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The effects of varenicline on stress-induced and cue-induced craving for cigarettes

Lara A. Ray[a,b,*], Katy Lunny[a], Spencer Bujarski[a], Nathasha Moallem[a], Jennifer L. Krull[a], Karen Miotto[b]

[a] University of California, Los Angeles, Department of Psychology, United States
[b] University of California, Los Angeles, Department of Psychiatry and Biobehavioral Sciences, United States

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ABSTRACT

Background: Varenicline is a partial agonist of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor approved by the FDA for the treatment of nicotine dependence. While the clinical efficacy of varenicline for smoking cessation is well-supported, its biobehavioral mechanisms of action remain poorly understood. This randomized, crossover, placebo-controlled, human laboratory study combines guided imagery stress exposure with in vivo presentation of cigarette cues to test the effects of varenicline on stress-induced and cue-induced craving for cigarettes.
Method: A total of 40 (13 females) daily smokers (≥10 cigarettes per day) completed a guided imagery exposure (stress and neutral) followed by the presentation of cigarette cues at the target dose of varenicline (1 mg twice per day) and on matched placebo.
Results: Multilevel regression models revealed a significant main effect of varenicline ($p < .01$) such that it reduced cigarette craving across the experimental paradigm, compared to placebo. There was also a significant medication × stress × trial interaction indicating that varenicline attenuated cue induced craving following neutral imagery but not when cues were preceded by stress induction (i.e., stress + cues).
Conclusions: These results elucidate the biobehavioral effects of varenicline for nicotine dependence and suggest that varenicline-induced amelioration of cigarette craving is unique to tonic craving and cue-induced craving following neutral imagery but does not extend to the combination of stress plus cues.

1. Introduction

Stress has been implicated as a central mechanism to drug relapse (Uhart and Wand, 2009), including cigarette smoking, with prospective research demonstrating that psychological stress and negative affect predict smoking lapses (Shiffman and Waters, 2004). In a recent study, 62% of smokers attributed their inability to stop smoking to stress (Hughes, 2009). Likewise, research has shown that cue-reactivity is a predictor of smoking behavior and relapse (Niaura et al., 1989; West, 2009), although recently this association has been called into question (Perkins, 2012). Preclinical studies provide compelling evidence of the ability of cue- and stress-exposure to reinstate nicotine-seeking behavior. For example, reintroduction to visual stimuli that had previously been paired with nicotine reinstated nicotine-seeking behavior in rats (Liu et al., 2006) and presentation of nicotine-associated cues following extinction produces reinstatement, above and beyond nicotine priming (LeSage et al., 2004). Likewise, preclinical models of stress exposure (e.g., foot shock paradigm) have supported stress-induced nicotine reinstatement (Buczek et al., 1999), which in turn represents a pharmacological treatment target (Yamada and Bruijnzeel, 2011; Zislis et al., 2007). Together, the preclinical data suggest that both cigarette cues and stress play a critical role in nicotine reinstatement and nicotine-seeking behaviors.

While preclinical studies have effectively dissociated mechanisms of stress- and cue-induced reinstatement, psychological models of craving argue that stress serves as an internal or affective cue, which in turn triggers craving in a similar fashion to smoking cues (Baker et al., 2004). Early experimental studies documented increases in smoking during conditions of stress (Schachter et al., 1977) and anxiety (Pomerleau and Pomerleau, 1987). In addition, several recent studies found that psychosocial stress, induced using the Trier Social Stress Test, reliably increases cigarette craving (Buchmann et al., 2010; Childs and de Wit, 2010) and that smokers have overall lower hormonal stress responsivity (al'Absi et al.,

* Corresponding author at: University of California, Los Angeles, Psychology Department, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, United States. Tel.: +1 310 794 5383; fax: +1 310 206 5895.
E-mail address: lararay@psych.ucla.edu (L.A. Ray).

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2003). Further, stress-induction using a personalized script was associated with decreased ability to resist smoking in the laboratory as well as potentiation of subjective reward from smoking (McKee et al., 2010).

This study extends the literature by testing the effects of varenicline on stress-induced craving followed by the presentation of smoking cues. As recommended by McKee (2009), human laboratory models should be validated with known medications before they can be used to screen for novel pharmacotherapies for smoking cessation (McKee, 2009). The present study is consistent with this approach and examines varenicline, a partial agonist of $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChR) with proven efficacy as a pharmacotherapy for smoking cessation (Fagerstrom and Hughes, 2008; Gonzales et al., 2006; Oncken et al., 2006). Varenicline is a well-established and FDA-approved medication for smoking cessation. It has been hypothesized that binding of $\alpha_4\beta_2$ nAChR increases the dopamine tonus in the ventral tegmental area which in turn decreases craving for nicotine and alleviates nicotine withdrawal symptoms (Fagerstrom and Hughes, 2008). Varenicline blocks the effects of nicotine itself and recent studies suggest that it improves attention (Rhodes et al., 2012) and reduces craving and cigarettes per day among non-treatment seekers (Ashare et al., 2012). Preclinical studies suggested that varenicline significantly attenuated cue-induced nicotine reinstatement (Biala et al., 2011; Le Foll et al., 2011) and nicotine self-administration (Le Foll et al., 2011). In humans, varenicline reduced cue-induced cigarette craving as well as tonic levels of craving (i.e., steady state craving, non-cue induced) in a sample of daily smokers (Brandon et al., 2011). The present study extends the literature on the mechanisms of action of varenicline by testing its effects on stress-induced and cue-induced craving for cigarettes.

This study enrolled non treatment-seeking daily smokers in a placebo-controlled, randomized, crossover study of varenicline (1 mg twice per day). The human laboratory design combined stress induction, using guided imagery procedures (Sinha, 2009) followed by the systematic presentation of cigarette cues (Monti et al., 1987). This study tested whether varenicline attenuates stress-induced and cue-induced craving for cigarettes in daily smokers. Based on the emerging literature on the effects of varenicline on cigarette craving (Ashare et al., 2012; Brandon et al., 2011), we hypothesized that varenicline would attenuate craving for cigarettes after stress induction and after presentation of smoking cues, compared to placebo.

2. Method

2.1. Participants

Participants ($n = 40$, 13 females) were healthy daily smokers ($\geq$10 cigarettes per day) between the ages of 18 and 55. Exclusion criteria were the following: (1) more than 3 months of smoking abstinence in the past year; (2) self-reported use of cocaine, methamphetamine, heroin or other illicit drugs (other than marijuana) in the past 60 days (verified by urine toxicology screen); (3) lifetime history of psychotic disorders, bipolar disorder, or major depression with suicidal ideation; (4) self-reported current feelings of active suicidality, as indicated by a score $\geq$2 on the suicidal ideation item of the BDI-II; (5) self-reported symptoms of depression in the moderate range, as indicated by a score $\geq$20 on the BDI-II; (6) currently taking insulin or oral hypoglycemic medication; (7) serious medical illness present during the physical exam and laboratory tests; and (8) pregnancy, as verified by a urine pregnancy screen.

The majority of randomized participants ($n = 40$) were male ($n = 27$, 67.5%) and the average age was 36.03 (SD = 10.13). The ethnic composition of the randomized sample was 32.5% Caucasian, 32.5% African American, 5% Latino, 2.5% Asian, 25% Mixed Ethnicity, and 2.5% did not report. The average score on the Fagerstrom Test of Nicotine Dependence (FTND) was 4.03 (SD = 1.76). The average number of cigarettes on a typical day in the past month was 14.87 (SD = 5.85) and the average carbon monoxide (CO) level at baseline was 17.50 ppm (SD = 11.09). Participants reported drinking, on average, once per week and consuming 4.20 drinks per drinking occasion (SD = 4.78). The average score on the Alcohol Use Disorders Identification Test (AUDIT; Allen et al., 1997) was 3.13 (SD = 3.43).

2.2. Procedures

Study procedures were approved by the Human Research Committee at the University of California, Los Angeles and all participants provided written informed consent after receiving a full explanation of the study. Following telephone screening, participants completed an in-person assessment visit. Eligible participants based on the in-person assessment were invited for a physical exam. Self-reported smoking pattern was verified by a urine cotinine test, and only participants whose cotinine test was consistent with regular smoking ($\geq$100 ng/mL of cotinine) were enrolled in the study. Self-reported drug use was verified by a urine toxicology screen and individuals who tested positive for drugs (other than marijuana) were excluded. Medically eligible participants were then randomized to receive the first study medication (varenicline or placebo) for a total of 10 days. On medication day 10, participants completed the first laboratory experimental session consisting of guided imagery exposure (stress and neutral) followed by the presentation of cigarette cues. After the first session, participants were given the second study medication (varenicline or placebo) for a total of 10 days and returned to the laboratory on medication day 10 to complete the second experimental session. Participants were required to abstain from smoking for 12 h prior to each experimental session. Expired carbon monoxide levels of less than 10 ppm (or below 50% of initial baseline value) were used to verify overnight smoking abstinence, and breathalyzers were used to ensure a breath alcohol concentration of 0.000 g/dl at testing.

A total of 536 individuals were screened over the phone, of whom 167 were initially eligible and invited for an in-person screening session. Of the 167 recruits invited, 109 completed the in-person screening visit and of those, only 58 were eligible and therefore invited to complete the physical exam. A total of 46 participants completed the physical and 40 were medically eligible, all of whom were randomized to receive the study medication or matched placebo. Of the 40 randomized participants, 2 did not return for the experimental session and 1 completed only one medication condition, resulting in 37 completers.

2.3. Stress-induction and smoking cue

During the initial screening session, participants completed individual differences measures, received standardized relaxation training and imagery training, and provided detailed descriptions of two recent stressful life events and one neutral event. This information was used to generate tape recorded personalized scripts for the neutral and stressful experimental conditions, following well-established procedures (Sinha, 2009; Sinha et al., 1992, 2000). Participants were asked to identify and describe recent stressful experiences and to rate them on a 0–10 Likert scale, where 10 is the most stressful. Only stressful events rated $\geq$8 were used in script development. Stressful events that were resolved were not used in script development to ensure the salience of the stimuli presented. All scripts were evaluated by the first author (LR) for stressful and neutral content prior to implementation. Different stressful events

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were randomly selected to be used in experimental sessions 1 and 2.

During each experimental session, participants completed two guided imagined exposures, stress and neutral, in a randomized and counterbalanced fashion which consisted of 5-minute tape recorded scripts recounting stressful (or neutral) recent events in the participants' lives, including cognitions and physical feelings associated with their reports of the experience. Procedures were separated by one hour to avoid carryover effects. Each guided imagery condition was followed by presentation of smoking cues (Monti et al., 1987, 2001) during which participants were systematically exposed to cigarette cues (e.g., asked to hold and smell an unlit cigarette), without a neutral/control cue.

2.4. Study medication

Consistent with FDA guidelines, patients were titrated on varenicline as follows: days 1–3, .5 mg once per day; days 4–7, .5 mg twice per day, and days 8–10, 1 mg twice per day. Placebo pills were matched in number of pills and packaging of the active medication. Since there were two medication conditions, varenicline and placebo, the 10-day period between medications was considered a washout period. Therefore, participants who received varenicline first received placebo for 10 days prior to their second testing session and vice versa. Consistent with our previous pharmacotherapy studies (Hutchison et al., 2006; Ray and Hutchison, 2007), the study medications were packed into opaque capsules with 50 mg of riboflavin (B2). At each visit, a urine sample was tested for riboflavin content by examining it under an ultraviolet light. Pill count was also conducted at each visit. Participants were given a 24 h telephone number for calling the physician to discuss side effects, and physician office hours were available as needed. Side effects were collected in an open-ended fashion and then counted in categories. The short form of the Systematic Assessment for Treatment Emergent Events (SAFTEE) (Jacobson et al., 1986; Levine and Schooler, 1986) was administered at each experimental session.

2.5. Measures

The following individual differences measures were collected during the study: (a) a demographics questionnaire used to collect information on age, sex, marital status, SES, ethnicity, income, and education; (b) the Beck Depression Inventory-II (BDI-II) administered at baseline to screen out individuals with current feelings of active suicidality and those with moderate to severe symptoms of depression; (c) frequency and quantity of alcohol/drug use; (d) a Smoking History Questionnaire used to collect detailed history of nicotine use and quit attempts; (e) the Fagerstrom Test of Nicotine Dependence (FTND) assessed nicotine dependence (Heatherton et al., 1991); (f) the Wisconsin Smoking Withdrawal Scale (WSWS) was used to measure nicotine withdrawal symptoms (Welsch et al., 1999); (g) the Time Line Follow Back (TLFB) assessed smoking and alcohol use over the past 30 days (Sobell et al., 1986). CO levels and a urine cotinine test were used to verify self-reported smoking pattern.

During the experimental sessions, the following measures were administered at baseline, post-imagery, and post-smoking cue on both the stress and neutral imagery conditions: (a) the questionnaire of smoking urges-brief (QSU-Brief) was used to measure urge to smoke, which is the primary dependent variable in the study (Cox et al., 2001; Toll et al., 2006, 2004). The QSU is widely used in smoking research and has been found to be sensitive to exposure to smoking-related cues, such as the one conducted in the present study (Morgan et al., 1999); and (b) the differential emotion scale (DES) (Izard et al., 1993) consists of 30-items and has been widely used in human laboratory studies of emotional states (Sinha et al., 2000). The DES served to verify that the stress-induction and cue-exposure procedures produced the intended effects on mood as indexed by the following mood dimensions: joy, sadness, anxiety/arousal, anger, fear, and relaxation. The TLFB (covering the past 10 days on study medication), the WSWS, and the SAFTEE were administered at each experimental session.

2.6. Data analysis

Analyses were conducted using a multilevel regression-based framework (Singer, 1998) using PROC MIXED in SAS version 9.1 to test the effect of medication (varenicline versus placebo) on stress-induced and cue-induced craving for cigarettes. In all analyses, we modeled individual intercepts as a function of medication, trial (baseline, post imagery, post cues), stress (stressful versus neutral conditions), and their interactions. Specifically, in the multilevel models medication, trial, and stress were Level 1 variables nested within subjects. Trial was coded using 2 contrast codes, the first comparing baseline to post imagery (imagery trial) and the second comparing baseline to post cue exposure (cue trial). The primary dependent variable was craving for cigarettes, measured by the QSU.

3. Results

3.1. Pre-test comparisons

Fisher's exact tests (Fisher, 1922) were conducted comparing the medication versus placebo on each of the 24 items from the SAFTEE. Results revealed a significant medication effect on night sweats, which occurred in 2 of the patients taking varenicline compared to 1 on placebo (Fisher's exact test, $p < .05$). Varenicline was well-tolerated and there were no serious adverse events during the study. All urine samples tested positive for riboflavin, suggesting that individuals were compliant with the medication prior to each appointment. Regarding cigarette craving, there was no evidence of medication order effect (varenicline versus placebo first) ($p = .63$), no imagery order effect (stress versus neutral first; $p = .59$), no Medication Order × Imagery Order interaction ($p = .98$), and no overall effect of time (chronological assessment time; $p = .30$). To test carryover effects we compared baseline assessments in each imagery condition and found no significant differences across all outcome variables ($ps > .53$). Regarding the medication blind, 84% of the participants guessed correctly while in the placebo condition and 58% guessed correctly while in the varenicline condition, $\chi^2(1) = 5.17$, $p < .05$. Given that Brandon et al. (2011) found that correctly guessing the medication condition moderated the experimental results, we tested blind fidelity as a covariate and doing so did not change the results reported herein. Participants were compliant with the required 12-hours of abstinence and there was a trend towards lower CO levels on varenicline (mean = 6.05) versus placebo (mean CO = 6.68), $F(1,36) = 3.58$, $p = .066$. Analysis of naturalistic ad-lib smoking for the 10 days on medication revealed no differences in cigarettes per day on varenicline (mean = 12.89) versus placebo (mean = 12.32), $F(1,36) = 0.49$, $p = .49$. There was no medication effect on baseline withdrawal ($p = .14$) but there was a significant main effect of varenicline in reducing urge to smoke at baseline compared to placebo ($\beta = -0.79$, $SE = 0.25$, $t = -3.14$, $p < .01$).

3.2. Manipulation check

To test the stress manipulation effect, we compared the baseline to post-imagery conditions on placebo only. There was a significant stress × trial effect ($p < .01$) for urge to smoke, positive mood ($p < .0001$), negative mood ($p < .01$), anger/frustration

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($p < .01$), fear ($p < .05$), and relaxation ($p < .0001$), such that the stress manipulation increased urge to smoke, negative mood, fear, anger/frustration and decreased positive mood and relaxation compared to the neutral imagery condition. Presentation of smoking cues increased craving ($p < .05$), such that craving ratings were stronger post cues, as compared to post imagery, across both stressful and neutral imagery conditions. There were significant stress × trial interactions such that smoking cues decreased positive mood ($p < .05$) and relaxation ($p < .01$), and increased anger/frustration ($p = .058$) after the stress but not neutral imagery condition. These results suggest that stress- and cue-exposure elicited the hypothesized effect on cigarette craving and mood.

3.3. Medication effects on cigarette craving

Results of mixed model analysis revealed a significant main effect of medication ($\beta = -0.79$, $SE = 0.23$, $t = -3.44$, $p < .01$), such that varenicline decreased craving for cigarettes across the trial. There was a main effect of stress ($\beta = 0.50$, $SE = 0.07$, $t = 6.71$, $p < .0001$), such that individuals reported higher overall craving for cigarettes during the stress versus neutral condition. There was no significant main effect of imagery trial ($p > .10$), however there wasa significant main effect of cue trial ($\beta = 0.23$, $SE = 0.09$, $t = 2.50$, $p = .01$), such that craving for cigarettes increased during the cue presentation as compared to baseline. Furthermore, analysis revealed a significant two-way interaction between imagery trial and stress condition ($\beta = 1.04$, $SE = 0.17$, $t = 5.99$, $p < .0001$), and between cue trial and stress condition ($\beta = 0.69$, $SE = 0.17$, $t = 3.99$, $p < .0001$). In order to probe these significant two-way interactions, simple effects were analyzed and results revealed a significant effect of imagery trial in the neutral condition ($p < 0.001$) and in the stress condition ($p < .001$); however, these effects were in opposite directions (Fig. 1A). Specifically, craving for cigarettes increased following the stress imagery condition and decreased during the neutral imagery condition, as compared to baseline. No significant three-way interaction between medication, stress and imagery trial (BA vs. Imagery) was observed. ($p > .10$). Post hoc analysis of the cue trial by stress interaction revealed a significant effect of cue trial in the stress condition ($p < .001$) but not the neutral condition ($p > .10$), such that cue presentation increased cigarette craving compared to baseline in the stress condition only.

A three-way interaction was observed between medication, cue trial (Baseline (BA) vs. Cue) and stress condition ($\beta = 0.93$, $SE = 0.35$, $t = 2.68$, $p < .01$). Follow-up analyses were conducted to decompose this three-way interaction into two-way interactions between medication and cue trial (BA vs. Cue) at each level of stress (i.e., stressful versus neutral). Results revealed a significant medication × cue trial interaction in the neutral imagery condition ($p = 0.05$), such that varenicline reduced craving following neutral imagery and cue presentation relative to baseline, but placebo did not. Further, there was a trend level medication × cue trial interaction in the opposite direction in the stress imagery condition ($p = .06$), such that varenicline increased craving following stressful imagery and cue presentation relative to baseline to a greater extent than did placebo (see Fig. 1A).

To further the interpretation of this complex pattern of results, and to disentangle imagery and cue presentation insofar as possible with this design, we have decomposed these findings to the simplest level of effects. To that end, trial was analyzed using different contrast codes allowing for comparisons of baseline to post imagery (duplicating the imagery trial contrast in the previous analysis), and from post imagery to post cue. As shown in Fig. 1B, consistent with the findings from the previous analysis, comparisons from baseline to post imagery in the neutral condition indicate significant and similar decreases in cigarette craving on both varenicline ($\beta = -0.62$, $SE = 0.17$, $t = -3.61$, $p < .001$) and placebo ($\beta = -0.42$, $SE = 0.17$, $t = -2.41$, $p < .05$; no medication by trial simple interaction, $p > .10$). Comparisons between post imagery and post cue craving in the neutral condition revealed a significant cue-induced increase in the placebo condition ($\beta = 0.54$, $SE = 0.17$, $t = 3.09$, $p < .01$), that was not present in the varenicline condition ($p > .1$), though the difference between these two effects did not achieve conventional levels of significance ($p = .266$). This exploratory analysis is thus not conclusive, but it does suggest that the significant medication effects on differences between baseline and imagery + cue craving are more likely due to differential effects of cue presentation following imagery than differential responses to the imagery itself. That is, varenicline attenuates cue-induced craving in the presence of neutral imagery.

In the stress condition, there were significant and similar increases in cigarette craving from baseline to post imagery on both varenicline ($\beta = 0.64$, $SE = 0.17$, $t = 3.74$, $p < .001$) and placebo ($\beta = 0.40$, $SE = 0.17$, $t = 2.29$, $p < .05$; no medication by trial simple interaction, $p > .10$). There were no significant differences between post imagery and post cue craving for either medication in the stress condition. In summary, the results of this study clearly show that varenicline attenuated tonic craving for cigarettes (i.e., main effect of medication) and suggest that varenicline was more effective in attenuating cue-induced craving for cigarettes when cues were not preceded by (or combined with) stress induction.

4. Discussion

Evidence from both preclinical (LeSage et al., 2004; Liu et al., 2006) and human models of nicotine dependence (Buchmann et al., 2010; Pomerleau and Pomerleau, 1987; Schachter et al., 1977; Waters et al., 2004) suggests that exposure to stress and/or cues provokes reinstatement, cigarette smoking, and relapse, respectively. While preclinical studies have shown pharmacotherapy effects that are specific to stress-induced reinstatement, as opposed to cue-induced reinstatement (e.g., Schank et al., 2011; Zislis et al., 2007), the unique and combined effects of stress and smoking cues are seldom examined. The present study used a novel combination of human laboratory paradigms of stress- and cue-craving induction to test the mechanisms of action of varenicline, a well-validated smoking cessation aid.

Consistent with recent research (Brandon et al., 2011), the present findings suggest an overall main effect of varenicline, over placebo, in attenuating craving for cigarettes at baseline, and throughout the experimental paradigm. Notably, there was a significant stress × cue interaction such that varenicline dampened cue-induced craving when cues were presented following neutral imagery but did not attenuate cue-induced craving after stress induction, as compared to placebo. The absence of stress-specific reductions in cigarette craving by varenicline may be interpreted in light of the neural dissociation between mechanisms of stress- and cue-induced craving (Schank et al., 2011; Zislis et al., 2007). Thus, it is plausible to hypothesize that varenicline may be well-suited for combination with agents that can more directly target the stress pathway in addiction. Alternatively, it may be that individuals on varenicline may be more reactive to complex cues (i.e., stress + smoking cues), which may be due to the overall lower tonic craving on varenicline versus placebo, producing a "rebound" effect. In brief, these results suggest that varenicline is effective in dampening the urge to smoke and that it may be most effective in attenuating reactivity to smoking cues during neutral conditions, as compared to stressful ones.

While the clinical efficacy of varenicline for nicotine dependence is well established (Gonzales et al., 2006; Oncken et al., 2006), less is known about its biobehavioral mechanisms of action. A recent study found that varenicline reduced craving for cigarettes and

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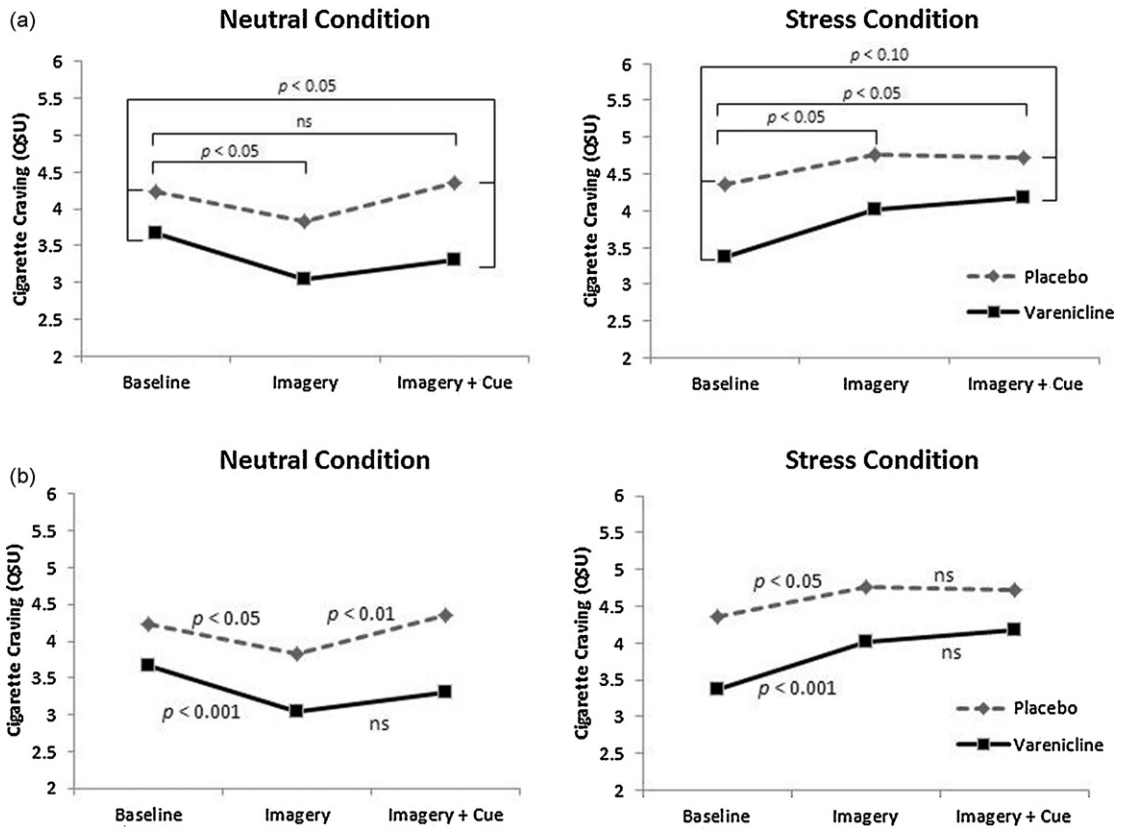

Fig. 1. Predicted values and interactive (1A) and simple effects (1B) derived from the multilevel models for cigarette craving (QSU) by medication conditions (placebo and varenicline), trial (baseline, post imagery, and post cue exposure), and imagery condition (stress and neutral). Panel B displays comparisons from baseline to post imagery and from post-imagery to post cue.

attenuated self-report reward from smoking (Brandon et al., 2011). Recent studies suggest that varenicline may attenuate craving for alcohol, particularly among heavy drinking smokers (Fucito et al., 2011; McKee et al., 2009). Varenicline has been found to potentiate the negative subjective effects of alcohol (Childs et al., 2012), indicating its biobehavioral effects may include the dampening of subjective reward for both cigarettes (Brandon et al., 2011) and alcohol (Childs et al., 2012). This is clinically relevant as alcohol use is found to precipitate smoking lapses (Kahler et al., 2010) and heavy drinking smokers represent a sizeable and hard-to-treat segment of nicotine dependent patients (Romberger and Grant, 2004). Nevertheless, the degree to which varenicline-induced attenuation of reactivity to smoking cues represents a clinical mechanism of action of this medication should be interpreted with caution. As noted by Perkins (2012), the literature does not support a reliable association between cue reactivity and smoking behavior such as quit success (Perkins, 2012). Recent studies have also underscored the role of intrinsic motivation for change as a moderating variable in human laboratory studies of smoking cessation medications (Perkins et al., 2006). Interestingly, a recent study found reduction in smoking urges and cigarettes per day in a 21-day placebo-controlled trial of varenicline among non-treatment seeking smokers (Ashare et al., 2012).

It should be noted that this study is comprised of non-treatment seeking daily smokers. While several behavioral pharmacology studies of etiology and treatment of nicotine rely on non-treatment seeking smokers (e.g., Buchmann et al., 2010; Childs and de Wit, 2010; McKee et al., 2010, 2012), including human laboratory studies of varenicline (Brandon et al., 2011), it should be noted that these findings may not generalize to treatment seeking samples. Nonetheless, one of the strengths of the behavioral pharmacology approach with non-treatment seekers is that it allows for examination of the pure pharmacological effects of the medication in question, without the influence of motivation to quit. Further, the sample of daily smokers in this study compared well to some studies in terms of cigarettes per day and FTND scores (e.g., Buchmann et al., 2010; Childs and de Wit, 2010) but was slightly less dependent than others (Brandon et al., 2011; McKee et al., 2010). Although the 12-h of abstinence are thought to build high levels of craving, our primary outcome, differences in sample characteristics should also be considered in interpreting these results. On balance, this study is consistent with the behavioral pharmacology approach, the sample is generally representative of daily smokers, and yet future studies are needed to extend these findings to treatment-seeking samples.

The observed biobehavioral effects on craving are also consistent with the neuropharmacological effects of varenicline whereby binding of $\alpha_4\beta_2$ nAChR is hypothesized to increase the dopaminergic tonus in the mesolimbic system thus decreasing nicotine craving and withdrawal (agonist effects). As a partial agonist, varenicline has both agonist and antagonist effects with the latter subserving the dampening of nicotine's rewarding effects by blocking nicotine binding of the $\alpha_4\beta_2$ nAChR, which in turn reduces nicotine-induced dopamine release (Rollema et al., 2007). In sum, the results presented herein are largely consistent with the known neuropharmacological mechanisms of varenicline and extends a growing body of literature delineating its biobehavioral effects through controlled human laboratory paradigms.

The present study has a number of strengths including the double-blind randomized and crossover design, which increased statistical power by allowing individuals to serve as their own controls. The high retention and medication compliance rates also

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strengthen the conclusions drawn from this study. Study limitations include the lack of randomization between imagery condition (stress versus neutral) and in vivo cue exposure, which should be accounted for in future studies. Further, as noted by Shaham and colleagues (2003), human lab studies such as this one would benefit from the addition of drug-taking behavior to measures of subjective craving. The absence of biological verification of the stress manipulation (i.e., cortisol levels) is also a limitation of this study. In conclusion, the present study extends the literature on the biobehavioral mechanisms of action of varenicline for nicotine dependence by indicating that varenicline attenuates tonic craving as well as cue-induced craving post neutral imagery, but not after stress-induction. If supported, these findings may inform clinical practice and suggest that patients taking varenicline for smoking cessation may be especially vulnerable to smoking lapses during stressful situations, which in turn can be targeted by adjunctive behavioral strategies.

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The funding agencies had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

The first author (LR) conceptualized the manuscript, undertook the statistical analysis, and wrote the first draft of the manuscript. The second author (RM) contributed to manuscript preparation and literature review. The third and fourth authors (IC and DY) directed the project, collected and managed the data, and contributed to manuscript preparation. The last author (MZ) designed the MIDAS Project, wrote the protocol, and contributed to the writing of the manuscript and its conceptualization. All authors contributed to and have approved the final manuscript.

Conflict of interest

The first author, LAR, is a consultant for GlaxoSmithKline. None of the authors have any other conflicts of interest to disclose.

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