Pharmacology, Biochemistry and Behavior 91 (2008) 165–169

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

The influence of acute varenicline administration on smoking and eating behavior in humans

William W. Stoops [a,*], Andrea R. Vansickel [a,b], Paul E.A. Glaser [c,d], Craig R. Rush [a,b,c]

[a] Department of Behavioral Science, University of Kentucky College of Medicine, United States
[b] Department of Psychology, University of Kentucky College of Arts and Sciences, United States
[c] Department of Psychiatry, University of Kentucky College of Medicine, United States
[d] Department of Anatomy and Neurobiology, University of Kentucky College of Medicine, United States

ARTICLE INFO

Article history:
Received 3 April 2008
Received in revised form 25 June 2008
Accepted 8 July 2008
Available online 13 July 2008

Keywords:
Varenicline
Methylphenidate
Eating
Smoking
Humans

ABSTRACT

Varenicline (Chantix®) is a novel smoking-cessation agent that acts at a number of nicotinic acetylcholine receptors. The aim of this study was to determine the behavioral effects of acute varenicline administration in human subjects. The effects of doses of varenicline (0.5, 1 and 2 mg), methylphenidate (40 mg; positive control) and placebo were assessed in 8 (7 males, 1 female) cigarette smokers. Staggered, double blind dosing was used to examine eating and smoking behavior during the peak effects of varenicline and methylphenidate. Starting at the published time to peak plasma levels of these drugs, subjects were allowed to smoke and eat ad libitum for 4 h. Acute varenicline was devoid of behavioral effects. Methylphenidate produced prototypical stimulant-like effects (e.g., increased smoking behavior; decreased caloric intake). The present results indicate that acute varenicline administration does not alter smoking behavior although the low number of subjects limits the ability to detect small effects. Future research should examine the effects of chronic varenicline on smoking and eating behavior in humans, particularly using operant techniques to determine whether varenicline alters the reinforcing effects of cigarettes and food in humans.

1. Introduction

Varenicline (Chantix®) is novel smoking-cessation agent that produces its effects via partial agonist activity at α4β2 nicotinic acetylcholine receptors (nAchRs) (Rollema et al., 2007a). Varenicline has been shown to have high relative affinity for α4β2 nAchRs, but the intrinsic efficacy of varenicline to produce evoked inward currents is approximately 50 to 66% that of nicotine (Coe et al., 2005; Rollema et al., 2007b). Varenicline likely produces its effects via interactions with α7 and α3β4 receptors, as well (Mihalak et al., 2006). Varenicline-induced dopamine turnover, a measure of dopamine utilization and synthesis, is approximately 33% of the maximal effect observed with nicotine (Coe et al., 2005). Microdialysis measures of dopamine release also reveal that varenicline-induced dopamine efflux is 40% less than that produced by nicotine and nicotine-evoked dopamine efflux is attenuated by varenicline (Coe et al., 2005). Mecamylamine blocks varenicline-induced dopamine efflux, indicating that this effect is mediated by nicotinic systems (Rollema et al., 2007b).

Results of nonhuman laboratory animal experiments are concordant with the pharmacology of varenicline. In a series of studies, the reinforcing efficacy of varenicline was less than that of nicotine on a progressive-ratio schedule, even though varenicline did function as a reinforcer (Rollema et al., 2007b). Moreover, varenicline was shown to attenuate the reinforcing effects of nicotine on a fixed-ratio schedule when administered acutely as a pretreatment agent (Rollema et al., 2007b). Importantly, this effect was selective in that varenicline administration did not alter food-maintained responding. In a drug-discrimination study reported in the same paper, varenicline produced dose-dependent increases in nicotine-appropriate responding, fully substituting at the highest doses tested. Mecamylamine pretreatment blocked this effect (Rollema et al., 2007b). Taken together, the results of preclinical studies supported the use of varenicline as a smoking-cessation agent.

A number of placebo-controlled, clinical trials have been published demonstrating varenicline's safety and efficacy in decreasing cigarette smoking (Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006). The results of these trials showed that varenicline was more effective than placebo and sustained-release bupropion as a smoking-cessation agent. For example, in one study, during the last four weeks of treatment, nearly 44% of subjects randomized to varenicline were likely to be continuously abstinent from cigarette smoking relative to nearly 30 and 18% for bupropion and placebo, respectively (Jorenby et al., 2006).

Given positive preclinical and clinical findings with varenicline, it is important to note that there are few published human laboratory studies on the behavioral effects of varenicline. Two recently published studies warrant mention. First, one pharmacokinetic study examined the effects of acute doses of varenicline in smokers and nonsmokers

* Corresponding author. 140 College of Medicine Office Building, Lexington, KY 40536-0086, United States.
E-mail address: william.stoops@uky.edu (W.W. Stoops).

0091-3057/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2008.07.001

(Faessel et al., 2006). In that study, acute administration of varenicline was shown to produce its peak blood levels approximately 3 h after dosing (Faessel et al., 2006). Varenicline was safe and tolerable up to 1 mg in nonsmokers and up to 3 mg in smokers when administered acutely. The most common adverse events reported in that study were nausea and vomiting. In another study, the abuse potential of varenicline (1 and 3 mg) was compared to that of *d*-amphetamine (15 and 30 mg) in smokers and nonsmokers (McColl et al., 2008). In that study, *d*-amphetamine produced prototypical stimulant-like effects (e.g., increased drug liking) whereas varenicline was generally devoid of behavioral effects, with the exception of some negative subject-rated effects produced by the 3 mg dose, in both smokers and nonsmokers.

The purpose of the present study was to examine further the behavioral effects of acute varenicline administration under controlled-laboratory conditions in human cigarette smokers. Importantly, this study sought to examine the influence of varenicline on an array of behaviors, including smoking and eating, as well as subject-rated and cardiovascular effects. To this end, a range of doses of varenicline (0.5, 1 and 2 mg) and placebo was administered to eight healthy subjects. After dosing, smoking and eating behavior were measured using an ad libitum cigarette and food access model previously shown to be sensitive to the effects of stimulant drugs (Rush et al., 2005; Vansickel et al., 2007). A single dose of methylphenidate, 40 mg, was also included as a positive control. This dose has been shown to produce stimulant-like behavioral effects, increase smoking behavior and decrease eating behavior (Rush et al., 2005; Vansickel et al., 2007).

2. Methods

2.1. Subjects

Eight healthy adult cigarette smokers (7 males, 1 female) were recruited via newspaper ads, flyers and word-of-mouth to participate in this experiment. Potential subjects had to meet the following inclusion criteria: (1) report smoking 10–20 cigarettes daily (mean=16), (2) not attempting to quit smoking, (3) score less than 18 on an Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale, (4) no significant medical or psychiatric disorders, other than nicotine dependence, (5) negative urine pregnancy test for women (Mainline confirms human chorionic gonadotropin) and (6) no medical contraindications to stimulant drugs. Subjects were excluded if they had a history of ADHD or other Axis I psychiatric disorders. Subjects were compensated for their participation.

Subjects completed questionnaires assessing drug use, medical and psychiatric histories and provided written informed consent before participating. Drug urine tests conducted during screening were negative for amphetamine, benzodiazepines, barbiturates and cocaine (OnTrak Teststik, Lake Forest, CA).

2.2. General procedures

The Institutional Review Board of the University of Kentucky Medical Center approved this study and the informed consent document, which was signed by all subjects prior to enrollment. Subjects enrolled as outpatients at the Laboratory of Human Behavioral Pharmacology (LHBP) at the University of Kentucky Medical Center. Subjects were informed that during their participation, they would receive various drugs and these could include placebo, medications indicated for smoking cessation and medications indicated for ADHD. Subjects were told that the purpose of the study was to see how these drugs affect mood and behavior. Other than receiving this general information, subjects were blind to the type of drug administered and were given no instructions regarding what they were "supposed" to do or what outcomes might be expected.

The experimental procedures used in the current experiment have been described in detail previously (Rush et al., 2005; Vansickel et al., 2007). Briefly, subjects completed one practice session to familiarize them with the laboratory and daily procedures. Subjects then reported to the LHBP for a total of six experimental sessions. Arrival time varied across subjects, but was held constant for individual subjects. Most subjects arrived at the LHBP at approximately 08:00 AM and all provided a urine sample before drug administration, which was screened for the presence of amphetamine, barbiturates, benzodiazepines, cocaine, opioids and THC as well as an expired air specimen, which was assayed for the presence of alcohol using a hand-held breathalyzer (Intoximeters, Inc., St. Louis, MO). In order for an experimental session to commence, drug urine screens had to be negative for cocaine, amphetamine, benzodiazepines, barbiturates and opioids, expired air specimens had to be negative for the presence of alcohol and CO levels had to be ≤10 ppm.

A first set of capsules containing varenicline or placebo was administered approximately 1 h after arrival (e.g., 9:00 AM). A second set of capsules containing methylphenidate or placebo was administered approximately 2 h after the first set of capsules (e.g., 11:00 AM). This staggered dosing was used because varenicline and methylphenidate vary in their time to peak blood levels following administration (3 h for varenicline, 1 h for methylphenidate) (Dayton et al., 1970; Faessel et al., 2006). Varenicline and methylphenidate were never administered in combination. One hour after the second capsule set administration (e.g., 12:00 PM), subjects were provided with a pack of their preferred brand of cigarettes and an assortment of snacks and decaffeinated drinks. Subjects were then allowed to smoke, eat and drink ad libitum for 4 h. Subjects completed the self-reported drug-effect questionnaires 1, 2, 3, 4 and 5 h after drug administration. As a safety precaution, heart rate and blood pressure were recorded using an automated blood-pressure monitor (DINAMAP XL, Johnson and Johnson, Alexandria, TX) hourly after the initial capsule administration. Carbon monoxide levels were recorded immediately before the subject completed the self-reported drug-effect questionnaires.

Outcome measures used to assess smoking included total cigarettes smoked, total puffs and expired carbon monoxide (CO) levels. Experimental sessions were digitally recorded and smoking within each session was double-scored by a primary and secondary observer, both of whom were blind to the dose conditions. If the interobserver reliability was greater than or equal to 85%, data from the primary observer were used for data analysis. If the interobserver reliability was less than 85%, the session was rescored by both observers. Interobserver reliabilities exceeded 98%.

Food intake after drug administration was measured to determine the effects of varenicline and methylphenidate on eating behavior. Both the number of items consumed and the total caloric intake were determined. The number of items consumed was calculated at the end of each experimental session by counting the number of food packages and beverage containers opened by the subject. To calculate caloric intake, the available food items and beverages were weighed before being served. At the end of the session, if a food item or beverage was only partially consumed, it was reweighed and the proportion consumed was multiplied by the caloric content of the entire food item. If a food or beverage item was completely consumed, the caloric content for the entire item was recorded. The number of calories consumed for each food item and beverage was then summed to calculate the total caloric intake for the experimental session.

Subject-rated drug-effect questionnaires included a locally developed Drug-Effect Questionnaire and an Adjective-Rating Scale (Rush et al., 2003; Oliveto et al., 1992). As noted above, these questionnaires were completed approximately 30 min before the first capsule set administration and 1, 2, 3, 4 and 5 h after the second capsule set administration. Approximately 5 h after the second set of capsules was administered, subjects completed a five-item cigarette rating scale as well as a five-item food rating scale which served to evaluate the quality of the cigarettes and food that were freely available throughout the session. Other than the words "cigarettes" and "food," these scales were identical in wording. The items rated were: (1) Did you "ENJOY"

your cigarettes/food more than usual during today's session?; (2) Did you "CRAVE" cigarettes/food more than usual during today's session?; (3) Did your cigarettes/food "TASTE" better than usual during today's session?; (4) Did you "LIKE" your cigarettes/food more than usual during today's session?; and (5) Did you get more "PLEASURE" from your cigarettes/food during today's session? Subjects responded to these questions using five options: Not At All, A Little Bit, Moderately, Quite A Bit and Extremely (scored numerically from 0 to 4).

2.3. Drug administration

The drug conditions were varenicline (0.5, 1 and 2 mg), methylphenidate (40 mg) and placebo. Each active dose of varenicline and methylphenidate was tested once, while placebo was tested twice. Dosing orders for subjects were determined randomly, with the exception that the highest dose of varenicline was never administered prior to administration of a lower dose. All dose conditions were administered in a double-blind, double-dummy fashion. Commercially available drug (varenicline from Pfizer Inc. New York, NY; methylphenidate from CelTech, Rochester, NY) was over-encapsulated in a size 0 capsule to prepare the doses. Cornstarch was used to fill the remainder of these capsules. Placebo capsules were prepared by filling a size 0 capsule with cornstarch. At least 48 h separated all drug administrations.

2.4. Data analysis

Data were analyzed statistically as raw scores for all measures. Effects were considered significant for $p \leq 0.05$. Preliminary analyses indicated no significant differences between the two placebo sessions on primary outcome variables (i.e., eating and smoking behavior). For all subsequent analyses, data were averaged across the two placebo sessions.

For all measures, data were analyzed by one-factor repeated measures analysis of variance (ANOVA) with Dose (0.5, 1 and 2 mg varenicline, 40 mg methylphenidate and placebo) as the factor (Prism, Graphpad Software Inc., San Diego, CA). If the effect of Dose attained statistical significance, Fisher protected least significant difference (PLSD) post hoc tests were conducted to compare each of the active dose conditions to placebo. Carbon monoxide levels were analyzed as peak effect (i.e., maximum level observed during the 4-h smoking period). For the Adjective-Rating Scale, Drug Effect Questionnaire and cardiovascular measures, data after the first hour during the ad libitum session was considered uninterpretable because subjects determined the amount they smoked (i.e., they smoked varying numbers of cigarettes with different nicotine contents). For this reason, only data collected at the beginning of the ad libitum session were used in the analyses for these measures.

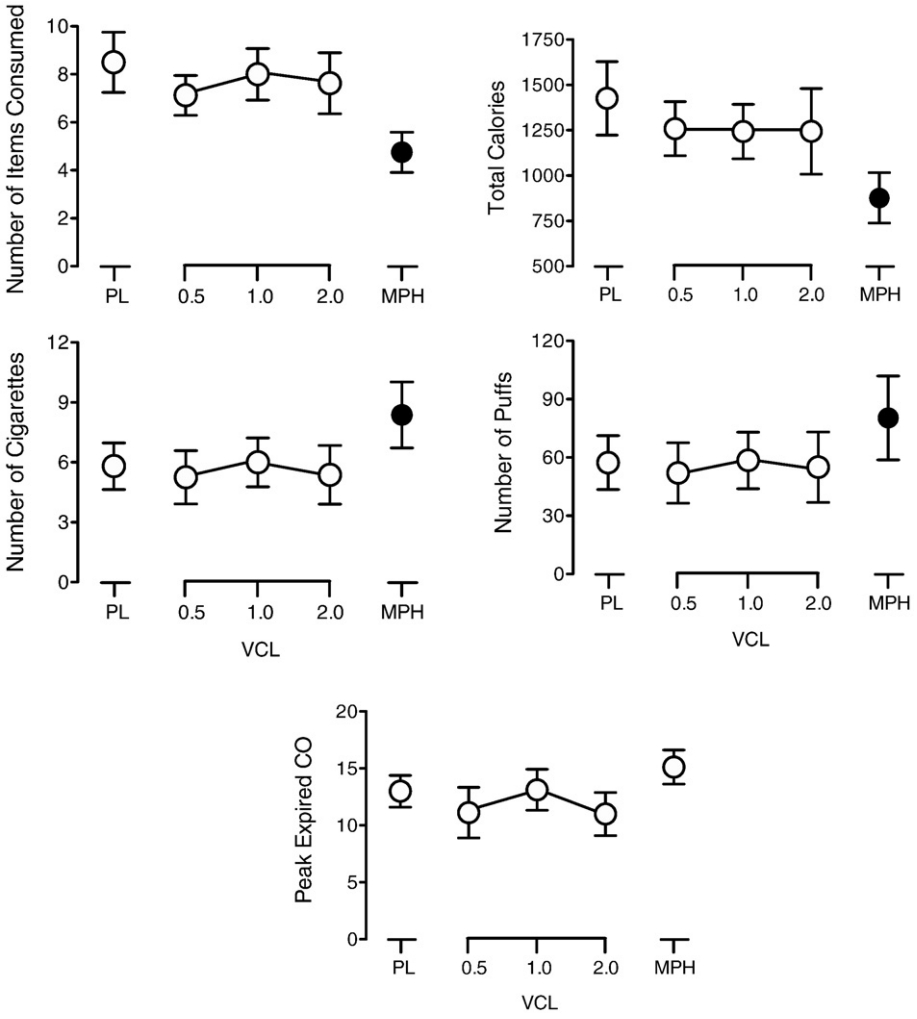

Fig. 1. Dose–response functions for number of items consumed (top left panel), total calories consumed (top right panel), number of cigarettes (middle left panel), number of puffs (middle right panel) and peak expired CO (bottom panel) during the ad libitum session. *x*-Axes: varenicline (VCL) dose in mg and 40 mg methylphenidate (MPH); data points above PL designate placebo values. Data points show means of 8 subjects. Brackets indicate one S.E.M. Filled symbols indicate those values that are significantly different from the placebo value using Fisher PLSD post hoc tests.

3. Results

3.1. Smoking behavior

The one-way ANOVA that included the five experimental conditions revealed a significant effect of Dose on the number of cigarettes smoked ($F_{4,28}$=6.0, p<0.01) and number of puffs ($F_{4,28}$=3.4, p<0.05) within the ad libitum session. Post hoc tests revealed that only methylphenidate increased the number of cigarettes and puffs significantly above placebo levels (Fig. 1). A trend was observed for peak expired CO ($F_{4,28}$=2.6, p=0.06) which is likely attributable to increases on this measure following methylphenidate administration (Fig. 1). No significant effects were detected in the one-way ANOVA that included the five experimental conditions on the Cigarette Rating Scale.

3.2. Eating behavior

The one-way ANOVA that included the five experimental conditions revealed a significant effect of Dose on the number of items consumed ($F_{4,28}$=5.5, p<0.01) and total caloric intake ($F_{4,28}$=3.8, p<0.05) within the ad libitum session. Post hoc tests revealed that only methylphenidate decreased the number of items and calories consumed significantly below placebo levels (Fig. 1). No significant effects were detected in the one-way ANOVA that included the five experimental conditions on the Food Rating Scale.

3.3. Subject-rated effects

The one-way ANOVA that included the five experimental conditions revealed a significant effect of Dose on the total score of the Sedative Subscale of the Adjective Rating Scale ($F_{4,28}$=2.8, p<0.05). Post hoc tests revealed that only methylphenidate decreased scores on this scale significantly below placebo levels (data not shown). No significant effects were detected in the one-way ANOVA that included the five experimental conditions on any other subject-rated measures.

3.4. Physiological effects

No significant effects were detected in the one-way ANOVA that included the five experimental conditions on systolic or diastolic blood pressure or heart rate.

4. Discussion

The results of the present experiment demonstrate that varenicline, over a range of therapeutic and supra-therapeutic doses, resulted in no adverse events when administered acutely to cigarette smokers. In addition, combining cigarette smoking and varenicline did not result in any adverse events. These findings are concordant with clinical usage, in that smokers are instructed to continue to smoke for a short period after initiating varenicline therapy (www.chantix.com). Varenicline was essentially devoid of other behavioral effects. The results of the present experiment are also concordant with our previous findings, in that increases in cigarette smoking behavior and decreases in eating behavior were observed following methylphenidate administration.

That varenicline did not alter cigarette smoking behavior is discordant with previously reported findings with nonhuman animals (Rollema et al., 2007b). In that study, pretreatment with varenicline significantly attenuated nicotine-maintained responding. The reason for the discrepancy between human and nonhuman laboratory findings is unknown, but could be due to differences between species or methodologies (i.e., spontaneous smoking versus operant responding for nicotine) or the relatively small sample enrolled in the present experiment (see below). The present findings are also discordant with those from clinical trials demonstrating the efficacy of varenicline for smoking cessation (Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006). Again, the reason for this discrepancy is unknown, but could be due to differences in dosing (acute versus chronic), population characteristics (non-treatment seeking versus treatment seeking smokers) or sample size. One important aspect of the present study is that spontaneous smoking was studied by giving subjects ad libitum access to tobacco cigarettes following acute administration of a pretreatment agent. This model is sensitive to the influence of stimulants on smoking behavior (Rush et al., 2005; Vansickel et al., 2007), but may not be as sensitive to the effects of putative or proven medications for nicotine dependence in a predictive manner (Benowitz et al., 1998; Cousins et al., 2001; Hatsukami et al., 1998, 2007). In studies employing nicotine patches, high dose levels are required to effectively decrease cigarette smoking (Benowitz et al., 1998; Hatsukami et al., 2007). Importantly, these high dose levels are associated with increased side-effects (Hatsukami et al., 2007). In another study, acute administration of bupropion actually increased cigarette smoking in an ad libitum access model (Cousins et al., 2001). Thus, while nicotine replacement, bupropion and varenicline are clearly effective as cigarette smoking cessation agents, ad libitum laboratory smoking models may not be an optimal screen for medication efficacy. There is some evidence to suggest that the use of operant techniques may be more sensitive to the effects of medications for nicotine dependence on nicotine or cigarette self-administration (Perkins et al., 2001; Shahan et al., 2000).

The general dearth of subject-rated effects and effects on eating behavior observed following varenicline administration are concordant with previously published research (McColl et al., 2008; Rollema et al., 2007b). In the first study, 1 and 3 mg varenicline were also essentially devoid of effects (i.e., were placebo-like), with the exception that the higher dose did produce some negative effects (McColl et al., 2008). Importantly, that dose is higher than what is used clinically, is associated with nausea and may not be well tolerated by nonsmokers (Faessel et al., 2006). In the second study, varenicline did not alter food maintained responding in rats (Rollema et al., 2007b).

As has been demonstrated previously, methylphenidate produced prototypical stimulant-like effects (Rush et al., 2005; Vansickel et al., 2007). The increases observed in smoking behavior and decreases observed in eating behavior are similar to those reported in our previous research. These results lend additional support to the notion that dopamine agonists selectively increase smoking behavior (see Vansickel et al., 2007). In addition, methylphenidate produced modest stimulant-like subject-rated effects (e.g., decreased scores on the Sedative Subscale of the Adjective Rating Scale). More robust effects on subject ratings and cardiovascular indices have been observed with similar doses, however, the analytical strategy and study design (i.e., subjects were smoking ad libitum one hour after drug administration and effects could not be solely attributed to drug administration or smoking thereafter) likely limited our ability to observe more effects (Rush et al., 2001; Stoops et al., 2004; 2005).

There are a number of limitations to the present experiment that need to be acknowledged. First, the low number of subjects enrolled likely limited our ability to detect a significant, small effect of varenicline. In the present study, the maximum change produced by varenicline relative to placebo on two primary outcome variables, number of cigarettes smoked and number of food items consumed, demonstrated relatively small effect sizes (Cohen's d's of 0.15 and 0.46, respectively). Our power to detect the significance of these effects with 8 subjects was 0.18 and 0.20, respectively. Such limited power suggests that a much larger sample would be necessary to detect the statistical significance of these effects. Second, the gender distribution in the present study was not equal and may limit the generalizability of the findings. Third, varenicline was administered acutely, which may partially account for the lack of effect observed here. When used clinically, varenicline is administered chronically.

In conclusion, the present study demonstrates that varenicline, when administered acutely is essentially devoid of behavioral effects. Future research should examine the effects of chronically administered

varenicline on a number of consummatory behaviors, particularly using operant methodology, as opposed to ad libitum access models.

Acknowledgements

This work was supported by seed funds from the Departments of Behavioral Science (to WWS) and Psychiatry (to CRR) at the University of Kentucky College of Medicine. The authors declare no financial relationships with persons or organizations that could be perceived to bias the work described herein. We would like to thank Frances Wagner, R.N. for excellent medical supervision and Neena Khanna, Ph.D. for excellent technical supervision of this study.

References

Benowitz NL, Zevin S, Jacob 3rd P. Suppression of nicotine intake during ad libitum cigarette smoking by high dose transdermal nicotine. J Pharmacol Exp Ther 1998;287:958–62.

Coe JW, Brooks PR, Vetelino MG, Wirtz MC, Arnold EP, Huang J, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. J Med Chem 2005;48:3474–7.

Cousins MS, Stamat HM, de Wit H. Acute doses of d-amphetamine and bupropion increase cigarette smoking. Psychopharmacology 2001;157:243–53.

Dayton PG, Read JM, Ong W. Physiological disposition of methylphenidate C14 in man. Fed Proc 1970;29:354.

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;46:991–8.

Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006;296:47–55.

Hatsukami D, Lexau B, Nelson D, Pentel PR, Sofuoglu M, Goldman A. Effects of cotinine on cigarette self-administration. Psychopharmacology 1998;138:184–9.

Hatsukami D, Mooney M, Murphy S, LeSage M, Babb D, Hecht S. Effects of high dose transdermal nicotine replacement in cigarette smokers. Pharmacol Biochem Behav 2007;86:132–9.

Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006;296:56–63.

Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. Mol Pharmacol 2006;70:801–5.

McColl SL, Burstein AH, Reeves KR, Billing Jr CB, Stolar M, Sellers EM. Human abuse liability of the smoking cessation drug varenicline in smokers and nonsmokers. Clin Pharmacol Ther 2008;83:607–14.

Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, et al. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. Arch Intern Med 2006;166:1561–8.

Oliveto AH, Bickel WK, Hughes JR, Shea PJ, Higgins ST, Fenwick JW. Caffeine drug discrimination in humans: acquisition, specificity and correlation with self-reports. J Pharmacol Exp Ther 1992;261:885–94.

Perkins KA, Fonte C, Meeker J, White W, Wilson A. The discriminative stimulus and reinforcing effects of nicotine in humans following nicotine pretreatment. Behav Pharmacol 2001;12:35–44.

Rollema H, Coe JW, Chambers LK, Hurst RS, Stahl SM, Williams KE. Rationale, pharmacology and clinical efficacy of partial agonists of alpha4beta2 nACh receptors for smoking cessation. Trends Pharmacol Sci 2007a;28:316–25.

Rollema H, Chambers LK, Coe JW, Glowa J, Hurst RS, Lebel LA, et al. Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. Neuropharmacology 2007b;52:985–94.

Rush CR, Essman WD, Simpson CA, Baker RW. Reinforcing and subject-rated effects of methylphenidate and d-amphetamine in non-drug-abusing humans. J Clin Psychopharmacol 2001;21:273–86.

Rush CR, Stoops WW, Hays LR, Glaser PE, Hays LS. Risperidone attenuates the discriminative-stimulus effects of d-amphetamine in humans. J Pharmacol Exp Ther 2003;306:195–204.

Rush CR, Higgins ST, Vansickel AR, Stoops WW, Lile JA, Glaser PE. Methylphenidate increases cigarette smoking. Psychopharmacology 2005;181:781–9.

Shahan TA, Odum AL, Bickel WK. Nicotine gum as a substitute for cigarettes: a behavioral economic analysis. Behav Pharmcol 2000;11:71–9.

Stoops WW, Glaser PE, Fillmore MT, Rush CR. Reinforcing, subject-rated, performance and physiological effects of methylphenidate and d-amphetamine in stimulant abusing humans. J Psychopharmacol 2004;18:534–43.

Stoops WW, Lile JA, Glaser PE, Rush CR. Discriminative stimulus and self-reported effects of methylphenidate, D-amphetamine and triazolam in methylphenidate-trained humans. Exp Clin Psychopharmacol 2005;13:56–64.

Vansickel AR, Stoops WW, Glaser PE, Rush CR. A pharmacological analysis of stimulant-induced increases in smoking. Psychopharmacology 2007;193:305–13.

www.chantix.com Accessed 2 April 2008.