Results of repeated measures ANOVA are based on data from 27 consecutive calendar days. Baseline levels of smoking were accounted for through a subtraction procedure. Data for Day 6 and Day 12 represent self-reported cigarettes smoked the day prior to the study visit (calendar day 13 and 27).

**** Effect sizes for the study's primary dependent variables (changes in craving during CET sessions and breath CO) in S.D. units.

Table 3

Breath CO and salivary cotinine levels at baseline, day 6, day 12, and follow-up for participants that attended follow-up sessions (11 participants for each condition).

Dependent Measures	Experimental Conditions		Repeated-Measures ANOVA		
	Placebo Mean±SEM	D-cycloserine Mean±SEM	One-Way ANOVA F (p)	D-cycloserine F (p)	Time F (p)
Breath CO (ppm) *					
Baseline	25.9±2.0	22.0±3.8	.82(.37)		
Day 6	12.7±3.0	17.6±4.7	.78 (.39)		
Day 12	12.2±1.2	12.1±2.6	.002(.96)	.56(.46)	2.36(.008) .35(.97)
Follow-up				.42(.52)	.64(.53) 1.14(.33)
Salivary Cotinine (ng/ml) **					
Baseline **	412.3±43.6	491.8±91.5	.68(.43)		
Day 6	284.3±61.3	414.0±91.7	1.38(.25)		
Day 12	303.5±58.2	341.4±73.8	.16(.69)	.53(.37)	.58(.84) 1.27(.25)
Follow-up				.11(.75)	.186(.17) .45(.64)

* Results of repeated measures ANOVA are based on data from days 1 through 12 after accounting for baseline levels utilizing a subtraction procedure.

** Samples were available for 7 placebo and 6 D-cycloserine participants at baseline. Results of repeated measures ANOVA are based on data from days 1 through 12 during treatment and the 3 follow-up visits for follow-up.