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Varenicline's effects on acute smoking behavior and reward and their association with subsequent abstinence

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Abstract

Rationale—Varenicline may aid smoking cessation by attenuating smoking behavior and reward. We compared the effects of varenicline versus placebo on smoking behavior and reward, assessed both prospectively and retrospectively, and related these effects to subsequent success in a brief simulated quit attempt with medication.

Materials and methods—Smokers ($n=124$) with high or low interest in quitting smoking participated in a double-blind crossover study of varenicline versus placebo effects on smoking behavior and reward. In each of two phases, subjects received a week of medication run-up with varenicline (0.5 mg, b.i.d.) or placebo while continuing to smoke, followed the next week by an attempt to quit while on medication. At the end of each run-up week, subjects completed retrospective measures of smoking reward (liking) and number of cigarettes over the prior 24 hrs, and they provided an expired air carbon monoxide (CO) measure. They then completed a prospective session in which they ad lib smoked and rated the rewarding effects of one of their preferred cigarettes while blind to brand.

Results—Varenicline decreased smoking reward significantly in the prospective assessment, but only marginally in the retrospective assessment. Varenicline did not alter smoking behavior prospectively, but did reduce CO and retrospective report of smoking amount. None of these effects of varenicline predicted subsequent days of abstinence due to varenicline.

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Conclusions—During medication run-up, varenicline decreases acute smoking reward and may attenuate smoking behavior, but these effects do not appear to directly predict varenicline's influence on smoking abstinence in a short-term test.

Keywords

Smoking; Varenicline; Reward; Smoking cessation; Nicotine dependence

Varenicline is clearly effective in increasing long-term smoking abstinence in clinical trials (Aubin et al. 2008; Gonzales et al. 2006; Jorenby et al. 2006; Oncken et al. 2006), but the mechanisms responsible for this clinical efficacy are not completely clear. Varenicline relieves craving and negative affect, but not most other withdrawal symptoms, when smokers quit smoking (Gonzales et al. 2006; Jorenby et al. 2006; Patterson et al. 2009; West et al. 2008). Yet, rates of abstinence often increase over the first few weeks of varenicline use (Gonzales et al. 2006; Oncken et al. 2006) rather than decrease as with most other medications or while quitting without medication (e.g., Transdermal Nicotine Study Group 1991). An increase in abstinence over weeks suggests a medication influence on attenuating the rewarding and reinforcing effects of continuing to smoke, helping to initiate abstinence, and not just the relief of craving after achieving abstinence. Notably, varenicline is a partial agonist of $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChRs) and binds with lower affinity to $\alpha 7$ nAChRs (Mihalak et al. 2006; Rollema et al. 2007), actions that may alter the reinforcing effects of nicotine (O'Connor et al. 2010).

Varenicline reduces retrospective self-report ratings of smoking reward (e.g., "liking") and satisfaction in clinical studies (Aubin et al. 2008; Oncken et al. 2006; West et al. 2008), but the reliability of retrospective reports related to smoking has been questioned (Shiffman et al. 1997). A recent prospective study showed that varenicline (versus placebo) attenuates the rewarding effects of smoking a cigarette (Patterson et al. 2009). However, responses to smoking can be biased due to knowledge of the cigarette brand being smoked (Perkins et al. 2001; Wakefield et al. 2002), and prior studies of varenicline effects on smoking reward did not involve blind administration of cigarettes. Blind administration of cigarettes may reveal even stronger effects of varenicline on reward. Sofuoglu et al. (2009) compared the effects of intravenous nicotine administration in 12 smokers following 4 days of varenicline (1 mg, qd) versus placebo in a double-blind, within-subjects study. Varenicline attenuated several subjective effects of nicotine (drug strength, high, head rush, stimulated), but reward was not assessed. How strongly varenicline would attenuate the rewarding effects of cigarettes administered blind in a prospective study is not clear.

Much less research has assessed varenicline effects on smoking behavior per se. Stoops et al. (2008) assessed ad lib smoking prospectively over 4 h in eight smokers following a single dosing of varenicline (up to 2 mg), placebo, or methylphenidate (40 mg). Varenicline had no effect on smoking behavior, as measured by total puffs and expired air carbon monoxide (CO), but methylphenidate increased smoking, consistent with its stimulant effects. These results conflict with rodent studies showing a reduction in nicotine self-administration following varenicline pretreatment (O'Connor et al. 2010; Rollema et al. 2007). Yet, the results by Stoops et al. are consistent with studies of the acute effects of the smoking cessation medications nicotine replacement and bupropion on ad lib smoking behavior in humans. Nicotine replacement generally does not reduce ad lib smoking behavior (see Perkins et al. 2006), and bupropion, a drug with stimulant effects, may increase ad lib smoking, similar to results with amphetamine (Cousins et al. 2001). None of these studies of short-term medication effects on smoking examined cigarettes administered blind to brand. They also did not examine smokers interested in quitting permanently, and the clinical effects of cessation medications, particularly on smoking behavior, may be strongly influenced by the level of the smoker's motivation to

quit (Perkins et al. 2008). Thus, it is conceivable that these acute dosing studies lacked clinical validity as tests of the effects of medications on smoking behavior (Perkins et al. 2006).

The current study assessed the effects of a week of varenicline versus placebo use on acute ad lib smoking behavior and reward in a double-blind, crossover study. Smoking behavior and reward were assessed in the same participants in two ways—prospectively under blind administration in the lab as well as by retrospective self-report (as in most clinical trials). Subjects were smokers high versus low in current quit interest to determine whether acute medication effects on smoking responses may vary by quit motivation. We also related these acute effects of varenicline on smoking behavior and reward to subsequent abstinence with varenicline during a brief simulated quit attempt to determine the potential mechanisms of varenicline's efficacy for cessation. Several studies have related laboratory responses to acute smoking, nicotine, or abstinence to subsequent longer term smoking abstinence (e.g., Perkins et al. 2002; al'Absi et al. 2004; Kaufmann et al. 2004). However, we are aware of very few studies relating short-term medication effects on smoking responses to subsequent smoking abstinence with that medication and none with varenicline.

Materials and methods

Participants

This study was part of a project evaluating a short-term method to test for the efficacy of smoking cessation medications, with varenicline as a model medication (Perkins et al., in press; see also Perkins et al. 2006, 2008). Eligible subjects were those smoking at least ten cigarettes per day for at least 2 years and providing a CO ≥ 10 ppm. Recruitment ads sought smokers who did or did not already intend to quit permanently. Those intending to quit within the next 2 months were labeled high in quit interest, while those stating no intention of quitting within the next 6 months were labeled low in quit interest (those wanting to quit immediately were referred to other treatment programs and excluded from the study, as were those intending to quit in 2–6 months). Regardless of quit interest, all subjects were required to agree to try hard to quit for 1 week at the end of each medication phase (see “Procedure”).

Mean $\pm$ SE characteristics for those high ($n=57$) versus low ($n=67$) in quit interest, respectively, were: age of 34.2 ± 1.4 versus 30.2 ± 1.4 years, body mass index of 26.1 ± 0.6 versus 26.1 ± 0.7 , smoking rate of 15.5 ± 0.6 versus 16.9 ± 0.7 cigarettes/day, smoking history of 14.5 ± 1.3 versus 12.0 ± 1.4 years, and Fagerstrom Test of Nicotine Dependence (Heatherton et al. 1991) score of 4.5 ± 0.2 versus 4.6 ± 0.2 . Men comprised 43.5% of the sample. There were no differences in smoking characteristics or dependence due to quit interest. All 124 subjects were included in the retrospective assessment of varenicline's effects. Ten subjects were not included in the prospective assessment because they smoked a brand that could not be presented blind (e.g., roll your own or odd-sized cigarettes). For the 114 (51 high, 63 low quit interest) included in those analyses, the nicotine yield of their preferred brand was 0.93 ± 0.03 mg.

Dependent measures

The retrospective and prospective assessments of smoking behavior and reward were obtained in a single session during each medication run-up period prior to a week of a simulated quit attempt on medication (see “Procedure” below; see also Perkins et al., in press).

Retrospective assessment—Expired air CO and self-reported cigarette number and reward ratings were obtained to assess smoking behavior and reward. Subjects monitored on a tally form the number of cigarettes they smoked over the 24 h prior to the session and received \$5 for turning in the form. This method of assessment has been shown to be reliable (e.g., Perkins et al. 1996). CO was assessed upon arrival via Breathco CO monitor (Vitalograph,

Inc.; Lenexa, KS, USA). Responses to smoking their own brand over the prior 24 h included items asking about “liking” and “how strong,” each on a 0 to 100 visual analog scale (VAS) anchored by “not at all” and “extremely”, respectively.

Prospective assessment—Smoking topography (puff volume, number) and CO boost from smoking one of their preferred brands of cigarettes in blind fashion, and reward-related ratings of that cigarette were assessed prospectively after the retrospective assessment (above). Subjects were given a cigarette of their own brand with the markings covered and inserted into a portable topography assessment device from the Clinical Research Support System (CRSS; Borgwaldt KC, Inc., Richmond, VA, USA; www.plowshare.com), which assesses puff number and total puff volume. They were instructed to smoke at least one puff of the cigarette and rate it after they had finished smoking as much as they wanted. CO was assessed after completing the cigarette and compared with the CO reading upon arrival at the session to determine CO boost. Cigarette ratings were the “liking”, “how strong,” and “how much nicotine” items from the Rose Sensory Questionnaire (see Westman et al. 1996), each modified for rating on a 0 to 100 VAS. We also added an item asking “how similar to your own brand” was the cigarette on a 0 to 100 VAS.

Procedure

This study was approved by the University of Pittsburgh Institutional Review Board. All subjects provided written informed consent for participation after the nature and consequences of the study were explained. Subjects participated in two 3-week phases, each involving 1 week of baseline ad libitum smoking, 1 week of medication run-up while continuing to smoke, and 1 week of medication use while attempting to quit. Phases differed only in whether varenicline or placebo was administered during the second and third weeks. The order of varenicline and placebo between phases was counter-balanced between subjects within each quit interest group and sex. Varenicline and placebo tablets matched in size and appearance were provided by the manufacturer, Pfizer Inc. (New York, NY, USA).

The varenicline dose run-up regimen during week 2 was that recommended by Pfizer for those quitting smoking, 0.5 mg, qd, for 3 days followed by 0.5 mg, b.i.d., for 4 days. The full dose of 1.0 mg b.i.d. was administered throughout week 3 when participants attempted to quit. The same number of placebo tablets was taken during the placebo condition. Compliance with medication, determined by pill count from returned medication bottles, was 97% and 98% for placebo and varenicline phases, respectively. The retrospective and prospective assessments of smoking behavior and reward were obtained in the same session at the end of the medication run-up during week 2 of each phase, 7 days after starting the run-up (i.e., end of 4 days of run-up with 0.5 mg b.i.d., just before starting the full dose of 1.0 mg b.i.d. leading into week 3). The time of day of sessions was the same between medication conditions within subjects, and all subjects were tested between noon and 6 pm, after their first daily dosing but before their second (i.e., b.i.d. dosing). Daily abstinence was determined Mon–Fri during week 3 by a self-report of no smoking at all and CO <5 ppm (for reasons relevant to other goals of the project, week 3 of each phase also involved random assignment to \$12/day reinforcement for abstinence versus no reinforcement, with the same reinforcement condition in effect for both phases).

Data analyses

Four sets of primary analyses were conducted to examine varenicline effects on smoking reward and behavior, each analyzed via retrospective and prospective assessments in the same session, as described previously. Each primary analysis involved an analysis of variance (ANOVA), with varenicline versus placebo as the within-subjects factor and current quit interest (high/low) and sex as between-subjects factors. Follow-up comparisons were conducted using Fisher’s LSD *t* tests (Huitema 1980). Because of the number of subjective

cigarette ratings (four) in the prospective session, a multivariate ANOVA (MANOVA) was first conducted and then univariate ANOVAs on each item performed following a significant MANOVA. We also examined medication order (varenicline first versus placebo first) as a between-subjects factor, but medication order had no main or interaction effects on smoking reward or behavior and so is not discussed. In addition, preliminary analyses of results from the prospective assessment examined effects of time since their last cigarette (prior to arrival; 97.2 ± 14.4 versus 74.1 ± 11.3 min for varenicline versus placebo, respectively) and the amount of smoke intake (puff volume; see “Results”) during the assessment as both could influence subjective ratings of the cigarette. Neither was significant, however, and so neither variable was included as a covariate.

Using analysis of covariance, the differences between varenicline and placebo effects on smoking reward and behavior in the retrospective and prospective assessments were related to the difference between varenicline and placebo in days of smoking abstinence during week 3 of each phase, following the assessment session. Quit interest, abstinence reinforcement, and sex were between-subjects factors, and the difference in smoking reward and behavior, the primary predictors of interest, were included as a covariate. Because the difference in abstinent days due to varenicline versus placebo was not influenced by main or interaction effects involving the abstinence reinforcement manipulation in week 3, the reinforcement condition is not discussed further.

Results

Retrospective assessment of varenicline effects

Smoking reward ratings—Retrospective ratings of liking and how strong for cigarettes smoked over the prior 24 h were not significantly influenced by the main effect of varenicline (versus placebo), although the effect was marginal for liking [$F(1,107)=2.92, p<0.10$]. However, liking was influenced by quit interest [$F(1,107)=15.75, p<0.001$], the interaction of varenicline $\times$ quit interest [$F(1,107)=4.64, p<0.05$], and the interaction of varenicline $\times$ quit interest $\times$ sex [$F(1,107)=7.41, p<0.01$]. Liking was lower for those with high versus low quit interest, as shown in Fig. 1 (top). Varenicline (versus placebo) decreased cigarette liking among men with high but not low quit interest, while no influence of varenicline was seen among women (Fig. 1).

Smoking behavior—CO and cigarettes tallied in the prior 24 h were both slightly but significantly decreased by varenicline [$F(1,105)$ of 6.77 and 6.03, respectively, both $p<0.05$], as also shown in Fig. 1 (bottom). Mean $\pm$ SEM CO was also greater in those with high versus low quit interest (22.3 ± 1.3 versus 18.7 ± 1.2 , respectively) [$F(1,105)=4.26, p<0.05$], and marginally affected by varenicline $\times$ quit interest [$F(1,105)=3.20, p<0.10$]. Varenicline tended to decrease CO more in those with high versus low quit interest (not shown).

Prospective assessment of varenicline effects

Smoking reward and other ratings—The MANOVA of cigarette ratings during the prospective assessment showed a significant main effect of varenicline [$F(4,95)=4.56, p<0.005$] and no interaction effects involving varenicline. A main effect was also seen for sex [$F(4,95)=3.58, p<0.01$]. In the follow-up ANOVAs, the main effect of varenicline was significant for liking, how similar to own brand, and how much nicotine [$F(1,98)$ of 15.68, 11.97, and 4.54, respectively, $p<0.001, p<0.001$, and $p<0.05$], but not for how strong [$F(1,98)=2.67, p>0.10$]. Varenicline effects on attenuating these cigarette ratings are shown in Fig. 2. The interaction of quit interest $\times$ varenicline was marginal for liking [$F(1,98)=3.54, p<0.10$] as varenicline versus placebo tended to decrease liking more in those with high (43.9 ± 3.6 versus 57.7 ± 3.6) versus low quit interest (56.9 ± 3.2 versus 61.8 ± 3.3). Liking was also influenced by

the main effects of quit interest and sex [$F(1,98)$ of 4.03 and 12.46, respectively, $p<0.05$ and $p<0.001$]. Liking of their own brand of cigarettes under blind conditions was lower in those with high versus low quit interest (50.8 ± 3.2 versus 59.4 ± 2.8) and in women versus men (47.5 ± 2.8 versus 62.6 ± 3.2). The latter difference compares sharply with the lack of sex difference in liking ratings in the unblinded retrospective assessment (65.8 ± 2.5 versus 61.3 ± 2.8 for women versus men, respectively), suggesting a greater effect of cigarette blinding on smoking reward in women versus men.

Smoking behavior—Varenicline had few significant effects on smoking behavior, as shown in Fig. 3. Puff volume was lower in women than men (394.3 ± 26.9 versus 562.1 ± 30.7 ml, respectively) [$F(1,95)=16.93$, $p<0.001$], and puff number was lower among those with high versus low quit interest (8.0 ± 0.7 versus 10.4 ± 0.6 , respectively), [$F(1,95)=6.97$, $p<0.01$]. Puff volume was also influenced marginally by the interaction of varenicline $\times$ quit interest $\times$ sex [$F(1,95)=3.40$, $p<0.10$] as varenicline (versus placebo) tended to decrease puff volume among women high in quit interest, but not among the other groups (not shown).

Association with abstinence

Mean $\pm$ SEM days abstinent during week 3 of each phase due to varenicline and placebo were 2.1 ± 0.2 and 1.2 ± 0.2 , respectively, out of a maximum of 5 [$F(1,103)=45.68$, $p<0.001$]. The difference in days abstinent due to varenicline versus placebo was greater in those with high versus low quit interest [$F(1,103)=8.70$, $p<0.005$], as reported in more detail elsewhere (Perkins et al., in press). However, the varenicline effect on days abstinent was not significantly associated with the differences due to medication in smoking reward (liking) and smoking behavior at the end of week 2 in the retrospective assessment or in the prospective assessment.

Discussion

Our results show that varenicline acutely lowers self-reported smoking reward, assessed either retrospectively or prospectively, although varenicline effects on reward in the retrospective assessment were more modest and may be limited to men with high quit interest. These results are consistent with clinical studies (Aubin et al. 2008; Oncken et al. 2006; West et al. 2008) and with the few prospective studies of varenicline effects on subjective responses to smoking, in smokers not blind to brand (Patterson et al. 2009), or to intravenous nicotine (Sofuoglu et al. 2009). Varenicline also reduced smoking behavior in the retrospective assessment involving self-reported cigarettes over the prior 24 h and expired air CO. However, varenicline did not affect smoking in the prospective assessment of smoking topography and CO boost following a single cigarette, consistent with the lack of varenicline effects on acute smoking behavior in the prospective assessment by Stoops et al. (2008).

In any case, none of these effects of varenicline was associated with subsequent abstinence due to varenicline (versus placebo) during a week of medication use. Notably, smoking behavior and reward in response to varenicline did not vary much by quit interest, in contrast with the greater influence of varenicline on short-term abstinence in those with high versus low quit interest (see Perkins et al., in press). Therefore, motivation to quit smoking may not influence sensitivity to medication effects on these acute smoking responses even if quit motivation does influence sensitivity to medication effects on short-term abstinence (Perkins et al. 2006, 2008, in press). On the other hand, assessments of these effects in response to the full clinical dose of varenicline (1.0 mg, b.i.d.) in smokers actively attempting to quit permanently could reveal a stronger relationship between these variables and abstinence. In particular, such effects on smoking reward and behavior may be more robust and more strongly related to subsequent abstinence after extended duration of medication exposure, such as during lapses after quitting (see Shiffman et al. 2006), than during initial dose run-up prior to quitting

given the clinical observation that abstinence often increases over the first few weeks of varenicline use (Gonzales et al. 2006; Oncken et al. 2006). Alternatively, varenicline's efficacy in smoking cessation may stem from other actions such as reducing craving (West et al. 2008) or attenuating impairments in mood and cognition during abstinence (Patterson et al. 2009).

The pattern of varenicline effects differed somewhat between the retrospective and prospective assessments, with stronger effects on smoking reward in the prospective assessment but stronger effects on smoking behavior in the retrospective assessment. Retrospective self-reports of smoking reward or behavior could be less reliable than prospective assessments, as suggested by Shiffman et al. (1997), but the fact that CO upon arrival was also reduced by varenicline suggests that the self-report of cigarettes smoked over the prior 24 h was accurate. Because the retrospective assessment covered a 24-h period of smoking and the prospective assessment obtained smoking topography from a single cigarette, observing varenicline's effects on reducing smoking behavior may require an assessment period longer than a single cigarette (current study) or even 4 h (Stoops et al. 2008). However, conceivably, smoking via the CReSS topography device could have lowered the reinforcing value of the smoking experience during the prospective assessment, perhaps obscuring varenicline's effects in reducing smoking behavior.

Interestingly, the retrospective assessment also involved cigarette ratings of one's own brand in unblind fashion, while the prospective assessment involved ratings of one's own brand under blind conditions. Thus, the stronger impact of varenicline on smoking reward in the prospective assessment may better reflect the medication's true effects on reward after eliminating the influence of expectancies and other biases due to brand identification (Wakefield et al. 2002). Evidence of the influence of blinding is suggested by the moderate ratings of 50–60 (on a 0–100 scale) on the item “how similar to own brand” after smoking one of their own brand in the prospective assessment (Fig. 2), similar to previous results with blinding of preferred brand (Perkins et al. 2001). We also note that liking of one's own brand was similar between prospective and retrospective assessments among men but much lower in the prospective versus retrospective assessments among women, suggesting greater effects of blinding (or of smoking through the CReSS device) on smoking reward in women. This sex difference is perhaps consistent with other research showing greater responsivity of women than men to non-pharmacological smoking stimuli, including the smell of smoke or expectancies for nicotine (Perkins et al. 2001; Perkins 2009).

Strengths of this study included a fairly large sample of 124 smokers, comparison of varenicline and placebo effects in a within-subjects design, the simultaneous retrospective and prospective assessment of smoking reward and consumption in the same smokers, inclusion of smokers' preferred brand of cigarettes to increase generalizability of results to smoking in the natural environment, comparison of results between smokers high versus low in quit interest, and the analyses relating acute effects of varenicline to subsequent days of abstinence during a week-long simulated quit attempt with varenicline. Study limitations included the brief periods of assessment, of medication use, and of attempting to quit while on medication; the modest 0.5-mg b.i.d. dose of varenicline prior to assessments during the medication run-up period (half the full dose recommended for smoking cessation; www.Chantix.com); the somewhat variable timing of the prospective assessment since the most recent dosing; the use of smokers not attempting to quit permanently at the time of the study; and the confounding of blinding of cigarette administration with the comparison of prospective versus retrospective assessments. Future research should assess smoking reward and behavior due to larger doses of varenicline over longer periods in smokers both before and during an attempt to quit permanently. Follow-up of clinical cessation outcome could identify more clearly whether varenicline's effects on

smoking reward and behavior at the start of treatment relate to subsequent abstinence success with varenicline.

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Fig. 1.

Mean ($\pm$ SEM) self-reported reward (liking, top) and cigarettes in the prior 24 h and expired air CO (*bottom*) due to varenicline (0.5 mg, b.i.d.) versus placebo, by current level of quit interest where relevant, in the retrospective assessment. * $p < 0.05$; ** $p < 0.01$

Prospective Assessment

Fig. 2.

Mean ($\pm$ SEM) self-reported ratings of smoking one preferred brand cigarette under blind conditions due to varenicline versus placebo in the prospective assessment. *** $p < 0.001$. Other asterisks as in Fig. 1

Fig. 3. Mean ($\pm$ SEM) smoke intake from the smoking of one preferred brand cigarette under blind conditions due to varenicline versus placebo, by current level of quit interest, in the prospective assessment