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Varenicline attenuates some of the subjective and physiological effects of intravenous nicotine in humans

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Abstract

Rationale—Varenicline, a partial nicotinic acetylcholine receptor (nAChR) agonist, is approved for smoking cessation. A few preclinical studies examined the pharmacological effects of varenicline, alone or in combination with nicotine. How varenicline affects the pharmacological effects of pure nicotine has not been examined in humans. The goal of this study was to characterize varenicline's actions on nicotine's dose-dependent effects in abstinent smokers.

Methods—Six male and 6 female smokers participated in a double-blind, placebo-controlled, crossover study. Smokers had two, 4-day treatment periods, assigned in random sequence, to varenicline (1 mg/day) or placebo treatment. On day 4 of each treatment phase, smokers had an experimental session, where they received 3 escalating doses of intravenous (IV) nicotine (0.1, 0.4, and 0.7 mg/70 kg), in 30 minute intervals. Varenicline's effects were assessed through subjective, physiological and cognitive performance outcomes to nicotine administered via IV route.

Results—In response to IV nicotine, varenicline treatment attenuated the rating of drug strength, high, head rush, and stimulated. Varenicline also attenuated nicotine-induced increases in heart rate. Varenicline had mixed effects on cognitive performance. Smokers under varenicline treatment, compared with placebo, reported enhanced positive mood measured with the Positive and Negative Affect Schedule (PANAS).

Conclusions—These findings provide new insights into the mechanisms of action of varenicline in smoking cessation.

Keywords

varenicline; nicotine dependence; intravenous nicotine; nicotine abstinence

Introduction

Varenicline (Chantix®), a partial nAChR agonist, has recently been marketed as a pharmacological aid for smoking cessation (Hays and Ebbert 2008). Varenicline is a derivative of cytisine, a plant alkaloid used for smoking cessation in Eastern Europe (Etter et al. 2008). Preclinical studies have demonstrated that varenicline is a partial agonist at the $\alpha_4\beta_2$ nAChR, and a full agonist at the α_7 nAChR (Mihalak et al. 2006). Consistent with its partial agonistic effects on the nAChR, varenicline treatment reduced the nicotine-induced dopamine release in the nucleus accumbens of rats (Rollema et al. 2007). Furthermore, when administered alone, varenicline produced approximately 60 percent of the maximum dopamine release by nicotine in the nucleus accumbens (Coe et al. 2005). In addition, varenicline reduced nicotine self-administration in rats further supporting its partial agonistic effects on the nAChR (Rollema et al. 2007). More preclinical research is needed to better characterize pharmacological binding affinity and the functional potency of varenicline at different receptors as well as establish the precise mechanism of action for varenicline in smoking cessation (Balfour. 2006).

Recent human studies provide increased insight into the possible mechanisms of varenicline's efficacy in smoking cessation (Patterson et al. 2009; Stoops et al. 2008; West et al. 2008). Varenicline attenuated the severity of tobacco withdrawal symptoms, reduced the subjective rewarding effects of cigarette smoking, and improved cognitive performance in abstinent smokers (Patterson et al. 2009; West et al. 2008), which are consistent with preclinical studies mentioned above. Previous studies, however, did not evaluate varenicline's effects on pure nicotine responses in humans. This is an important gap in our knowledge base for varenicline since nicotine is the main addictive chemical in tobacco smoke and is a key factor in continued and compulsive tobacco use (Benowitz et al. 2009). The purpose of this study was to further characterize varenicline's pharmacological action in humans by evaluating its effects on pure nicotine, administered intravenously. The advantages of the IV route include rapid nicotine delivery, comparable to the bolus effect of smoking, and precise dosing. Varenicline's effects were assessed through subjective, physiological, endocrine, and cognitive performance outcomes. We hypothesized that varenicline would result in attenuated subjective response to IV nicotine, improve cognitive performance and alleviate urges for smoking in abstinent smokers. We did not have specific hypotheses for varenicline's effects on the endocrine and physiological responses to nicotine.

Materials and Methods

Participants

Twelve non-treatment seeking smokers (6 males and 6 females) were recruited from the New Haven, Connecticut area. Five additional smokers dropped out prior to study completion due to non-compliance with the study procedures and were therefore not included in the analyses. This sample of non-treatment seeking smokers was comprised of African-Americans (n=8), Caucasians (n=2), and Hispanics (n=2). The average age (SD) of the smokers was 34.0 (9.3). Participants smoked an average of 15.9 (4.6) cigarettes/day and had a Fagerstrom Test for Nicotine Dependence (Heatherton et al. 1991) score of 5.7 (1.5). Participants were not dependent on drugs or alcohol other than nicotine during the study and all physical, laboratory and psychiatric examinations were within normal limits. Participants provided written, signed consent prior to participating in the study. This study was approved by the VA Connecticut Healthcare System Human Subjects Subcommittee. Experimental sessions were conducted in the Biostudies Unit located at the VA Connecticut Healthcare System and participants were paid for participation.

Procedures

We utilized an outpatient randomized, double-blind, crossover study design. Following an adaptation session, smokers had two, 4-day treatment periods, assigned in random sequence, to varenicline (1 mg/day) or placebo treatment. Each treatment period was separated by a washout period lasting a minimum of 5 days, long enough to minimize carryover effects from varenicline, which has an elimination half-life of 24 hours (Faessel et al. 2006). During the initial adaptation session, smokers received 3 escalating doses of IV nicotine (0.1, 0.4, and 0.7 mg/70 kg), in 30 minute intervals. This procedure ensured that smokers tolerated the IV nicotine doses used during each experimental session.

On each of the first 3-days of treatment periods, smokers had daily clinic visits to receive the study medications and to complete outcome measures. Starting at midnight of day 3, smokers were asked to stop smoking until the morning of day 4. Abstinence from smoking was verified with expired carbon monoxide (CO; <10 parts-per-million). On day 4 of each treatment phase, smokers began an Experimental Session. First, smokers had an indwelling catheter placed in an antecubital vein. After baseline measures were collected, smokers received an oral dose of either varenicline or placebo. Three hours after the medication administration, when the peak plasma levels of varenicline are expected, smokers received three ascending doses of IV nicotine, (0.1, 0.4, and 0.7 mg/70 kg). The injections were given 30 minutes apart, similar to our previous studies (Sofuoglu et al. 2005; Sofuoglu et al. 2006; Sofuoglu et al. 2009). Our prior work demonstrated that 0.4 and 0.7 mg/70 kg dosing of nicotine produced robust physiological and subjective responses, and was self-administered in male and female smokers (Sofuoglu et al. 2008b). The 0.1 mg dose is less than the amount of nicotine inhaled from one puff of a cigarette (Djordjevic et al. 2000). The nicotine doses chosen for this study were lower than those used in our previous studies, in order to minimize adverse effects especially nausea, that have been reported when nicotine is combined with varenicline (PDR 2009).

Drugs

Nicotine and Varenicline Administration—Nicotine bitartrate was acquired from Interchem Corporation (Manchester, Connecticut). All nicotine samples were prepared by a research pharmacist at the VA CT Healthcare System. A total volume of 5 ml nicotine was injected over 60 seconds intravenously via a catheter located in a forearm vein. Varenicline was administered in the clinic daily by the study nurse. Patients started Varenicline (Chantix®) as a single daily 0.5 mg dose for 2 days, which was increased to 1 mg/day for the next 2 days. Although the manufacturer's recommended dose of varenicline for smoking cessation is 2 mg/day, a smaller, 1 mg/day, dose has been shown to be effective for smoking cessation (Oncken et al. 2006). Because nausea is a relatively frequent dose dependent side effect of varenicline (Hays and Ebbert 2008), we chose 1 mg/day dose to minimize the possibility of nausea from varenicline and IV nicotine combination.

Outcome measures—Our outcome measures assessed biochemical, physiological, subjective, and cognitive domains. Biochemical measures included CO, plasma cotinine, and cortisol levels. Expired CO and plasma cotinine concentrations were used to verify abstinence from smoking and level of smoking, respectively (Benowitz et al. 2002). Expired CO and plasma cotinine measurements were taken before each session. Plasma cortisol measurements were taken during the experimental sessions, at baseline, before each of three injections and at the end of the session. Plasma cortisol levels have been shown to be sensitive to nicotine withdrawal and to nicotine administration (al'Absi et al. 2002; Mendelson et al. 2005; Newhouse et al. 1990; Pickworth and Fant 1998). The physiological measures included systolic and diastolic blood pressure and heart rate, which were measured daily during medication treatment. Physiological measures were taken in the experimental sessions at -5, 1, 2, 3, 5, 8, 10, and 15 min in relation to nicotine deliveries. The subjective measures included the Nicotine

Withdrawal Symptom Checklist (NWSC), Center for Epidemiologic Studies Depression (CES-D) scale, Positive and Negative Affect Schedule (PANAS), and Drug Effects Questionnaire (DEQ). The NWSC measures withdrawal symptoms from tobacco and includes items of cigarette craving, irritability/anger, anxiety, difficulty concentrating, restlessness, increased appetite, depressed mood, and insomnia (Hughes and Hatsukami 1986; Hughes and Hatsukami 1997). We used a modified version of the NWSC in which smokers were asked to rate these symptoms on a 100 mm scale, from “not at all” to “extremely” (e.g., Buchhalter et al. 2005). The PANAS is a 20-item scale that assesses both negative and positive affective states (Watson et al. 1988). Smokers rate adjectives describing affective states on a scale of 1 to 5 using a specified time period (i.e., now, today, past week, etc.). This scale is sensitive to the affective symptoms of tobacco withdrawal (Kenford et al. 2002). The CES-D is a 20-item self-report measure of depressive symptoms (Radloff 1977). The CES-D has been shown to be a reliable and valid scale and it has been used in several epidemiological studies including with smokers (Son et al. 1997; Weissman et al. 1977). This scale was included to assess varenicline’s effects on depressive symptoms. The CES-D, and PANAS were administered each day during the study. On day 4, the NWSC and PANAS were given at baseline, prior to nicotine administration and at the end of the session. The DEQ was used to measure acute effects from IV nicotine and consisted of 7 items: drug strength, high, feel stimulated, good effects, bad effects, head rush, and like the drug. Smokers rated each item on a 100 mm scale, from “not at all” to “extremely.” The DEQ was given at 1, 3, 5, 8, 10, and 15 minutes after nicotine administration.

Cognitive performance was assessed with two cognitive tasks: the Sustained Attention to Response Test (SART) and modified Stroop task. The SART is a Go No-Go task (Robertson et al. 1997; Sofuoglu et al. 2008a), which assesses the ability to withhold responses to an infrequently occurring target (No-Go trials). Reaction times (RTs) and errors on Go trials are also assessed. The modified Stroop task assesses attentional responses to smoking and negative affect cues (Sofuoglu et al. 2008a; Waters et al. 2005). Briefly, smokers completed two counterbalanced blocks (60 trials per block). One block contained smoking words (e.g., tobacco) and neutral words (e.g., bookcase) presented in a mixed order. The other block contained negative affect words (e.g., death) and a different set of matched neutral words (e.g., couch). RTs to indicate the colors of the words were assessed. The two cognitive tasks were administered twice in each experimental session: two hours and forty five minutes after varenicline or placebo administration and 30 minutes after the last nicotine injection. Due to computer error, data from 1 smoker were missing for one session on the SART. On the modified Stroop task, RTs less than 100 ms were excluded as were RTs greater than 1501 ms (>3 SDs above the grand mean).

Data Analysis

Study outcomes were analyzed using a mixed-effect repeated-measures crossover models using the Statistical Analysis System, Version 9.1.3. (SAS Institute Inc. 2007). Each model included fixed main effect terms for treatment (placebo or varenicline), and time of measurement (day in the study or time since treatment), as well as the interaction of these two effects. We also included a random effect for subject and a blocking factor for treatment sequence. For blood pressure, heart rate, and DEQ measurements, where multiple measurements were collected before and after each nicotine dose, a change score (maximum post dose score minus predose baseline) was used in the analysis. Values of $p < 0.05$ were considered statistically significant, based on two-tailed tests, unless otherwise specified. Significant treatment or treatment-by-time interactions ($p < 0.05$) were followed up by post hoc comparisons of varenicline relative to placebo for different nicotine doses (0.1, 0.4 and 0.7 mg/kg). To account for multiple testing, for these comparisons, statistical significance was set at $p < 0.016$.

Results

Physiological response to IV nicotine

Following nicotine administration, peak heart rate and blood pressure values were reached within 5 minutes and returned close to baseline values within 15 minutes (Figure 1). There was a treatment effect on IV nicotine responses for heart rate [$F(1,55) = 38.9$; $p < .0001$], with attenuated responses under varenicline treatment. There were no treatment effects for systolic [$F(1,55) = 0.01$; $p > 0.05$] or diastolic [$F(1,55) = 0.02$; $p > 0.05$] blood pressure. As shown in Figure 2, there was a significant dose effect for the heart rate ($p < 0.001$).

Subjective responses to IV nicotine

Following nicotine administration, peak subjective responses were reached within 5 minutes and returned close to baseline values within 15 minutes (Figure 3). The treatment effects on the subjective response to IV nicotine measured with DEQ are shown in Figure 4. There were significant treatment effects for the ratings of drug strength [$F(1,54) = 13.0$; $p < 0.0001$], high [$F(1,54) = 10.5$; $p < 0.01$], feel stimulated [$F(1,54) = 6.3$; $p < 0.05$], and head rush [$F(1,54) = 16.9$; $p < 0.001$]. For each of these items, varenicline treatment was associated with attenuated subjective response. The ratings for good effects [$F(1,54) = 1.3$; $p > 0.05$], bad effects [$F(1,54) = 0.7$; $p > 0.05$], and drug liking [$F(1,54) = 0.1$; $p > 0.05$] did not significantly differ under varenicline or placebo treatment. A significant nicotine dose effect was observed for all DEQ items ($p < 0.01$).

Mood and tobacco withdrawal severity

For the first 3 days of each treatment period, there was a significant treatment effect on the positive subscale of PANAS [$F(1,54) = 10.8$; $p < 0.01$], with higher ratings under varenicline treatment. A treatment effect was not observed on the negative subscale of PANAS [$F(1,54) = 0.4$; $p > 0.05$]. The CES-D showed a treatment effect with lower ratings under varenicline treatment [$F(1, 54) = 5.7$; $p < 0.05$].

For the experimental sessions, there was no treatment effect on the total NWSC change scores [$F(1, 98) = 3.1$; $p > 0.05$]. For the individual items, a significant treatment effect was observed for “difficulty concentrating,” with lower rating under varenicline treatment [$F(1,98) = 4.9$; $p < 0.05$]. For the positive subscale of PANAS, there was a significant main effect for treatment [$F(1, 98) = 25.9$; $p < 0.0001$], with higher ratings under varenicline. For the negative subscale of PANAS, the main effect for treatment was close to significance [$F(1,98) = 3.8$; $p = 0.05$], with lower ratings under varenicline.

Biochemical Measures

Cotinine levels (SEM) before the experimental sessions were 202 ng/mL (41) under the placebo, and 185 ng/mL (38) ng/mL under the varenicline treatment [$F(1,10) = 1.1$; $p > 0.3$]. No significant treatment effects were observed for plasma cortisol levels [$F(1,81) = 4.1$; $p > 0.05$].

Cognitive Measures

On the SART, there were no significant treatment effects on number of errors on No-Go trials, number of errors on Go trials, or RTs on Go trials (p values > 0.1). On the modified Stroop task (Table 1), a main effect of treatment on RTs was observed on the smoking block [$F(1,77) = 9.57$; $p < 0.01$]. Smokers were faster to indicate the color of words on varenicline (Mean = 638.7 ms, SE = 26.7) than on placebo (Mean = 701.3 ms, SE = 26.7). The treatment-by-word type and treatment-by-time interactions were not significant (p values > 0.1). The main effect of word type was also not significant (p value > 0.1) (Means (SE): smoking words = 674.9 ms (26.7), neutral words = 665.1 ms (26.7)). On the negative affect block, no significant treatment

effects were observed (all p values > 0.1), e.g., the main effect of treatment was not significant (p value > 0.1) (Means (SE): Varenicline = 640.2 ms (28.4), Placebo = 668.6 ms (28.4)).

Adverse Events

No adverse events were encountered during the study.

Discussion

Following a brief course of varenicline treatment (1 mg/day for 4 days), abstinent smokers displayed attenuated responses to many subjective effects of IV nicotine, including the rating of drug strength, high, head rush, and stimulated. Other subjective effects including good effects and drug liking were not attenuated by varenicline treatment. These findings are consistent with previous studies which reported attenuated subjective rewarding effects from cigarette smoking under varenicline treatment. Patterson et al. (Patterson et al. 2009) reported reduced subjective effects from a programmed lapse to smoking in smokers, following a 3-days of abstinence. Similarly, West et al. (West et al. 2008) reported reduced reward from smoking in smokers who were trying to quit smoking. Our work extends these findings by evaluating varenicline's effects on subjective responses to pure nicotine administered intravenously. These findings are consistent with the partial agonistic effects of varenicline on the $\alpha_4\beta_2$ nAChRs, which have been shown to be critical for the nicotine reward in preclinical studies (Fowler et al. 2008; Picciotto and Corrigan 2002).

Varenicline attenuated nicotine-induced heart rate increases for all three doses of nicotine. We are not aware of any previous studies evaluating varenicline's effects on nicotine-induced cardiovascular responses. The nicotine-induced heart rate increases are thought to be mediated by $\alpha_3\beta_4$ subtype nAChRs which are implicated in peripheral nervous system functions (Aberger et al. 2001; Dhar et al. 2000; Ji et al. 2002). However, varenicline was shown to have very low affinity to $\alpha_3\beta_4$ nAChR in equilibrium binding experiments; its affinity to the $\alpha_3\beta_4$ subtype is 4,000 times less than to $\alpha_4\beta_2$ subtype (Coe et al. 2005). This low affinity makes it unlikely that varenicline can affect functions mediated by the $\alpha_3\beta_4$ nAChR. Although in functional assays, varenicline showed significant potency at $\alpha_3\beta_4$ nAChR as well as α_7 subtypes, further expanding the effect of varenicline beyond the $\alpha_4\beta_2$ nicotinic receptors (Mihalak et al. 2006). These findings suggest that in clinically used doses, varenicline may attenuate heart rate increases induced by nicotine by its partial agonist effect in $\alpha_3\beta_4$ nAChR. In addition to $\alpha_3\beta_4$, other nAChR subtypes, especially α_7 may also be involved in mediating the cardiovascular effects of nicotine (Ji et al. 2002). These possibilities need to be examined in future studies.

Smokers under varenicline treatment, compared with placebo, reported enhanced positive mood measured with PANAS. Interestingly, varenicline's effect on positive mood was also observed under ad lib conditions (the first 3 days of each treatment period), as well as after abstinence from smoking (day 4 of each treatment period). These findings were not due to changes in smoking behavior since there were no treatment effects on plasma cotinine levels obtained on day 4 of each treatment period. Our findings are consistent with a previous study where smokers had greater positive mood with varenicline treatment during a 3-day smoking abstinence (Patterson et al. 2009).

Varenicline had mixed effects on cognitive functioning. Varenicline significantly speeded RTs on the smoking block of the modified Stroop task. The absence of a treatment by word type interaction indicates that the varenicline-induced speeding was consistent on both smoking and neutral words. There are two possible explanations for the data. First, varenicline may reduce the salience of smoking cues, leading to faster responses on both smoking and neutral words in the smoking block (because the smoking words are less attention-grabbing under

varenicline). This explanation leans on the evidence that carry-over effects on mixed Stroop tasks have often been documented in addiction Stroop tasks. Specifically, responses on words that follow drug-related words can be slower, possibly due to disengaging attention from the salient drug-related word (Cane et al. 2009; Waters et al. 2003), and varenicline may reduce a carry-over effect. Second, varenicline may simply cause a generalized speeding of cognitive functioning. However, the observation that varenicline did not significantly speed RTs on the negative affect block of the modified Stroop task or on Go trials in the SART argues against this second explanation. In a recent study, varenicline treatment improved performance in sustained attention and working memory tasks in abstinent smokers (Patterson et al. 2009). Our study extends these findings further by demonstrating varenicline's effect on another cognitive task. On the Go-NoGo trial, varenicline did not reduce the frequency of incorrect responses on No-Go trials. Thus, it did not exert a significant effect on impulsive responding in this task. Further research is required to determine the effects of varenicline on cognitive functioning.

Our study had several limitations. First, the study did not have a nicotine-placebo condition. We used the 0.1 mg nicotine as a placebo dose since previous studies suggested that this nicotine dose was below discrimination threshold in smokers (Djordjevic et al. 2000; Perkins et al. 1994). However, the 0.1 mg dose produced significant subjective and heart rate increases. Further work needs to be conducted to determine threshold doses of IV nicotine that produces subjective and physiological effects. Second, we used only one dose of varenicline, 1 mg/day, in conjunction with relatively low doses of IV nicotine. Future studies using higher doses of varenicline and nicotine may further elucidate the interaction between varenicline and nicotine. Third, the treatment duration was brief, only four days, and it is possible that longer treatment with varenicline may produce different effects.

Our findings have a number of clinical implications for the clinical efficacy of varenicline for smoking cessation. First, attenuation of nicotine's subjective effects may contribute to varenicline's efficacy in preventing relapse in abstinent smokers. The first few puffs of cigarette smoke in abstinent smokers (lapses) are regarded to be highly rewarding and linked to full relapse in smoking (Brandon et al. 1990; Kenford et al. 1994). Second, our study as well as the Patterson study (2009), suggests that varenicline may elevate positive mood in abstinent smokers. Negative affect is an important component of tobacco withdrawal and improvement of mood has been proposed to contribute to the efficacy of bupropion, another smoking cessation medication (Lerman et al. 2002). Third, our preliminary findings and the Patterson (2009) study suggest that varenicline may improve cognitive function for some tasks in smokers. Varenicline also improved the self-report item of "difficulty concentrating" in abstinent smokers. Reduced cognitive function is a component of tobacco withdrawal and nicotine's capacity to enhance cognitive function has been suggested to contribute to its reinforcing effects especially in individuals with compromised cognitive function e.g. attention deficit hyperactivity disorder or schizophrenia (Evans and Drobles 2009). Thus, improvement of cognitive function may contribute to varenicline's efficacy for smoking cessation. Lastly, our findings suggest that varenicline treatment may attenuate some of the cardiovascular effects of nicotine in individuals who continue to smoke. Whether varenicline treatment can reduce the cardiovascular risks associated with ongoing smoking needs to be further examined.

To summarize, varenicline attenuates some of the subjective and physiological (i.e., heart rate) responses to IV nicotine in smokers. Varenicline also improves mood in smokers. These findings are consistent with the partial nicotinic agonist effects of nicotine. Further studies are warranted to examine which of these effects contribute to varenicline's efficacy in smoking cessation.

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References

- Aberger K, Chitravanshi VC, Sapru HN. Cardiovascular responses to microinjections of nicotine into the caudal ventrolateral medulla of the rat. *Brain Res* 2001;892:138–146. [PubMed: 11172759]
- al'Absi M, Amunrud T, Wittmers LE. Psychophysiological effects of nicotine abstinence and behavioral challenges in habitual smokers. *Pharmacol Biochem Behav* 2002;72:707–716. [PubMed: 12175468]
- Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol* 2009;29–60. [PubMed: 19184645]
- Benowitz NL, Jacob PI, Ahijevich K, Jarvis MJ, Hall S, LeHouezec J, Lichenstein E, Henningfield JE, Tsoh J, Hurt RD, Velicer W. Biochemical verification of tobacco use and cessation. Report from the SRNT Subcommittee on Biochemical Verification. *Nicotine & Tobacco Res* 2002;4:149–159.
- Brandon TH, Tiffany ST, Obremski KM, Baker TB. Postcessation cigarette use: the process of relapse. *Addict Behav* 1990;15:105–114. [PubMed: 2343783]
- Buchhalter AR, Acosta MC, Evans SE, Breland AB, Eissenberg T. Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction* 2005;100:550–559. [PubMed: 15784070]
- Cane J, Sharma D, Albery I. The addiction Stroop task: examining the fast and slow effects of smoking and marijuana-related cues. *J Psychopharmacol* 2009;23:510–519. [PubMed: 18562413]
- Coe JW, Brooks PR, Vetelino MG, Wirtz MC, Arnold EP, Huang J, Sands SB, Davis TI, Lebel LA, Fox CB, Shrikhande A, Heym JH, Schaeffer E, Rollemma H, Lu Y, Mansbach RS, Chambers LK, Rovetti CC, Schulz DW, Tingley FD 3rd, O'Neill BT. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *J Med Chem* 2005;48:3474–3477. [PubMed: 15887955]
- Dhar S, Nagy F, McIntosh JM, Sapru HN. Receptor subtypes mediating depressor responses to microinjections of nicotine into medial NTS of the rat. *Am J Physiol Regul Integr Comp Physiol* 2000;279:R132–R140. [PubMed: 10896874]
- Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *J Natl Cancer Inst* 2000;92:106–111. [PubMed: 10639511]
- Etter JF, Lukas RJ, Benowitz NL, West R, Dresler CM. Cytisine for smoking cessation: a research agenda. *Drug Alcohol Depend* 2008;92:3–8. [PubMed: 17825502]
- Evans DE, Drobos DJ. Nicotine self-medication of cognitive-attentional processing. *Addict Biol* 2009;14:32–42. [PubMed: 18855804]
- Faessel HM, Smith BJ, Gibbs MA, Gobey JS, Clark DJ, Burstein AH. Single-dose pharmacokinetics of varenicline, a selective nicotinic receptor partial agonist, in healthy smokers and nonsmokers. *J Clin Pharmacol* 2006;46:991–998. [PubMed: 16920893]
- Fowler CD, Arends MA, Kenny PJ. Subtypes of nicotinic acetylcholine receptors in nicotine reward, dependence, and withdrawal: evidence from genetically modified mice. *Behav Pharmacol* 2008;19:461–484. [PubMed: 18690103]
- Hays JT, Ebbert JO. Varenicline for tobacco dependence. *N Engl J Med* 2008;359:2018–2024. [PubMed: 18987369]
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br. J. Addictions* 1991;86:1119–1127.
- Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986;43:289–294. [PubMed: 3954551]
- Hughes JR, Hatsukami DK. Effects of three doses of transdermal nicotine on post-cessation eating, hunger and weight. *J Subst Abuse* 1997;9:151–159. [PubMed: 9494946]

- Ji S, Tosaka T, Whitfield BH, Katchman AN, Kandil A, Knollmann BC, Ebert SN. Differential rate responses to nicotine in rat heart: evidence for two classes of nicotinic receptors. *J Pharmacol Exp Ther* 2002;301:893–899. [PubMed: 12023516]
- Kenford SL, Fiore MC, Jorenby DE, Smith SS, Wetter D, Baker TB. Predicting smoking cessation. Who will quit with and without the nicotine patch. *Jama* 1994;271:589–594. [PubMed: 8301790]
- Kenford SL, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Predicting relapse back to smoking: contrasting affective and physical models of dependence. *J Consult Clin Psychol* 2002;70:216–227. [PubMed: 11860048]
- Lerman C, Roth D, Kaufmann V, Audrain J, Hawk L, Liu A, Niaura R, Epstein L. Mediating mechanisms for the impact of bupropion in smoking cessation treatment. *Drug Alcohol Depend* 2002;67:219–223. [PubMed: 12095672]
- Mendelson JH, Sholar MB, Goletiani N, Siegel AJ, Mello NK. Effects of low- and high-nicotine cigarette smoking on mood states and the HPA axis in men. *Neuropsychopharmacology* 2005;30:1751–1763. [PubMed: 15870834]
- Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at $\alpha 4\beta 2$ and a full agonist at $\alpha 7$ neuronal nicotinic receptors. *Mol Pharmacol* 2006;70:801–805. [PubMed: 16766716]
- Newhouse PA, Sunderland T, Narang PK, Mellow AM, Fertig JB, Lawlor BA, Murphy DL. Neuroendocrine, physiologic, and behavioral responses following intravenous nicotine in nonsmoking healthy volunteers and in patients with Alzheimer's disease. *Psychoneuroendocrinology* 1990;15:471–484. [PubMed: 1966302]
- Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, Anziano R, Reeves K. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med* 2006;166:1571–1577. [PubMed: 16908789]
- Patterson F, Jepson C, Strasser AA, Loughhead J, Perkins KA, Gur RC, Frey JM, Siegel S, Lerman C. Varenicline improves mood and cognition during smoking abstinence. *Biol Psychiatry* 2009;65:144–149. [PubMed: 18842256]
- PDR. Physicians' Desk Reference:PDR. Medical Economics Data, Medical Economics Data. 2009
- Perkins KA, DiMarco A, Grobe JE, Scierka A, Stiller RL. Nicotine discrimination in male and female smokers. *Psychopharmacology (Berl)* 1994;116:407–413. [PubMed: 7701041]
- Picciotto MR, Corrigan WA. Neuronal systems underlying behaviors related to nicotine addiction: neural circuits and molecular genetics. *J Neurosci* 2002;22:3338–3341. [PubMed: 11978809]
- Pickworth WB, Fant RV. Endocrine effects of nicotine administration, tobacco and other drug withdrawal in humans. *Psychoneuroendocrinology* 1998;23:131–141. [PubMed: 9621394]
- Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurements* 1977;1:385–401.
- Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J. 'Oops! ': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia* 1997;35:747–758. [PubMed: 9204482]
- Rollema H, Coe JW, Chambers LK, Hurst RS, Stahl SM, Williams KE, Hogg RC, Bertrand D. Rationale, pharmacology and clinical efficacy of partial agonists of $\alpha 4\beta 2$ nACh receptors for smoking cessation. *Trends Pharmacol Sci* 2007;28:316–325. [PubMed: 17573127]
- SAS Institute Inc.. The SAS System for Windows. Cary, NC: SAS Institute Inc.; 2007.
- Sofuoglu M, Mouratidis M, Yoo S, Culligan K, Kosten T. Effects of tiagabine in combination with intravenous nicotine in overnight abstinent smokers. *Psychopharmacology (Berl)* 2005;181:504–510. [PubMed: 15983800]
- Sofuoglu M, Poling J, Mouratidis M, Kosten T. Effects of topiramate in combination with intravenous nicotine in overnight abstinent smokers. *Psychopharmacology (Berl)* 2006;184:645–651. [PubMed: 16432681]
- Sofuoglu M, Waters AJ, Mooney M. Modafinil and nicotine interactions in abstinent smokers. *Hum Psychopharmacol* 2008a;23:21–30. [PubMed: 17868195]
- Sofuoglu M, Waters AJ, Mooney M, O'Malley SS. Minocycline reduced craving for cigarettes but did not affect smoking or intravenous nicotine responses in humans. *Pharmacol Biochem Behav* 2009;92:135–140. [PubMed: 19041336]

- Sofuoglu M, Yoo S, Hill KP, Mooney M. Self-administration of intravenous nicotine in male and female cigarette smokers. *Neuropsychopharmacology* 2008b;33:715–720. [PubMed: 17534380]
- Son BK, Markovitz JH, Winders S, Smith D. Smoking, nicotine dependence, and depressive symptoms in the CARDIA Study. Effects of educational status. *Am J Epidemiol* 1997;145:110–116. [PubMed: 9006307]
- Stoops WW, Vansickel AR, Glaser PE, Rush CR. The influence of acute varenicline administration on smoking and eating behavior in humans. *Pharmacol Biochem Behav* 2008;91:165–169. [PubMed: 18675291]
- Waters AJ, Sayette MA, Franken I, Schwartz J, Paty JA. Generalizability of carry-over effects in the emotional Stroop task. *Behavior Research and Therapy*. 2005 (in press).
- Waters AJ, Sayette MA, Wertz JM. Carry-over effects can modulate emotional Stroop effects. *Cognition and Emotion* 2003;17:501–509.
- Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988;54:1063–1070. [PubMed: 3397865]
- Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol* 1977;106:203–214. [PubMed: 900119]
- West R, Baker CL, Cappelleri JC, Bushmakina AG. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology (Berl)* 2008;197:371–377. [PubMed: 18084743]

Fig. 1.

Average ($\pm$ SEM) heart rate, systolic and diastolic pressure responses to 0.1, 0.4, and 0.7 mg / 70 kg intravenous nicotine administration under placebo treatment. The doses were given in an ascending order, 30 minutes apart. Measurements were taken just before and 1, 2, 3, 5, 8, 10, 15 and 25 min after dose delivery. Some of the time-point error bars are not shown for clarity.

Fig. 2.

Average ($\pm$ SEM) systolic blood pressure, diastolic blood pressure, and heart rate responses to 0.1, 0.4 and 0.7 mg/ 70 kg intravenous nicotine under placebo and varenicline conditions. Bars represent the change (maximum post dose-baseline). * indicates significant treatment differences ($p < 0.016$).

Fig. 3.

Average (with standard error of the mean – SEM) selected subjective responses to 0.1, 0.4, and 0.7 mg/70 kg intravenous nicotine administration under placebo treatment. The doses were given in an ascending order, 30 minutes apart. Measurements were taken at 1, 3, 5, 8, and 10 min after dose delivery. Some of the error bars are not shown for clarity.

Fig. 4. Average (+SEM) peak subjective responses to 0.1, 0.4, and 0.7 mg/ 70 kg intravenous nicotine under placebo and varenicline conditions. Bars represent the mean maximum score. * indicates significant treatment differences ($p < 0.016$).

Table 1

Mean RT (SD) on the modified Stroop Task (N = 12).

	Pre		Post		Pre		Post	
	Smoking	Neutral	Smoking	Neutral	NA	Neutral	NA	Neutral
Varenicline	660.1 (137.8)	652.1 (115.5)	624.2 (100.1)	618.6 (104.7)	665.8 (177.1)	644.8 (122.8)	631.7 (128.6)	618.6 (108.5)
Placebo	722.3 (131.3)	702.3 (148.6)	693.1 (129.4)	686.7 (134.1)	679.0 (104.1)	692.5 (117.5)	641.3 (114.9)	661.5 (111.1)

Key: Smoking = smoking words; NA = negative affect words; Neutral = neutral words; Pre = pre-nicotine; Post = post-nicotine