Published in final edited form as:

Drug Alcohol Depend. 2013 June 01; 130(1-3): 135–141. doi:10.1016/j.drugalcdep.2012.10.021.

Dissociable effect of acute varenicline on tonic versus cue-provoked craving in non-treatment motivated heavy smokers

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Abstract

Rationale—The effectiveness of varenicline for smoking cessation has been established, but little is known about the psychological processes that mediate this clinical outcome.

Objectives—This study evaluated the effect of a single dose of varenicline on tonic and cue-provoked changes in craving, withdrawal, and affect using a randomized, double-blind, placebo-controlled, cross-over design.

Methods—Following overnight abstinence, 38 non-treatment-motivated smokers received either varenicline 2 mg or matched placebo, then tonic measures of craving, withdrawal, and positive and negative affect were obtained at 30-minute intervals. At 4-hours post-administration, a cue exposure session obtained the same subjective measures at three time-points following the physical handling of a lit cigarette versus the sharpening and handling of a pencil.

Results—At 4-hours post-administration, varenicline reduced tonic craving as well as craving across the smoking and neutral cue conditions, relative to placebo. By contrast, the capacity of the smoking cue to enhance craving relative to the neutral cue was unaffected by varenicline.

Measures of withdrawal and positive and negative affect produced mixed results.

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Conclusions—Acute varenicline selectively attenuates tonic but not cue-provoked craving. This dissociation provides insight into the specific psychological processes that might mediate the effectiveness of varenicline, and highlights cue-provoked craving as a discrete target for advancing smoking cessation pharmacotherapy.

Keywords

Smoking cessation; Craving; Cue-reactivity; Varenicline; Nicotine withdrawal; Affect

1. Introduction

Varenicline, a selective partial agonist of $\alpha 4\beta 2$ nicotinic acetylcholine receptors in the brain (Rollema et al., 2007), has proven effectiveness for smoking cessation compared with placebo and bupropion (Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006; Tonstad et al., 2006). A meta-analysis of 11 trials (Cahill et al., 2011) showed that treatment with varenicline and behavioral counseling increased the chances of long-term abstinence (i.e., 6 months) between two and three times compared with counseling only.

The therapeutic effect of varenicline on smoking cessation is mediated in part by its attenuation of cigarette craving, smoking reward, and withdrawal severity (Patterson et al. 2009; Perkins et al., 2010; Sofuoglu et al., 2009; West et al., 2008). However, a question remains as to whether or not varenicline also attenuates reactivity to smoking paired cues. Although smokers experience some level of craving throughout the day due to periods of abstinence (Chandra et al., 2011; Shiffman et al., 1997), superimposed on this background or “tonic” craving are episodes of intense “phasic” craving elicited by exposure to environmental cues associated with smoking (Shiffman et al., 1997; Shiffman et al., 1996). Despite the paucity of direct evidence linking cue-reactivity to relapse (Munafò and Hitsman, 2010; Perkins, 2009), the observations that (1) cue-provoked craving persists after tonic levels of craving subside following acute withdrawal (Ferguson and Shiffman, 2009), (2) cue-reactivity controls smoking behavior during ad libitum smoking (Hogarth et al., 2010; Mucha et al., 1998), and (3) lapse-induced phasic surges in craving predict relapse above and beyond tonic craving levels (Shadel et al., 2011), are consistent with a role for cue-provoked craving in relapse. Neither chronic nicotine replacement therapy (NRT) or bupropion have a significant effect on cue-provoked craving (Ferguson and Shiffman, 2009). Under transdermal nicotine patch treatment, cue-provoked craving is a significant predictor of relapse (Waters et al., 2004). The implication of these findings is that the propensity to smoke or relapse is influenced jointly by tonic and cue-provoked craving states (Witkiewitz and Marlatt, 2004). Effective smoking cessation pharmacotherapies selectively attenuate the tonic state, leaving the cue-provoked state as a more isolated determinant of smoking behavior.

Whether varenicline attenuates cue-provoked craving in addition to tonic craving has been addressed in two recent studies. Brandon and colleagues (Brandon et al., 2011) randomized non-treatment-motivated smokers to 2 weeks of varenicline or placebo and assessed tonic and cue-provoked craving on three occasions following overnight abstinence (with normal smoking otherwise): at baseline; 5–7 days after starting medication; once full dosage (2 mg/

day) was established at 12–15 days. Varenicline reduced tonic levels of craving after 5–7 days, but reduced cue-provoked craving only after 12–15 days. Varenicline had no effect on overall withdrawal at any time-point during the study. Brandon and colleagues speculated that, although acute varenicline did not have a direct effect on cue-provoked craving, chronic varenicline, in contrast, attenuated smoking reward, which may have extinguished the cue-reward contingency, therefore attenuating cue-provoked craving at 12–15 days. The effect of chronic varenicline on cue-provoked craving may be secondary to its effect on smoking reward. Alternatively, as Brandon and colleagues considered, a direct effect of chronic varenicline on cue-provoked craving may only occur after therapeutic blood levels are reached. Complicating interpretation, however, varenicline was associated with greater attrition (17.9%, vs. 7.4% for placebo) and lower compliance with overnight abstinence instructions. Thus, reduced cue-provoked craving under chronic treatment with varenicline could have been influenced by selective drop-out of low reactors or acute smoking satiety.

Franklin and colleagues (Franklin et al., 2011) tested non-abstinent, non-treatment-motivated smokers before and after 3 weeks of treatment with varenicline 2 mg/day versus placebo in a cue exposure session in which smoking-related video clips were played during perfusion functional magnetic resonance imaging. Subjective craving increased significantly from pre-exposure to cue exposure, but the magnitude of change did not differ between varenicline and placebo groups following 3 weeks of treatment. Post-hoc analysis indicated that whereas craving increased significantly from pre-exposure to smoking cue exposure in the placebo group, this cue effect was not significant in the varenicline group. Thus, this study provided equivocal evidence as to whether varenicline attenuates cue-provoked craving.

The purpose of the current study was to evaluate whether a single dose of varenicline 2 mg versus placebo would differentially influence subjective craving, nicotine withdrawal, and positive/negative affect measured under “tonic” conditions (i.e., in the absence of cues) versus cue-provoked conditions (i.e., following physical handling of a lit cigarette versus sharpening and handling of a pencil). Participants were non-treatment-motivated heavy smokers in a state of overnight abstinence. Selectivity of varenicline’s effect on tonic versus cue-provoked measures would provide insight into the specific psychological mechanisms of this treatment.

2. Materials and methods

2.1. Participants

Participants were smokers between 18 and 65 years of age who were not currently intending or attempting to quit smoking. They were required to have smoked at least 20 cigarettes/day on average during the prior year, have had no period of abstinence greater than 3 months during the prior year, and expired carbon monoxide (CO) ≥ 15 parts per million (ppm) at screening. Additional inclusion criteria included good health, determined by medical history, physical exam, vital signs, 12-lead electrocardiogram (ECG), laboratory testing, and weight greater than or equal to 100 pounds (45.5 kg) with body mass index between 15 and 35.

To minimize any potential influence of health conditions or medications on craving, nicotine withdrawal, or affective state, candidates were excluded for history of alcohol or drug abuse/dependence (other than tobacco); treatment with another investigational drug within 1 month of enrollment or plans to take another investigational drug within 1 month of study completion; current treatment with antidepressant, antipsychotic, or antianxiety medication; use of nicotine replacement products or bupropion within the last 3 months; history of seizures, including febrile seizures, childhood seizures, and seizures associated with alcohol withdrawal; and any history of clinically significant medical or psychiatric disease.

Participants who completed the study ($n=38$) averaged 36.2 years (standard deviation [SD]=14.4), were Caucasian (97%), reported smoking on average 21.3 cigarettes/day (SD=4.7) for 19 years (SD=13.6), had baseline expired CO levels of 20 ppm (SD=7.9) and a mean (SD) Fagerström Test of Nicotine Dependence (FTND) (Fagerström et al., 1990; Heatherton et al., 1991) score of 5.7 (1.9). Seventy-nine percent (30/38) reported smoking their first cigarette of the day within 30 min of awakening.

2.2. Procedure

2.2.1. Eligibility screening and enrollment—The study was approved by Institutional Review Board of The Miriam Hospital and conducted between November 2000 and April 2001. Recruitment was conducted through print and radio advertisements, and candidates were initially screened via a brief telephone interview during which their medical history was reviewed. Candidates who met initial eligibility requirements attended an in-person screening session and completed the following measures: expired CO for measurement of baseline smoking rate, detailed physical examination (including blood pressure and pulse, height, and weight), 12-lead ECG, an 8-item smoking history questionnaire and the FTND. Eligible participants began the study within 5–10 days of their screening visit.

2.2.2. Design and experimental sessions—A randomized, double-blind, placebo-controlled, single-dose, cross-over design was used. Participants were randomly assigned to either a single dose of varenicline 2 mg by mouth (two 1 mg tablets) or matching placebo for the first session. The rationale for the 2 mg dose was that it would produce a maximum plasma concentration ($C_{\max}$) similar to that produced after repeated dosing with 1 mg twice a day, and that any effect on subjective craving would be related to $C_{\max}$. After a minimum 7-day washout period, participants returned for identical procedures but alternate treatment (varenicline or placebo). Research staff and participants were blind to the content of tablets. The timeline for each session is presented in Figure 1.

Participants arrived for the experimental session between 0800 and 1000 hours, and confirmation of overnight abstinence was confirmed via expired CO levels <15 ppm (Pomerleau et al. 1994; Thornley et al. 2009). A 12-lead ECG, blood pressure and pulse were taken and concomitant medications recorded. A battery of questionnaires was administered to assess craving, withdrawal, and affect (described later). Between 30 and 60 minutes after eating a standard meal, participants ingested blinded tablets with 240 mL of water under supervision of the study staff. Participants were asked to report any side effects

that occurred over the post-dosing period. Craving, withdrawal, and affect measures were repeated every 30 minutes thereafter for 4 hours.

The cue exposure session began 4 hours after dosing. Based on other phase 1 studies (unpublished at the time), this time-point was expected to coincide with the maximum plasma concentration of varenicline (Faessel et al., 2006). The validity of the cue exposure protocol has been demonstrated in prior studies (Niaura et al., 1998; Sayette and Hufford, 1994). During each cue session of approximately 60 minutes, participants were exposed to a smoking cue and a neutral cue in a randomly assigned sequence of either smoking-neutral or neutral-smoking. The sequence was balanced and preserved for each participant's second treatment session. Each cue exposure lasted for 1 minute and was preceded by a 5 minute adaptation period (i.e., participants were instructed to rest for 5 minutes) during a 6-minute block of time. In the smoking cue condition, participants lit and held their preferred brand of cigarette and then extinguished it. In the neutral cue condition, participants sharpened a pencil and then held it. They completed the craving, withdrawal, and affect questionnaires immediately after each cue exposure, and again 5 and 10 minutes later. Participants were monitored unobtrusively via closed-circuit video and audio equipment located outside the experimental room to ensure compliance with the cue exposure protocol.

Following cue exposure, an hour elapsed before participants were fed lunch. They were monitored for adverse events (AEs) for the rest of the day and were required to refrain from tobacco use. A follow-up visit was held 1 week after the second session, or early termination for two participants who completed only the first session. Participants underwent a brief physical examination (blood pressure and pulse, ECG, weight) and gave a blood sample for safety testing and pharmacokinetic analysis of varenicline plasma concentrations at 168 hours post-dosing. A urine pregnancy test was performed for all females. Upon completion of the study, participants were paid \$150.00.

2.2.3. Study completion—Forty participants were enrolled and dosed; two discontinued after completing the first session; 38 completed both conditions. One participant received a single dose of placebo and withdrew consent during the 7-day washout period prior to the second session. No reason for withdrawal of consent was provided to study staff. A second participant who received varenicline discontinued due to having stopped smoking during the washout period. All participants achieved overnight abstinence.

2.2.4. Measures—Cigarette craving, nicotine withdrawal, positive/negative affect, and AEs were measured at baseline prior to drug dosing and throughout the protocol. Craving was measured using a scale consisting of 5 items: "I have a desire for a cigarette right now"; "If it were possible I would smoke now"; "All I want right now is a cigarette"; "I have an urge for a cigarette"; and "I crave a cigarette right now" (Shiffman et al., 2003). Responses were rated from 0 (not at all) to 100 (strongest feeling possible), and averaged over the 5 items to produce a craving intensity score. Nicotine withdrawal was measured using the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami, 1986), which comprises nine questions: urge to smoke, depressed mood, irritability, anxiety, difficulty concentrating, restlessness, increased appetite, and two sleep questions, each rated from 0 to 4: 0=not at all, 1=slight, 2=moderate, 3=quite a bit, 4=extreme. A composite withdrawal

score was computed by summing items 2–9. Although item 1 of the MNWS measures urge to smoke, the primary assessment of craving was based on the 5-item craving scale as pre-specified in the protocol. Affect was measured using the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988), which comprises 20 mood descriptors each rated from 1 (very slightly or not at all) to 5 (extremely), with 10 items for positive and negative affect, respectively. AEs experienced during the treatment sessions were assessed by asking participants a non-leading question, such as “how do you feel?” or volunteered by participants. AEs were evaluated for intensity (mild, moderate, or severe).

3. Results

3.1. 4-hour pre-cue period

Figures 2A–D shows the “tonic” measure obtained at nine time-points during the 4-hour post-dosing period. A baseline score was calculated by averaging times 0 and 30, and a peak score by averaging times 210 and 240. An analysis of variance (ANOVA) model was applied with terms of treatment (varenicline, placebo), time (baseline, peak), and interaction of treatment by time. The variables session (first, second) and order (varenicline first, placebo first) were omitted from the analysis for simplicity, and because evaluation of these variables revealed no interaction with the primary factors of the design. Analysis of the gender variable did not reveal any significant differences in the effects reported below, so this was also omitted from the analysis.

3.1.1. Craving—ANOVA of 5-item craving scale scores (Figure 2A) incorporating the variables treatment (varenicline, placebo) and time (baseline 0/30, peak 210/240) yielded significant effects of treatment ($F(1,262) = 9.59$, $P = 0.002$), time ($F(1,262) = 97.48$, $P < 0.001$), and critically, a treatment by time interaction ($F(1,262) = 9.57$, $P = 0.002$). Furthermore, the treatment effect was significant at peak time ($t(262) = 4.39$, $P < 0.001$), but not baseline ($t(262) = 0.00$, $P = .99$).

3.1.2. MNWS withdrawal—A comparable ANOVA of MNWS withdrawal scores (Figure 2B) yielded significant effects of treatment ($F(1,251) = 27.72$, $P < 0.001$) and time ($F(1,250) = 15.43$, $P < 0.001$), but no significant treatment by time interaction ($F(1,250) = 1.59$, $P = 0.21$). Moreover, the treatment effect was significant at the baseline and peak times ($t(250)$, $t(251) > 2.87$, $P < 0.005$).

3.1.3. Negative affect—ANOVA of negative affect (Figure 2C) also yielded significant effects of treatment ($F(1,251) = 8.16$, $P < 0.005$) and time ($F(1,249) = 9.96$, $P = 0.002$), but no significant treatment by time interaction ($F(1,249) = 1.08$, $P = 0.30$). The treatment effect was significant at peak time ($t(251) > 2.74$, $P < 0.01$), but not at baseline ($t(249) = 1.30$, $P = 0.19$).

3.1.4. Positive affect—ANOVA of positive affect (Figure 2D) yielded no significant effects of treatment ($F < 1$), but a significant effect of time ($F(1,250) = 5.27$, $P = 0.02$) and treatment by time interaction ($F(1,250) = 6.74$, $P = 0.01$). The treatment effect was significant at baseline ($t(250) = 2.08$, $P = 0.04$), but not at peak time ($t(251) = -1.59$, $P = 0.11$).

3.2. Cue exposure session

Figures 2E–H shows craving, withdrawal, and affect measures obtained following smoking and neutral cue exposure. Means and SDs are given in Table 1. The three time-points after each cue exposure (1: 255, 260, 265; 2: 275, 280, 285) were averaged because this time variable did not interact with treatment and cue on any of the measures. An ANOVA model was applied with terms of treatment (varenicline, placebo), cue (smoking, neutral), and interaction of treatment by cue. Examination of the session (first, second) and order (varenicline first, placebo first) variables revealed no selectivity of effects to specific portions of the design, so these variables were omitted from the analysis below. Finally, analysis of the gender variable did not reveal any significant differences in the effects reported below, so this was also omitted.

3.2.1. Craving—ANOVA of 5-item craving scale scores (Figure 2E) with the variables treatment (varenicline, placebo) and cue (smoking, neutral) yielded a significant effect of treatment ($F(1,413) = 29.32, P < 0.001$), indicating that varenicline attenuated craving overall, and a significant effect of cue ($F(1,413) = 11.24, P < 0.001$), indicating that the smoking cue provoked craving. There was no significant treatment by cue interaction ($F < 1$), demonstrating that, in contrast to overall craving, varenicline did not modify the capacity of the smoking cue to provoke craving.

3.2.2. MNWS withdrawal—A comparable ANOVA of withdrawal scores (Figure 2F) yielded a significant effect of treatment ($F(1,408) = 39.29, P < 0.001$), but non-significant effects of cue ($F(1,408) = 0.05, P = 0.83$), and treatment by cue interaction ($F(1,408) = 0.19, P = 0.66$).

3.2.3. Negative affect—ANOVA of negative affect scores (Figure 1G) similarly yielded a significant main effect of treatment ($F(1,413) = 7.99, P < 0.005$), but non-significant effects of cue ($F(1,413) = 0.20, P = 0.66$) and treatment by cue interaction ($F(1,413) = 0.54, P = 0.46$).

3.2.4. Positive affect—Finally, ANOVA of positive affect scores (Figure 1H) yielded no significant main effects or interaction ($F \leq 2.00, P > 0.15$).

3.3. Adverse events

There were no serious AEs or withdrawals resulting from AEs during the study. Most AEs were of mild intensity (see Table 2). Four AEs were moderate in intensity (one incidence each of headache, nausea, vomiting, and somnolence). No AEs of severe intensity were reported.

4. Discussion

The study produced the following key findings. First, smoking cue exposure amplified craving compared with neutral cue exposure, but there was no such cue effect on nicotine withdrawal or positive and negative affect. Second, tonic craving declined from baseline across the 4-hour post-dosing period, and acute administration of varenicline 2 mg accelerated this decline relative to placebo. Similarly, varenicline reduced overall craving in

the smoking and neutral cue conditions versus placebo, consistent with an effect on background craving. The critical result, however, was that varenicline did not influence the capacity of smoking cue exposure to amplify craving above neutral cue exposure, relative to placebo. This dissociable effect of varenicline suggests that cigarette craving is determined by distinct tonic and phasic components (Shiffman, 2000), and that acute varenicline acts solely on tonic craving, at least during acute dosing. Finally, varenicline had an effect on withdrawal and negative affect across the 4-hour post-dosing period and over the smoking and neutral cue conditions. However, these effects appear to be confounds of treatment, rather than a direct effect of treatment, because they manifested at baseline and early on in the post-dosing period rather than selectively at the peak period post-dosing.

The dissociable effect of varenicline on tonic and phasic craving is corroborated in part by Brandon and colleagues (Brandon et al., 2011). Abstinent non-treatment-seeking smokers received chronic varenicline or placebo (0.5 mg/day for days 1–3, 1 mg/day on days 4–7, 2 mg/day on days 8–15). In a test conducted on days 5–7, varenicline decreased tonic levels of craving but had no effect on cue-provoked craving. Varenicline did however attenuate cue-provoked craving on days 12–15. Chronic NRT dosing (i.e., transdermal patch) (Havermans et al., 2003; Morissette et al., 2005; Rohsenow et al., 2007; Tiffany et al., 2000; Waters et al., 2004), bupropion (Hussain et al., 2010), and acute smoking satiety (Drobes and Tiffany, 1997; Maude-Griffin and Tiffany, 1996) have all been shown to attenuate tonic, but not cue-provoked craving (Ferguson and Shiffman, 2009).

Several studies provide insight into the therapeutic action of varenicline. Learning theorists have discovered that goal-directed reward-seeking (lever pressing) is governed by an expectation of the current incentive or consummatory *value* of the reward, whereas cue-elicited reward seeking is governed by an expectation of the current *probability* of the reward (Delamater, 1995) independently of its value (Colwill and Rescorla, 1990; Corbit et al., 2007; Holland, 2004; Rescorla, 1994). These expectations of reward value and probability are independent and additive in motivating reward-seeking (Balleine et al., 2011) and smoking behavior (Hogarth et al., 2010). Analogue learning procedures designed for human smokers have recently shown that whereas goal-directed tobacco-seeking is modified by smoking satiety (Hogarth and Chase, 2011) and by acute administration of 1 mg nicotine nasal spray (Hogarth, 2012), cue-elicited tobacco-seeking is sensitive to neither treatment. However, Brandon and colleagues found that chronic administration of varenicline for 12–15 days, compared to 5–7 days, attenuated both tonic and cue-provoked craving (Brandon et al., 2011).

These diverse findings can be reconciled by claiming that the primary action of varenicline is to mimic an internal state of smoking satiety. This would acutely reduce the expected value of smoking and thus attenuate goal-directed tobacco-seeking and its subjective counterpart, tonic craving, but acutely would not influence the expected probability of tobacco and so would leave cue-elicited tobacco-seeking unaffected. However, the experience of smoking reward would be attenuated (Hajek et al., 2011; Patterson et al., 2009; Sofuoglu et al., 2009). Consequently, administering chronic varenicline while still smoking would allow individuals to verify that the state produced by varenicline predicts a low value of smoking reward, driving further reductions in goal-directed drug-seeking

(Hutcheson et al., 2001) and tonic craving (Brandon et al., 2011) under drug. Furthermore, chronic varenicline while still smoking would modify the contingency between smoking cues and smoking thereby reducing cue-elicited drug-seeking (Hellemans et al., 2006) and cue-elicited craving (Brandon et al., 2011). This analysis may help explain why chronic varenicline treatment before a quit attempt (i.e., combined with smoking) achieves a superior therapeutic outcome (Hajek et al., 2011), whereas acute treatment exerts a dissociable effect on tonic versus cue-elicited craving.

Our findings have important clinical implications that require further study. To the extent that our account of the psychological processes that mediate the effect of varenicline is correct, increasing durations of varenicline treatment before smoking cessation attempts should achieve better outcomes because this allows individuals to learn the relationship between varenicline and the low value of smoking (modifying goal-directed tobacco seeking), and the relationship between smoking cues and the low value of smoking (modifying cue-elicited tobacco-seeking). In addition, the reduction in tonic craving that we observed after acute dosing in a short time frame among varenicline-naïve smokers indicates that varenicline's rapid effect on craving may be an important factor in facilitating initial abstinence, and thus has potential as a relatively fast acting 'rescue' medication in the context of relapse prevention (e.g., as has been suggested for nicotine gum) (Shiffman et al., 2003).

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Figure 1.
Timeline of experimental sessions.

Figure 2.

Mean (and standard error) craving, withdrawal, negative and positive affect scores during the 4-hour period (top row), and least-squares mean (and standard error) during the cue-exposure session (bottom row). MNWS = Minnesota Nicotine Withdrawal Scale; PANAS = Positive and Negative Affect Scale.

Craving, withdrawal, and positive and negative affect scores (means and standard deviations) during the cue-exposure session as a function of treatment condition and cue type.

Table 1

Variable	Time post-drug administration (min)						
	255	260	265	275	280	285	Average
Cigarette craving (5-item scale)							
Placebo							
Active	58.1 (32.7)	50.0 (30.7)	47.2 (30.0)	59.0 (36.4)	52.4 (37.2)	51.3 (35.3)	53.1 (33.4)
Neutral	48.1 (34.5)	50.2 (35.6)	49.6 (35.3)	44.2 (30.4)	41.6 (28.3)	36.9 (27.6)	45.1 (31.7)
Varenicline							
Active	46.9 (35.6)	35.6 (29.9)	34.6 (32.0)	47.6 (41.0)	41.7 (38.5)	36.5 (37.2)	40.5 (35.5)
Neutral	37.3 (31.9)	38.2 (35.3)	37.9 (35.9)	32.1 (32.5)	31.7 (32.7)	30.8 (32.9)	34.6 (32.9)
Withdrawal (MNWS)							
Placebo							
Active	6.2 (5.1)	7.3 (5.7)	7.0 (4.7)	7.7 (6.9)	8.6 (7.2)	7.9 (6.5)	7.4 (6.0)
Neutral	6.1 (5.9)	7.1 (6.6)	7.0 (6.2)	7.0 (4.5)	9.2 (6.3)	7.8 (5.7)	7.3 (5.9)
Varenicline							
Active	4.6 (3.9)	4.7 (4.4)	6.0 (4.9)	5.0 (6.8)	5.1 (6.1)	5.1 (6.4)	5.1 (5.4)
Neutral	4.3 (5.2)	4.7 (5.0)	4.7 (5.9)	5.6 (4.9)	6.0 (5.1)	6.5 (5.6)	5.3 (5.2)
Positive affect (PANAS)							
Placebo							
Active	2.3 (0.6)	2.1 (0.5)	2.2 (0.6)	1.8 (0.8)	1.7 (0.7)	1.6 (0.7)	1.9 (0.7)
Neutral	1.7 (0.7)	1.7 (0.6)	1.6 (0.6)	2.1 (0.6)	2.1 (0.5)	1.9 (0.5)	1.9 (0.6)
Varenicline							
Active	2.3 (0.8)	2.1 (0.8)	2.1 (0.8)	1.8 (0.7)	1.7 (0.6)	1.7 (0.7)	2.0 (0.7)
Neutral	1.8 (0.8)	1.7 (0.5)	1.7 (0.6)	2.1 (0.7)	2.1 (0.8)	2.2 (0.8)	1.9 (0.7)
Negative affect (PANAS)							
Placebo							
Active	1.3 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.5)	1.4 (0.5)	1.4 (0.4)	1.4 (0.4)
Neutral	1.3 (0.4)	1.3 (0.4)	1.3 (0.5)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)
Varenicline							

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Variable	Time post-drug administration (min)					
	255	260	265	275	280	285
Active	1.3 (0.2)	1.2 (0.2)	1.3 (0.4)	1.3 (0.5)	1.3 (0.5)	1.3 (0.6)
Neutral	1.2 (0.4)	1.3 (0.4)	1.3 (0.5)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
Average						

Means are presented with standard deviations in parentheses. Average = mean and standard deviation of scores across the six time points.
MNWS = Minnesota Nicotine Withdrawal Scale; PANAS = Positive and Negative Affect Scale.

Table 2

Adverse events occurring in response to varenicline and placebo.

AE	Varenicline (2 mg) <i>n</i> = 39	Placebo <i>n</i> = 39
Headache	6	3
Bradycardia	3	3
Nausea	3	0
Tachycardia	1	0
Vomiting	1	0
Peripheral edema	1	0
Somnolence	1	1
Maculopapular rash	1	0
Fungal infection	1	0
Respiratory disorder	1	0
Diarrhea	0	1
Back pain	0	1
Increased SGPT	0	1
Total number of AEs reported	19	10
Number participants reporting AEs	14	7

AE data are presented on all participants who received at least one dose of study drug.

AE = adverse event; SGPT = serum glutamic pyruvic transaminas