Original Investigation

Efficacy of Varenicline to Prompt Quit Attempts in Smokers Not Currently Trying to Quit: A Randomized Placebo-Controlled Trial

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Abstract

Introduction: Nicotine replacement therapy to aid smoking reduction increases the probability of a future quit attempt among smokers not currently planning to quit smoking. We tested whether varenicline, a partial nicotine agonist, would also increase future quit attempts.

Methods: This randomized, placebo-controlled trial recruited 218 smokers who were interested in quitting but had no plans to quit in the next month. Participants used varenicline (2 mg/day) or placebo for 2–8 weeks plus received brief counseling on methods to reduce cigarettes/day. The primary measure was the incidence of a quit attempt within 6 months of study entry. Secondary measures were point prevalence abstinence, motivation to stop smoking, and reduction in cigarettes/day.

Results: Varenicline increased the incidence of a quit attempt more than placebo at the Nebraska site (73% vs. 41%; $p < .001$) but not at the Vermont site (45% vs. 51%; $p = .45$). Varenicline increased most other measures of quit attempts, motivation and abstinence, independent of site. The beneficial effects of varenicline in quit attempts appeared to be mediated by greater reductions in cigarettes/day, dependence, craving, and cigarette satisfaction. Varenicline had a greater effect on quit attempts in less-dependent smokers, in minority smokers, and in those who had less prior cessation or reduction activity. Adverse events were minimal.

Conclusions: Varenicline increased quit attempts in smokers who are not currently trying to quit at one of the two study sites and improved most all secondary outcomes independent of site. This appeared to be due to decreasing cigarettes/day and level of dependence.

Introduction

The majority of smokers wish to quit, but are not ready to make a quit attempt (Wewers, 2003). Several tobacco control policies, for example, increased taxes, increased smoking restrictions, and counter-marketing, have been used to increase the prevalence of quit attempts in a given year among adult U.S. smokers. Despite these efforts, the annual quit attempts have actually decreased, in the past 17 years from 47% in 1993 to 40% in 2007 (Thorne, Malarcher, Maurice, & Caraballo, 2008). In addition, only 8% of U.S. smokers plan to quit in the next month (Boyle et al., 2000; Wewers, Stillman, Hartmann, & Shopland, 2003). Similar results have occurred in other countries with significant tobacco-control activities (Boyle et al., 2000).

These results suggest a need for new methods to prompt smokers to make a quit attempt. Although most efforts to prompt quit attempts have been focused on policy changes, efforts focused on individual smokers have included physician advice (Stead, Bergson, & Lancaster, 2008), motivational interviewing (Rubak, Sandbaek, Lauritzen, & Christensen, 2005), and proactive messaging (Velicer, Prochaska, & Redding, 2006), all of which have produced some success. Recent studies by ourselves and others have shown that reducing smoking is another method to prompt quitting (Hughes & Carpenter, 2006). This may be because when smokers reduce their smoking (a) their self-efficacy about quitting increases, (b) they learn skills to combat urges and high-risk-for-relapse situations, (c) conditioned cravings to cues to smoke are disrupted, and (d) their level of nicotine dependence decreases. Many prior studies have shown that nicotine replacement therapies (NRTs) can aid in this reduction (Hughes & Carpenter, 2005). In fact, in Europe, several countries have approved NRT for reduction in smokers who plan to quit at a later date (in the United States, NRT is indicated only for those who are currently making a quit attempt). Whether

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other medications would also help reduction and later quitting has been tested in only one study (of bupropion) and that study produced negative results (Hughes & Carpenter, 2006).

The current study tested the efficacy of varenicline use in ambivalent smokers to prompt new quit attempts. Varenicline is a partial nicotine agonist that is approved in the United States for use as a smoking cessation aid among smokers who are currently trying to quit (Cahill, Stead, & Lancaster, 2008; Keating & Siddiqui, 2006). One reason to believe varenicline might be especially beneficial is that it blocks the reinforcing effects of nicotine; thus, smokers who use varenicline and continue to smoke experience a reduction in the pleasure from cigarettes (Cappelleri et al., 2007; Keating & Siddiqui, 2006). This may increase smokers' ability to reduce cigarettes/day and their self-efficacy, and decrease their dependence on cigarettes, which, in turn, should increase the probability that they make a future quit attempt (Hughes & Carpenter, 2006).

The major purpose of the present study was to test varenicline, not in those ready to quit, but in those who want to quit sometime in the future but not right now. Furthermore, given this was a pilot study, our primary outcome was initiation of a quit attempt. Our primary hypothesis was that, among ambivalent smokers, use of varenicline for 2–8 weeks will increase the incidence of a quit attempt in the next 6 months more than use of placebo. Secondary hypotheses were that varenicline will (a) increase other measures of motivation to quit, (b) reduce cigarettes/day, (c) block smoking reward, and (d) not generate significant adverse events (AEs). If we found varenicline increases quit attempts, we hypothesized that reduction in smoking reward, dependence, and cigarettes/day will mediate this increase.

Methods

Study Design

This was a double-blind, parallel-groups, randomized, controlled trial of varenicline versus placebo. Participants were smokers who wished to quit at some point but had no current plans to quit smoking. The intervention was medication plus four brief (10–15 min each) counseling sessions over 2–8 weeks to help smokers reduce cigarettes/day and consider a quit attempt. The primary outcome was the incidence of quit attempts during the 6 months from study entry.

We included a placebo condition to insure that any observed effects were due to the pharmacological effects of varenicline, not to expectancy effects due to simply taking a drug. We believed use of a placebo was ethical because (a) although there are many medications that are proven to help smokers once they have already initiated a quit attempt, there is no proven medication that prompts smokers to make a quit attempt and (b) we foresaw no clinically serious or irreversible harm from inclusion in the placebo group (Hughes, 2009).

Participants

We recruited smokers in 2008–2009 in Burlington, VT, USA and Omaha, NE, USA, via newspaper, radio, and flyer advertisements that included messages such as “Smokers, not quite ready to quit? We are testing a new medication to help you reduce and control your smoking and be less addicted. Compensation up to

\$75 provided. This is a research study conducted by the University of Vermont.” A few participants were recruited by referral from study participants.

We chose a sample size to detect an increase in the incidence of a quit attempt by a factor of two, from 20% over a 6-month period (the expected for U.S. smokers who receive no treatment) (MMWR, 2009) to 40%. We chose 110/group to have 90% power with an alpha of 0.05 via a two-tailed test (it would be important to rule out negative effect of varenicline) to detect this effect. Given this sample size and the likelihood of low abstinence rates (<10%) in this group of ambivalent smokers, our power to detect an increase in abstinence was low, that is, our power to detect a doubling of point prevalence quit rates from 5% to 10% at 6 months was only 0.28 (Fleiss, 1981).

Inclusion criteria were (a) wish to eventually stop smoking, (b) no intention to quit smoking in the next month, (c) daily smoking ≥ 8 cigarettes/day (to insure sufficient smoking to make reduction feasible and to notice effects of varenicline), (d) no history of use of varenicline, (e) not currently using a smoking cessation medication, (f) not currently or planning to be pregnant or breastfeeding and negative pregnancy test, (g) ≥ 18 years old, (h) no current or past history of medical or psychological problems that would, in the judgment of the investigators, place the participant at significant risk of an AE, including lifetime suicidal attempt or current depression, (j) drink fewer than 16 alcoholic beverages per week, (k) no current use of a sedating medication (to minimize possible psychiatric AEs from varenicline), and (l) no current kidney disease or frequent nausea.

The major reasons for excluding potential participants were that they had previously used varenicline, used a medication that caused drowsiness, or planned to quit in the next 30 days. In addition, about a third of the eligible smokers did not attend the first session or consent (not unexpected given our inclusion criteria of no current interest in quitting), leaving 218 designated participants.

Study Procedures

A research assistant initially screened smokers by telephone to determine eligibility. At the baseline visit at the Omaha site, but not at the Burlington site, a medical history and physical exam were conducted as well. Both sites conducted a urine test for pregnancy, if indicated. In those eligible, we advised about the study and the medication, including the biological rationale for our belief that varenicline will decrease their satisfaction from cigarettes, make them less addicted to cigarettes, and help them reduce their smoking, and that this might make it easier for them to decide to quit. We stated they did not have to make a quit attempt to continue in the study. Enrolled participants signed a consent form. The University of Vermont Committees on Human Research and the University of Nebraska Medical Center Institutional Review Board approved the study.

One of the authors (PC) randomized study IDs, stratifying by study site. Block sizes of four were used within each site to ensure an approximately equal distribution to active and placebo groups within site. The list of IDs and assignment was sent to either a pharmacist (at Nebraska site) or a research assistant (at Vermont site) who prepared the appropriate aliquot of pills for each ID. Neither PC nor the pharmacist/research

assistant had contact with participants during the study. At each site, consented participants were assigned to the next ID in sequence. Clinicians were unaware of the randomization details (e.g., block size) and were blinded as to participant condition.

Intervention

The intervention began at the baseline visit when participants were provided medication to use for 2–8 weeks. Brief counseling about reduction occurred at baseline, 2, 4, and 8 weeks later. Follow-up phone calls by research assistants blind to study conditions to collect data occurred at 3, 4, 5, and 6 months from study entry. If participants reported abstinence at the 6-month call, they were asked to come in to have a breath test for carbon monoxide (CO) to verify abstinence (SRNT Subcommittee on Biochemical Verification, 2002). Participants were reimbursed for their time.

The clinicians had either an M.S. degree in a behavioral science or an M.D. The clinician briefly discussed the participant's prior attempts to stop smoking and their response to prior treatments. Participants were told varenicline blocks the rewarding effects of nicotine and our hypothesis that the medication would help them reduce cigarettes/day and increase the probability that they would make a quit attempt. The clinician explicitly told participants that it was unclear whether reducing cigarettes/day improves health.

The clinician provided 3–5 weeks of prepackaged medication to participants. Participants began using the medication the next day. Participants took one pill/day (0.5 mg/day or placebo) for the first 3 days, then two pills/day (0.5 mg each or placebo) for 4 days, and then two pills/day (1.0 mg each or placebo) for the remainder of treatment. The clinician stated participants should take the medication for at least 2 weeks unless they had significant side-effects, and we encouraged them to use it for up to 8 weeks. The clinician stated they had a 50% chance of receiving active or placebo medication. The clinician requested them not to use other smoking cessation medications while using our pills.

At the second visit 2 weeks later, the clinician asked if participants had noticed any medication effects or AEs. The clinician encouraged them to reduce cigarettes/day for the next 2 weeks because prior studies indicate that reduction among ambivalent smokers increases the probability of later quit attempts and successful quitting (Hughes & Carpenter, 2006); however the clinician encouraged smoking reduction only to a degree that did not cause significant craving or withdrawal. If they agreed the clinician discussed the two most commonly used reduction methods (Carpenter, Hughes, & Keely, 2003; Carpenter, Hughes, Solomon, & Callas, 2004; Riggs, Hughes, & Pillitteri, 2001); that is, (a) systematically increasing the minimum amount of time between cigarettes, and (b) rank-ordering cigarettes from easiest to give up to hardest and systematically foregoing easiest to hardest cigarettes. The clinician suggested the participant set a very achievable initial goal (e.g., reduce by five cigarettes over the next 2 weeks) to increase the chances of initial success. At all sessions, participants were asked if they had made a quit attempt since the last session but were never explicitly advised to quit. The treatment did not focus on elements of motivational interviewing (Fiore et al., 2008; Rubak et al., 2005).

At the 4-week visit, the clinician queried about medication effects and success with reduction. He/she encouraged smokers to either maintain that level of smoking, or set a new reduction goal. At the last visit at 8 weeks, the clinician reminded participants that we cannot provide them with further medication unless they set a quit date in the next 2 weeks. If during any visit, participants stated they planned to try to stop smoking or had recently quit and were still abstinent, the session did not focus on reduction but rather on methods to prepare for or maintain abstinence.

The initiation of a quit attempt (and not abstinence) was the major outcome for the study; thus, we allowed quit attempters to undertake varied treatments after their quit attempt. They were given the option to continue on the same study medication for up to 3 months from their quit date to assist with their quit attempt, but were reminded that they may be receiving a placebo. For ethical reasons, the clinician did not prohibit quit attempters from using local psychosocial resources for quitting (e.g., phone counseling). They were also told they could purchase NRT or a prescription medication (including varenicline) if they thought it helpful and could still continue in the study; however, if they did purchase another medication, for safety reasons, they would have to stop using our pills. The clinician also told those who had quit and were abstinent, that if they wanted to know their study condition, we would let them know their treatment assignment. In summary, although we report abstinence rates as a secondary outcome, given the heterogeneity of use of treatments after a quit attempt, their interpretation is problematic.

The clinicians were trained via didactics, role-playing, and videotapes, and a semi-structured treatment manual was used. Although clinicians received informal feedback, the only formal measure of adherence to the protocol was completion of checklists of study tasks at each session.

Measures

Baseline demographic and smoking history data used questions from U.S. national tobacco surveys (Hughes, 2004; Pierce, 1989) so that we could compare our samples with national samples. At each visit, the counselor completed a Time Line Follow Back (TLFB) (Sobell, Brown, Leo, & Sobell, 1996) that recorded cigarettes/day for the prior seven days and smoking status (yes/no) for days prior to that since the last visit. The TLFB also asked for each day whether varenicline was used and whether a quit attempt occurred.

Our a priori-defined major dependent variable was the incidence of one or more quit attempts during the 6 months of the study. We also report four other quit attempt outcomes and three abstinence outcomes (Table 2). Participants also completed stage of change (Prochaska & DiClemente, 1983) and self-ratings of degree of motivation (Hughes, Keely, Fagerstrom, & Callas, 2005), self-efficacy (Dijkstra & DeVries, 2000), and addiction to cigarettes (Hughes et al., 2004). From these, we report six motivation-to-quit outcomes. Participants also completed the modified Cigarette Evaluation Questionnaire (to evaluate nicotine blockade) (Cappelleri et al., 2007), and the Minnesota Nicotine Withdrawal Scale—Revised (www.uvm.edu/~hbpl). In addition, they were asked about AEs from study medication. Outcomes during the first 2 months were collected by the counselors. No blindness assessment was done.

A research assistant who had no therapeutic contact with participants called at 3, 4, 5, and 6 months to complete the same TLFB about cigarettes/day, use of study medications, smoking status, quit attempts, varenicline use, and AEs. In addition, at 6 months, participants were mailed the cigarette evaluation, self-efficacy and withdrawal, and intention forms again plus they completed a form about any smoking cessation treatments (other than our treatment) used since the study started.

Data Analysis

Analyses were based on the 218 designated participants, unless stated otherwise. Similar to most smoking cessation trials, we assumed missing data indicated that neither a quit attempt, abstinence, nor reduction had occurred during that time and that scores on self-report measures were unchanged. To test the major hypothesis, a quit attempt was defined as a self-report of a quit attempt. For the primary outcome, we did not require 24 hr of abstinence as is often done due to our recent analyses that this may produce bias (Hughes & Callas, 2010b). Quit attempts accompanied by abstinence either on the day of the quit attempt or, since many smokers begin their quit attempt later in the day, on the following day was a secondary measure. Other secondary measures of quitting and abstinence are listed in Table 2, and secondary measures of motivation, cigarette reward, and withdrawal are listed in Table 3.

We conducted a logistic regression onto the primary outcome to determine if treatment (varenicline vs. placebo) predicted the occurrence of a quit attempt and included study site (Vermont vs. Nebraska site). Analyses of secondary outcomes used chi-square tests, *t*-tests, analyses of variance, Kruskal–Wallis tests, and survival analysis (Collins, 2006).

As stated above, due to our small sample size and lack of experimental control once a quit attempt is made, increasing abstinence outcomes was not a specific aim of the study; however, we examined whether point prevalence abstinence results showed a trend toward greater abstinence with varenicline than placebo. We defined abstinence as a dichotomous measure of no smoking in the last seven days prior to the 6-month follow-up (Hughes et al., 2003) in two ways: with and without verification by CO <10 ppm (SRNT Subcommittee on Biochemical Verification, 2002).

We did not undertake a formal mediation analysis as the sample size is small for such an analysis (MacKinnon, Fairchild, & Fritz, 2007). Instead, we tested whether treatment influenced the mediator, and whether the mediator was associated with the onset of a quit attempt. Mediators were the items in Table 4 and reduction in cigarettes/day. These were measured at baseline, after 2 weeks of medication, and after 4 weeks of medication. In addition, we examined days of use of study medication prior to making a quit attempt. We first examined if treatment influenced the change in the mediator from baseline to 2 weeks, and then whether the mediator

Table 1. Participant Characteristics^a

	Nebraska site		Vermont site		Average U.S. smoker (Hughes et al., 2010)
	Varenicline	Placebo	Varenicline	Placebo	
# of participants	52	58	55	53	
Demographics					
Mean age	45 (13)	45 (13)	43 (16)	37 (16)	40
% Women	39	39	40	47	46
% White, non-Hispanic	94	90	89	94	74
% Completed HS	100	98	95	96	72
% Married	39	45	20	27	
Smoking history					
Mean cigarettes/day	19 (9)	17 (7)	20 (10)	18 (6)	12
Use low T/N cigarettes (%)	56	70	38	33	
Age started smoking	17 (4)	17 (3)	15 (3)	16 (3)	
% Tried gradual cessation	66	68	74	63	
% Tried abrupt cessation	82	86	76	87	
% Used counseling	12	11	26	26	
% Used any medicine	59	39	52	55	
% Tried to reduce in last 6 months	40	30	38	44	
FTND	4.9 (2.0)	4.3 (2.2)	5.5 (1.9)	5.4 (2.1)	
Median and IQR time to first cigarettes (minutes)	15 (5–45)	30 (10–60)	15 (5–30)	10 (5–30)	
Self-rated addiction (0–10)	8.5 (1.5)	8.3 (1.3)	8.5 (1.5)	8.4 (1.9)	
Thinking of quitting in next month (%)	60	56	44	32	
Thinking of quitting in next 6 months (%)	96	95	76	77	
Ease of quitting for good (1–4)	3.5 (0.6)	3.4 (0.6)	3.5 (0.5)	3.5 (0.5)	
Confidence in quitting (1–5)	2.7 (0.8)	2.9 (0.9)	2.4 (0.8)	2.6 (0.8)	

Note. # = number; FTND = Fagerstrom Test for Nicotine Dependence; HS = high school; IQR = interquartile range; and T/N = tar/nicotine.

^aParentheses = SD; no characteristics differed between varenicline and placebo.

at 2 weeks predicted a later quit attempt. For this analysis, we excluded all those who had their first quit attempt prior to 2 weeks. We undertook a similar analysis for results at 4 weeks. For simplicity, we did not include site by treatment interactions in the mediator analysis. Moderator analyses were assessed by including relevant interaction terms into logistic regression models. Analysis of AEs focused on any serious events and incidence of discontinuing medication or dropping out due to AEs.

Results

Participants

The participants were similar to the average U.S. smoker (Hughes & Callas, 2010a) in age and sex; however, like most smoking intervention clinical trials, the sample had fewer minorities, was more educated, and were heavier smokers (Table 1). The prevalence of being married was low. The time to first cigarette (TTFC) and Fagerstrom Test for Nicotine Dependence (FTND) indicated most participants were dependent smokers (Piper, McCarthy, & Baker, 2006). Even though, at screening all participants stated they did not “plan” to stop smoking in the next month, on the baseline form filled out at the first visit, 48% stated they were “seriously thinking” of quitting in the next month. On our motivational ladder (where definitely do not “intend” to quit in next month = 0 and definitely do intend = 10), 27% scored 8, 9, or 10. None of the participant characteristics differed between active and placebo conditions.

Adherence

Despite their ambivalence about quitting, three-fourths of participants made all visits and remained in the study for the 2 months of treatment (Figure 1). Almost all participants used

Figure 1. Participant flow.

medication for the required 2 weeks (91% for active and 93% for placebo, $\chi^2_{(1)} = 0.3, p = .57$) and 61% used varenicline for the full 2 months. During the first 2 months, participants in the active condition used medication for 44 (20) (mean and SD) of a possible 60 days (73%) and those on placebo 41 (19) days (68%) ($t_{(216)} = 1.1, p = .29$).

Reduction

Participants in the varenicline condition reduced their cigarettes/day during the first 2 months more than those in the placebo condition (Table 3). About a third (32%) of those in the active condition decreased cigarettes/day by at least 50% versus 20% of those in the placebo condition ($\chi^2_{(1)} = 4.1, p = .04$). Those in the active condition reduced their CO by 21% whereas those in the placebo condition increased their CO by 4% ($t_{(216)} = 3.2, p = .002$).

Quit Attempts

Most (52%) of smokers made a quit attempt during the 6 months; 32% made only one quit attempt, and 20% made two or more attempts (Table 2). Most of the quit attempts occurred between 6 and 11 weeks after starting varenicline. Due to the small number of participants who made multiple quit attempts, our analyses focused only on the incidence of one or more quit attempts. Overall, 59% of the active and 46% of the placebo condition reported at least one quit attempt ($\chi^2_{(1)} = 3.7, p = .06$) (Figure 2). However, in a logistic regression, study site interacted with active versus placebo group (Wald $\chi^2_{(1)} = 7.7, p = .005$). In post hoc tests, varenicline increased the probability of a quit attempt at the Nebraska site (73% vs. 41%, $\chi^2_{(1)} = 11.2, p < .001$), but not at the Vermont site (45% vs. 51%, $\chi^2_{(1)} = 0.3, p = .57$).

To explore the site interaction, we examined several site differences in baseline characteristics. The Nebraska site smokers smoked a similar number of cigarettes/day to the Vermont site ($t_{(212)} = 0.9, p = .39$), but were more likely to endorse wanting to quit in the next month ($\chi^2_{(1)} = 8.3, p = .004$), and had lower scores on the FTND ($t_{(210)} = 3.1, p = .002$) and TTFC ($t_{(212)} = 3.2, p = .002$) measures of dependence than the Vermont site. The sites did not differ in the effect of varenicline to reduce cigarettes/day, $F(1,184) = .03, p = .87$. The Nebraska site participants used more medication during the first 2 months ($t_{(216)} = 2.1, p = .04$). When we entered all site differences into the analysis, the drug-by-site interaction persisted.

Figure 2. Major outcomes at 6 months.

Table 2. Cessation Outcomes

	Both sites		Main effect	Site interaction	Nebraska site		Vermont site	
	Varenicline	Placebo			Varenicline	Placebo	Varenicline	Placebo
Quit attempts during 6 months								
% > 1 quit attempt	-	-	-	$\chi^2_{(1)} = 7.7, p = .005$	73%	41%	45%	51%
% > 1 quit attempt with abstinence	-	-	-	$\chi^2_{(1)} = 3.1, p = .08$	63%	36%	42%	38%
% > 1 quit attempt during use of medicines	35%	17%	$\chi^2_{(1)} = 8.7, p = .003$	NS	-	-	-	-
Median (IQR) days to first quit attempt	-	-	-	$F(1,110) = 4.1, p = .04$	66 (40-78)	70 (40-79)	41 (25-71)	77 (43-114)
Abstinence at 6 months								
% 7-day abstinence, self-report	26%	10%	$\chi^2_{(1)} = 9.8, p = .002$	NS	-	-	-	-
% 7-day abstinence, CO verified	14%	7%	$\chi^2_{(1)} = 2.7, p = .10$	NS	-	-	-	-
Median (IQR) days of abstinence ^a	48 (3-101)	4 (1-60)	$\chi^2_{(1)} = 8.4, p = .004$	NS	-	-	-	-

Note. CO = carbon monoxide; IQR = interquartile range; and NS = not statistically significant.

^aFor longest quit attempt.

Table 3. Self-Report Outcomes^a

Variables	Varenicline BL	Placebo BL	Varenicline, 2 months	Placebo, 2 months	Main effect for drug ^b
Reduction					
Reduction in CPD	–	–	5.8	3.2	$t_{(214)} = 3.1, p = .003$
% Reduction CPD	–	–	29%	17%	$t_{(215)} = -2.3, p = .02$
Motivation to quit					
% Plan to quit in next month	52%	44%	74%	58%	NS
% Whose stage of change increased	–	–	36%	25%	$\chi^2_{(1)} = 3.2, p = .07$
Motivational ladder score (1–10)	5.3	4.7	7.3	5.6	$t_{(212)} = 2.2, p = .03$
% Whose motivation ladder score increased	–	–	50%	35%	$\chi^2_{(1)} = 4.6, p = .03$
Ease of quitting (1–4)	3.5	3.4	2.9	3.2	$t_{(214)} = -4.0, p < .001$
Confidence in quitting (1–5)	2.6	2.7	3.1	2.8	$t_{(215)} = 4.0, p < .001$
Dependence					
Perceived addiction (0–10)	8.6	8.3	7.2	7.7	$t_{(158)} = -2.7, p = .008$
Total withdrawal (MNWS) (0–27)	7.0	6.0	7.1	7.0	NS
Craving (MNWS) (0–3)	3.2	2.8	2.4	2.6	$t_{(200)} = -4.6, p < .001$
Cigarette reward (MCEQ)					
4.6	4.7	3.6	4.2	$t_{(150)} = -3.5, p < .001$	Satisfaction
4.0	4.0	2.8	3.3	$t_{(127)} = -2.6, p = .01$	Psychological reward
1.5	1.5	1.7	1.5	NS	Aversion
					Enjoy respiratory sensations
3.1	3.4	2.6	3.1	NS	Craving relief
4.8	5.2	4.3	4.9	NS	

Note. BL = baseline; CPD = cigarettes/day; cMCEQ = Modified Cigarette Evaluation Questionnaire; and MNWS = Minnesota Nicotine Withdrawal Scale; and NS = not statistically significant.

^aOnly site interaction was for MCEQ/enjoy respiratory effects (see text).

^b t scores are for differences in change scores for varenicline versus placebo.

There was also a site interaction for quit attempts associated with abstinence in which, again, the effect was greater at the Nebraska site; however, a similar trend did occur at the Vermont site. A site interaction occurred with time to a quit attempt, but here varenicline had a greater, not smaller, effect at the Vermont site. There was a main effect (with no interaction) that varenicline caused more quit attempts during the first 2 months of medication use.

Abstinence

Among those who made at least one quit attempt, 95% of the active condition and 63% of the placebo condition chose to continue to use their study medication during their quit attempt ($\chi^2_{(1)} = 19.1, p < .001$). Few participants (14%) used another psychosocial or medication treatment after their quit attempt, and this did not differ by experimental condition ($\chi^2_{(1)} = 0.01, p = .93$).

There were no site interactions for the three abstinence outcomes. At 6-month follow-up, 26% of the active condition and 10% of the placebo condition reported seven-day point-prevalent abstinence ($OR = 3.2, \chi^2_{(1)} = 9.8, p = .002$) (Figure 2). When CO verification (<10 ppm) was required, 14% of the active condition and 7% of the placebo were abstinent at 6 months ($OR = 2.1, \chi^2_{(1)} = 2.7, p = .10$). The effect of varenicline on abstinence did not differ between the Nebraska and Vermont sites.

Self-Reports of Motivation to Quit, Cigarette Effects, and Withdrawal

There were no site interactions for motivation, cigarette effect, and withdrawal outcomes. For the motivation out-

comes reported in Table 3, all participants were included and those abstinent were assigned the maximum score. For the ratings of addiction, cigarettes and withdrawal, only those who continued to smoke were included. Varenicline increased six of the seven self-report motivation measures more than placebo (Table 3). It also reduced the satisfaction and psychological reward from cigarettes and decreased craving more than placebo.

Mediators

Among the 2-week mediators, only greater reduction in cigarettes/day was influenced by treatment and predicted outcome (Table 4). Among the 4-week mediators, greater percent reduction in cigarettes/day, greater reduction in perceived addiction, smaller amounts of craving, and less satisfaction from cigarettes were both influenced by treatment and associated with quit attempts, thus, appeared to be mediators.

Moderators

Among the characteristics in Table 1, the effect of varenicline on making a quit attempt was greater in less-dependent smokers ($OR = 5.5$ when TTFC > 60 min vs. 1.0 when TTFC < 15 min, Wald $\chi^2_{(1)} = 4.6, p = .03$), those who had never previously had cessation counseling ($OR = 2.4$ vs. 0.4, Wald $\chi^2_{(1)} = 4.9, p = .03$), those who had not previously tried reducing cigarettes/day ($OR = 3.4$ when never tried vs. 1.0 when tried 10+ times, Wald $\chi^2_{(1)} = 6.6, p = .01$), and non-White smokers ($OR = 16.0$ vs. 1.4, Wald $\chi^2_{(1)} = 4.2, p = .04$).

Table 4. Mediator Analyses

	2 Weeks		4 Weeks	
	Tx influenced mediator	Mediator predicted quit attempts	Tx influenced mediator	Mediator predicted quit attempts
Reduction				
Cigarettes/day (CPD)	—	$t_{(198)} = 2.9^{**}$	—	$t_{(186)} = 2.9^{**}$
Reduction in CPD	$t_{(198)} = -2.1^*$	$t_{(198)} = 2.0^*$	$t_{(186)} = -3.6^{***}$	—
% Reduction CPD	—	$t_{(198)} = 3.0^{**}$	$t_{(186)} = -3.6^{***}$	$t_{(186)} = 2.9^{**}$
Motivation				
Intention to quit	—	—	—	$t_{(184)} = -2.8^{**}$
Ease of quitting	—	—	—	$t_{(186)} = 2.5^*$
Confidence	—	—	$t_{(187)} = 3.8^{***}$	—
Dependence related				
Perceived addiction	$t_{(198)} = -2.7^{**}$	—	$t_{(186)} = -3.35^{**}$	$t_{(186)} = 3.3^{**}$
Withdrawal	—	—	—	—
Craving	$t_{(198)} = -3.8^{***}$	—	$t_{(186)} = -4.5^{***}$	$t_{(186)} = 3.2^{**}$
Cigarette effects				
Satisfaction	—	—	$t_{(182)} = -2.4^*$	$t_{(182)} = 2.5^*$
Psych reward	—	—	$t_{(180)} = -2.2^*$	—
Aversion	—	—	—	—
Respiratory enjoyment	—	—	—	—
Craving relief	—	—	—	—

Note. $^*p < .05$; $^{**}p < .01$; $^{***}p < .001$.

Tx = treatment, Psych = psychological.

Adverse Events

There were no unexpected or serious AEs. In the active group, 12% stopped active medication due to an AE and 10% did so in the placebo group ($\chi^2_{(1)} = 0.3$, $p = .60$).

Discussion

When given to smokers not currently planning to quit, varenicline was beneficial in our primary outcome—the incidence of any quit attempt—at one of the two study sites. However, varenicline increased most other measures of quit attempts, motivation to quit and abstinence, independent of site, suggesting convergent validity.

Our mediator analyses suggested varenicline increased quit attempts by reductions in cigarettes/day and dependence. We thought that reduction in the reward for cigarettes would also mediate varenicline effects; however, this was true for only one of the five reward scales; thus, we found little support for our hypothesis that varenicline would be especially efficacious due to it blocking effects.

With our procedures, some smokers could continue on placebo medication during a quit attempt (Frank, Novick, & Kupfer, 2003). One could argue that our failure to provide a known effective treatment for smoking cessation at the time of the quit attempt is unethical (Hughes, 2009). We think not because (a) many smoking cessation trials employ placebos due to the arguments previously made that placebo-control trials can be ethical even when a proven treatment exists (Frank et al., 2003), and (b) more importantly, participants were clearly informed that if they think it in their best interest to seek a different medication or treatment for smoking, they are free to do so and this would not prejudice their continuation in the study.

One limitation of the current study was the relatively small sample size. Our sample size was based on quit attempt rates from the literature. Higher placebo rates were observed, perhaps because subjects volunteering for the study were more motivated than the general population. For example, although our subjects stated they did not “plan” to quit in the next month, many reported they were “thinking of quitting” in the next month and scored high on a motivation ladder. Whatever the reason, the higher placebo quit attempt rates lowered our power. Testing varenicline among smokers who are even less motivated to quit might produce different results.

Our use of varenicline was unusual not only in its use in ambivalent smokers but also in (a) not requiring smokers to set an a priori quit date (i.e., in allowing smokers to choose their own quit date) and (b) allowing smokers to use varenicline for a long period before quitting (in fact, most quit attempters used varenicline for a month or longer before trying to quit).

Many clinicians and scientists believe smokers who want to quit soon should be “committed” to quitting before obtaining medication, should not delay smoking cessation, and should stop abruptly (Fiore et al., 2008), and there is some evidence to support these beliefs (Hughes, Solomon, Livingston, Callas, & Peters, 2010). In contrast, our results and those of others (Hajek, McRobbie, Myers, Stapleton, & Dhanji, 2011; Hughes & Carpenter, 2006; Rennard et al., 2010; Shiffman & Ferguson, 2008) suggest that ambivalent smokers should be provided medication even though not committed to quitting, allowed to set their own quit date whenever they are ready (even if months in the future) and encouraged to gradually reduce prior to stopping. Although this suggests a tailoring of treatment approaches depending on how committed smokers are to stop is best, this may not be the case. For example, correlational data suggest ambivalent smokers who

delay quitting do worse (West & Sohal, 2006). Conversely, smokers actively trying to quit also appear to benefit from flexible quit dates and longer pretreatment durations (Hajek et al., 2011; Hughes & Carpenter, 2006; Rennard et al., 2010; Shiffman & Ferguson, 2008). Clearly, further experimental studies of different approaches among smokers of different motivations are needed.

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Declaration of Interests

Dr Hughes is currently employed by The University of Vermont and Fletcher Allen Health Care. In the last 3 years, he received research grants from the National Institute on Health and Pfizer Pharmaceuticals and accepted honoraria or consulting fees from Abbot Pharmaceuticals, Academy for Educational Development, Acrux DDS, Aradigm, American Academy of Addiction Psychiatry, American Psychiatric Association, Atrium, Cambridge Consulting, Celtic Pharmaceuticals, Cline, Davis, and Mann, Constella Group, Concepts in Medicine, Consultants in Behavior Change, Cowen Inc., Cygnus, Edelman PR, EPI-Q, Evotec, Exchange Limited, Fagerstrom Consulting, Free and Clear, Health Learning Systems, Healthwise, Insyght, Invivodata, Johns Hopkins University, J Reckner, Maine Medical Center, McNeil Pharmaceuticals, Nabi Pharmaceuticals, Novartis Pharmaceuticals, Oglivy Health PR, Pfizer Pharmaceuticals, Pinney Associates, Reuters, Shire Health London, Temple University of Health Sciences, United Biosource, University of Arkansas, University of Auckland, University of Cantabria, University of Greifswald, University of Kentucky, University of Madrid Medical School, U.S. National Institutes of Health, and Xenova and ZS Associates.

Dr. Rennard is currently employed by the University of Nebraska Medical Center, Omaha Nebraska. In the last 3 years, he has received research grants/contracts from Almirall, Biomark, Centocor, GSK, the Institute for Science and Health, Lorrillard, Mpex, Nabi, Novartis, Pfizer, RJReynolds, Roche, Astellas, AstraZeneca, Philip Morris, the National Heart Lung and Blood Institute, and the National Institute for Environmental Health Sciences. He has received honoraria for consulting or for speaking from Abbott, Almirall, Altana, Anthera, Aradigm, AstraZeneca, Biolipos, BoehringerIngelheim, Centocor, Critical Therapeutics, GSK, Johnson and Johnson, Novartis, Otsuka, Parengenix, Pfizer, Quintiles, Roche, Sanofi, Schering, TargeGen, Theravance, UBS, Talecris, Dey, Nycomed, Pharmaxis the American College of Chest Physicians, the American Board of Internal Medicine, and the American Thoracic Society.

Karl Fagerstrom is president of Fagerstrom Consulting and has, over the last 3 years, received honoraria and speaking fees from Novartis, Nicovum, Pfizer, Independent Pharmaceutica, McNeil, Institute for Science and Health and various professional networks, universities, and scientific organizations.

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