Cross-Validation of a New Procedure for Early Screening of Smoking Cessation Medications in Humans

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Brief procedures for evaluating medication efficacy may reveal which candidate drugs warrant further testing in clinical trials and which do not. We previously carried out a study of smoking abstinence, involving the nicotine patch, and established the sensitivity of our procedure. In this study, we sought to cross-validate our earlier work by comparing short-term smoking abstinence due to varenicline (relative to placebo) in smokers with high intrinsic quit interest ($n = 57$) and those with low intrinsic quit interest ($n = 67$). All the subjects were randomly assigned to either abstinence reinforcement ($12/day) or no reinforcement. In a crossover design, all the subjects participated in two 3-week phases: *ad libitum* smoking (week 1), dose run-up of varenicline (1.0 mg b.i.d.) or placebo (week 2), and quit attempt on medication verified daily by carbon monoxide <5 ppm (week 3). As with the nicotine patch in the previous study, varenicline (relative to placebo) increased abstinence more effectively in those with high intrinsic quit interest than in those with low quit interest but did not affect abstinence due to reinforcement. These data confirm the feasibility of a brief, sensitive test of the efficacy of cessation medications in smokers with high quit interest.

The significant costs and time required for clinical trials[1] often discourage their use in early evaluations of the potential efficacy of novel compounds, including those for smoking cessation. Alternative, short-term tests of medication efficacy that are not as costly or time consuming have been examined, such as the assessment of withdrawal relief in smokers quitting temporarily for study purposes or the analysis of decreases in *ad libitum* smoking behavior.[2] However, these approaches generally do not produce clinically valid results; that is, the findings do not accurately predict the efficacy of those same medications in clinical trials.[2,3] Therefore, innovative strategies are needed for more accurate, cost-effective screening of new medications in humans.[2–4]

We have begun a research program to evaluate a procedure to optimally combine features of short-term laboratory tests of medication efficacy with those of clinical trials.[2,5] The aim is to take advantage of the practical aspects of the former while providing the clinical validity of the latter. In this procedure, smoking abstinence is the main dependent measure (as in clinical trials but not in laboratory studies) rather than withdrawal, craving, or smoking amount. We also employ a within-subject crossover design (as in lab studies but not in clinical trials) so as to compare short-term abstinence during active medication relative to placebo conditions. This approach allows the use of a small sample without sacrificing statistical power.[6,7] Our immediate objective is to establish the sensitivity of this procedure with model medications already known to be clinically effective; our eventual goal is a brief and efficient procedure to screen for novel compounds with potential efficacy to result in smoking cessation.

In a previous study,[5] using a transdermal nicotine patch as the model medication, we tested the notion that greater motivation to quit—at least during the course of the study—would provide a more sensitive test of medication effects on abstinence. We varied "intrinsic" quit motivation by recruiting smokers who intended to quit within the next month (high motivation) and those who did not (low motivation). We also manipulated "extrinsic" quit motivation by randomizing both groups to an abstinence reinforcement condition ($12 per quit day) or no reinforcement. We found that, whereas

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high intrinsic quit interest (i.e., current intention to quit soon) increased the days of abstinence due to nicotine patch (relative to placebo), high extrinsic quit interest did not. Although it was found that monetary reinforcement for daily abstinence very effectively increased quitting,[8] subjects being reinforced for abstinence showed no greater sensitivity to nicotine patch efficacy (i.e., no interaction of medication with reinforcement). Thus, our results indicated that smokers whose current quit interest is high may provide a sample particularly sensitive to medication efficacy for short-term smoking abstinence in a crossover design.

This study examined whether these initial results with one medication, namely, the nicotine patch, could be replicated in another model medication, varenicline (Chantix). Cross-validation of findings is necessary to ensure that this new screening procedure is broadly sensitive to a variety of potential new compounds. Varenicline is a partial agonist of $\alpha_4\beta_2$ nicotine receptors,[9] which play a key role in the reinforcing effects of nicotine,[10] and is clearly effective in increasing long-term abstinence success in clinical trials.[11] In our study, smokers with high or low current quit interest were randomized to monetary reinforcement of daily abstinence or no reinforcement, just as in our nicotine patch study. All received varenicline or placebo in double-blind fashion in a within-subject, crossover design, and abstinence was assessed daily during the last week of medication use. Craving and withdrawal were also examined as possible mediators of varenicline effects. On the basis of the results of our previous study with the nicotine patch,[5] we hypothesized an interaction of medication with current quit interest, verifying that high intrinsic quit interest enhances sensitivity to medication efficacy. We did not expect an interaction of medication with abstinence reinforcement.

RESULTS

Participant characteristics

In the sample of 124 smokers, 57 had high and 67 had low current quit interest, as defined in the Methods section. Subject characteristics are presented in **Table 1**, categorized according to quit interest/abstinence reinforcement subgroup. Those with high quit interest were slightly older and, as previously observed,[5] had significantly more prior quit attempts than those with low quit interest. The subjects in the four subgroups did not differ in any other respect, including score on the Fagerstrom Test of Nicotine Dependence[12] and number of cigarettes per day. Four subjects discontinued participation because of adverse effects: three during the varenicline phase (two experienced nausea and one experienced agitation) and one during the placebo phase (sad mood).

Abstinence

Days of abstinence. Abstinence was assessed daily by self-report of no smoking over the prior 24 h and expired-air carbon monoxide <5 ppm. The mean number of abstinent days during varenicline vs. placebo weeks (Monday to Friday) is shown in **Figure 1**, categorized according to quit interest/reinforcement subgroup. In the primary analysis of variance, significant main effects on abstinence were seen for medication condition ($F(1, 108) = 40.12$, $P < 0.001$), current quit interest ($F(1, 108) = 5.22$, $P < 0.05$), and abstinence reinforcement ($F(1, 108) = 10.43$, $P < 0.005$). The interactions of greatest interest to us for the study were medication effects × current level of quit interest and medication effects × abstinence reinforcement because these could help determine whether the type of abstinence motivation might increase sensitivity for detecting medication efficacy. The interaction medication × quit interest was significant

Table 1 Demographic and smoking-history characteristics of subject groups (mean ± SE)

	Group									
	Low quit interest ($n = 67$)				High quit interest ($n = 57$)					
	No reinforcement ($n = 36$)		Reinforcement ($n = 31$)		No reinforcement ($n = 27$)		Reinforcement ($n = 30$)		Total ($N = 124$)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Characteristics										
Age[a]	29.8	1.9	30.7	2.2	31.9	1.6	36.7	2.3	32.1	1.0
Gender (% male)	38.9%		48.4%		46.7%		40.7%		43.5%	
BMI	25.7	0.9	26.7	1.0	25.4	0.9	26.8	1.0	26.1	0.5
Smoking history										
Cigarettes/day	16.9	1.0	16.9	1.1	15.5	0.7	15.6	1.0	16.3	0.5
FTND (0–10)	4.8	0.3	4.4	0.3	4.3	0.3	4.8	0.3	4.6	0.1
Years smoking	11.3	1.8	12.9	2.1	13.0	1.5	16.3	2.2	13.2	1.0
Previous quit attempts[b]	0.8	0.1	1.0	0.2	1.8	0.2	1.8	0.3	1.3	0.1
Longest duration of previous quit attempts (weeks)	16.5	10.8	22.5	4.4	14.6	5.5	77.3	31.1	31.1	8.2

BMI, body mass index; FTND, Fagerstrom Test of Nicotine Dependence.

[a]Significant effect of quit interest, $P = 0.05$. [b]Significant effect of quit interest, $P < 0.001$.

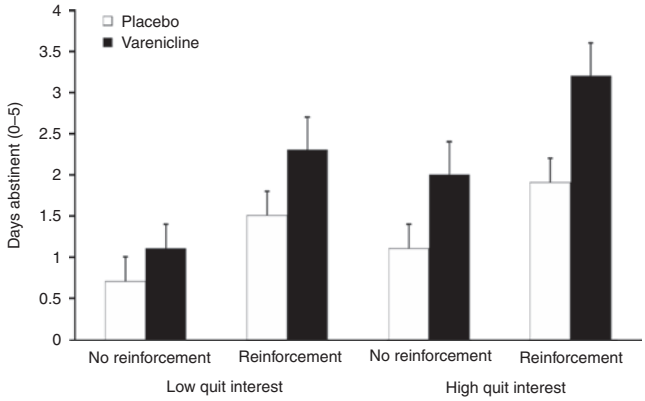

Figure 1 Mean (±SEM) days of abstinence during medication weeks attributable to varenicline (1.0 mg b.i.d.) relative to placebo, categorized according to current level of quit interest and abstinence reinforcement condition. The main effects of medication, quit interest, and reinforcement were significant. Most notably, the interaction of medication × quit interest level was significant, indicating greater sensitivity to varenicline's effects on abstinence among those with high quit interest as compared to those with low quit interest. No other interactions were significant.

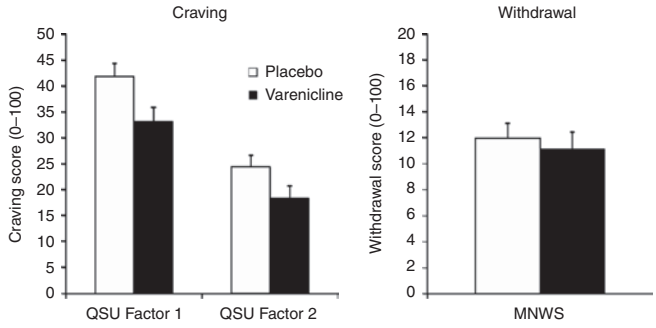

Figure 2 Mean (±SEM) scores for craving (QSU factors 1 and 2) and MNWS scores for withdrawal attributable to varenicline relative to placebo, collapsed across quit interest and abstinence reinforcement condition. The data relate only to the days when the subjects were abstinent, so as to avoid confounding responses to medication with relief from continued smoking. The main effect of medication was significant for each craving measure, but no interactions were significant. No effects were significant with regard to withdrawal. QSU, Questionnaire of Smoking Urges; MNWS, Minnesota Nicotine Withdrawal Scale.

($F(1, 108) = 3.89$, $P = 0.05$) with varenicline (relative to placebo), producing a greater increase in the number of abstinent days among those with high current quit interest (2.6 ± 0.3 vs. 1.5 ± 0.2 days, respectively) than among those with low current quit interest (1.7 ± 0.2 vs. 1.1 ± 0.2 days, respectively). The interactions of medication × reinforcement and medication × quit interest × reinforcement were not significant ($F(1, 108) = 2.33$, $P > 0.10$, and $F(1, 108) < 1$, respectively).

Medication order effects. Medication order effects are important to examine in a crossover study, in order to help in interpretation of findings and to gauge the feasibility of such designs for short-term tests of medication efficacy. The medication order across study phases (i.e., whether varenicline or placebo was administered during the first phase) influenced the number of days of abstinence ($F(1, 108) = 16.25$, $P < 0.001$). Those receiving varenicline in the first phase quit smoking for more days overall (i.e., under each medication condition) than those receiving placebo first (2.3 ± 0.2 vs. 1.1 ± 0.2 days per quit week, respectively). However, the medication × medication order interaction was not significant ($F(1, 108) = 1.54$, $P > 0.20$) because the increase in the number of abstinent days attributable to varenicline (relative to placebo) was similar whether varenicline was received in the first phase (2.8 ± 0.3 vs. 1.8 ± 0.2) or the second (1.4 ± 0.3 vs. 0.6 ± 0.2). Yet the triple interaction of medication × medication order × quit interest was significant ($F(1, 108) = 4.36$, $P < 0.05$). Varenicline (relative to placebo) increased the number of abstinent days in smokers with high quit interest whether varenicline was received in the first phase (3.2 ± 0.4 vs. 2.2 ± 0.3) or the second (2.1 ± 0.4 vs. 0.8 ± 0.3); however, varenicline increased the number of abstinent days in smokers with low quit interest only if varenicline was received in the first phase (2.5 ± 0.3 vs. 1.5 ± 0.3) and not if it was received in the second phase (0.8 ± 0.3 vs. 0.7 ± 0.3).

Other quit outcomes. Varenicline (vs. placebo) also significantly increased ability to quit on the target quit date (37.1% vs. 28.2%), to quit any time during the quit-assessment week (55.6% vs. 41.1%), to avoid relapse throughout the week among those who initiated quitting (29.8% vs. 12.1%), and to maintain continuous abstinence throughout the week (21.0% vs. 8.1%), z values of 2.12, 3.53, 3.13, and 3.77, respectively, P values of <0.05, 0.001, 0.005, and 0.001, respectively. However, medication effects on these other quit outcomes did not interact with the level of quit interest or abstinence reinforcement.

Other medication effects

Craving and withdrawal. Because nicotine absorbed via smoking would confound responses to medication condition, the analyses of craving and withdrawal included only the responses pertaining to abstinent days. Varenicline (relative to placebo) decreased Questionnaire of Smoking Urges craving factors 1 and 2, $F(1, 347)$'s of 29.74 and 23.94, respectively, both $P < 0.001$, but not overall Minnesota Nicotine Withdrawal Scale withdrawal, $F(1, 359) < 1$, as shown in **Figure 2**. These effects of varenicline did not have any association with quit interest or abstinence reinforcement.

Adverse effects of medication. Adverse effects were very mild, with the vast majority of subjects responding "0" (none at all) for each effect during both phases. The mean values for all effects were ≤0.3 on a scale of 0–3. Varenicline (relative to placebo) significantly increased nausea (0.19 vs. 0.07), constipation (0.15 vs. 0.07), and abnormal dreams (0.3 vs. 0.16).

Blinding as to identity of medication administered. The percentages of subjects identifying the medication as "Chantix," "no medication" (placebo), or "don't know" were 45.0, 10.8, and 44.1%, respectively, during the varenicline condition and 24.1, 27.7, and 48.2%, respectively, during the placebo condition ($z = 2.95$, $P < 0.005$ for difference in "Chantix" identification

between varenicline vs. placebo). Therefore, although the majority of subjects did not know their medication assignment during each condition, blinding subjects to medication may be a challenge in the case of varenicline, as has often been shown with other cessation medications, such as transdermal nicotine.[5] However, the percentages of correct identification did not differ depending on either quit interest or abstinence reinforcement, indicating that the greater therapeutic response to varenicline in those with high current quit interest was not due to a greater belief that the medication contained varenicline (i.e., expectancy of therapeutic benefit from medication).

DISCUSSION

Greater current intrinsic, but not extrinsic, interest in quitting smoking was shown to enhance sensitivity to the effects of varenicline (relative to placebo) on smoking abstinence over 1 week of assessment, confirming the results from our very similar study using a nicotine patch.[5] The cross-validation of results between two medications increases confidence in the conclusion that initial, brief screening of candidate medications for efficacy in cessation in a crossover design may be optimized by recruiting smokers intending to quit smoking soon.

Also consistent with our nicotine patch study, varenicline's effects on craving and withdrawal were not very useful in explaining the differential efficacy of varenicline between those high and low in intrinsic quit interest. Varenicline relieved craving but not withdrawal, relative to placebo. These findings partly concur with clinical research; varenicline has been shown to be more robust in relieving craving than withdrawal.[11,13–15] In this study, however, varenicline's relief of craving was similar in those with high intrinsic quit interest and those with low intrinsic quit interest, suggesting that greater relief of cravings is not the explanation for the greater increase in abstinence shown by those with a higher quit interest. The craving and withdrawal responses during abstinent days may have been confounded by the differences in the numbers of abstinent days for the varenicline and placebo phases (i.e., symptoms might have declined with longer duration of abstinence regardless of medication condition).

One finding in this study that differs from those of our previous nicotine patch study is that varenicline was effective even among those who had low intrinsic quit interest; by contrast, the nicotine patch had no effect on abstinence in this group in the earlier study.[5] Because clinical trials have shown varenicline to be more robustly effective than either the nicotine patch[16] or bupropion,[11,13] it is conceivable that the efficacy of very robust medications may be observed in our brief screening procedure even with smokers with low intrinsic quit interest. However, the efficacy of varenicline was weaker in the low quit interest group than in the high intrinsic quit interest group, as evidenced by the interaction of varenicline × quit interest. Moreover, the likely magnitude of the efficacy of novel medications evaluated using this screening procedure will not be known prior to testing, by the very nature of an initial screening test. Therefore, the routine enrollment of smokers with high intrinsic quit interest probably provides the most sensitive test for evaluating a candidate drug of unknown efficacy for smoking cessation.

The results of this study also support the utility of our novel within-subject crossover design for the assessment of short-term abstinence effects of active medication vs. placebo, although medication order effects were observed. Those receiving varenicline first quit on more days during both active and placebo conditions. This finding is similar to one reported by Patterson *et al.*[15] in a short-term crossover study of the effectiveness of varenicline (relative to placebo) in preventing relapse after simulated lapse. However, in our study, the magnitude of the difference due to varenicline (relative to placebo) was the same in the overall sample regardless of medication order. Order effects did differ by intrinsic quit interest; varenicline was significantly more effective than placebo among those who had low intrinsic quit motivation when it was administered in the first phase rather than in the second, whereas no such association was observed in those who had high intrinsic quit motivation. It is possible, as Patterson *et al.* have suggested,[15] that receiving varenicline in the first phase may have increased self-efficacy for quitting in the second phase (placebo) among those with low intrinsic quit interest. This observation further supports the proposal that smokers with high intrinsic quit motivation would be suitable subjects in this crossover procedure for medication screening.

Our ultimate goal is to apply this procedure to the screening of novel medications for smoking cessation, limiting subjects to the category of smokers with high current intrinsic quit interest, that is, the group that has now been shown, in two separate studies with two model medications, to provide the most sensitive test of the short-term efficacy of those medications. Such an approach could enhance the efficiency of use of drug development resources for evaluating new compounds as well as improve the success rate of drugs progressing to formal clinical trials (phases II and III).[2] Future research could also examine whether a similar approach, involving tests in subjects who have high intrinsic quit interest, might increase the sensitivity of short-term tests of candidate medications for treatment of other drug dependencies, such as alcohol dependency, thereby enhancing the efficiency of screening these medications.[17]

METHODS

This study was approved by the University of Pittsburgh Institutional Review Board. Except for the medication of interest (varenicline), most procedures were the same as those described in our previous trial with the nicotine patch.[5]

Subject recruitment. In order to have two groups varying in current quit interest, we sought smokers who either did or did not already intend to quit permanently. Our recruiting advertisements described the study as an "evaluation of the short-term effects of varenicline on smoking behavior" and noted that it was "not a treatment study." Prospective participants were briefly screened by means of a telephone interview, and then again in person, for smoking history, health, and intention to quit permanently. The eligibility criteria were as follows: smoking at least 10 cigarettes per day for 1 year or more, carbon monoxide reading of ≥10 ppm, and currently not in the process of quitting. Current intrinsic quit interest was assessed by asking subjects whether they intended to quit in the next 2 months, 4 months, 6 months, or 1 year, with each time frame addressed in a separate question. Those stating an intention to quit within the next

2 months were labeled "high" in current quit interest, and those stating they had no intention of quitting within the next 6 months were labeled "low" in quit interest. Those stating an intention to quit between 2 and 6 months were excluded from participation, and those interested in quitting immediately were referred to treatment programs elsewhere and not included in the study because our study design called for smoking resumption between crossover medication conditions. Participants were deemed to be eligible for the study only if they had given the same response to the question regarding quit intention in both the telephone interview and the subsequent in-person screening.

Validation of stated current quit interest. After completing the study, all subjects, regardless of stated quit interest, were offered free written cessation material and brief (10 min) counseling, and those accepting treatment set a quit date within 2 weeks. Free open-label varenicline was also offered. Three weeks after the end of the study period, all the subjects were contacted by telephone and asked about their smoking since the end of the study. They were asked to choose one of the following descriptions of smoking status: did not quit or cut down, cut down but did not quit, or quit. Those saying they had quit were asked how long they had stayed abstinent. Only those reporting that they had abstained from smoking for at least 24 h were viewed as having made a poststudy quit attempt. Poststudy quitting occurred in 61% of those with high intrinsic quit interest and 11% of those with low quit interest, generally consistent with their self-reported levels of quit interest at the time of entry into the study. Some of the smokers who had high intrinsic quit interest may have required greater assistance than we offered to be able to quit for at least 24 h. However, others in the self-professed high quit interest group may not have been seriously interested in quitting, although they knew that they were eligible to participate in the study even in the absence of such interest. In such a scenario, inclusion in the high-interest group of those who actually did not intend to quit soon would serve to weaken our test of current quit interest and medication response, perhaps leading to underestimation of the effect of quit interest on varenicline's efficacy.

Varenicline and placebo. Varenicline and placebo tablets, matched in size and appearance, were obtained from the manufacturer, Pfizer (New York, NY). The varenicline dose run-up regimen was the one recommended by Pfizer for those quitting smoking, 0.5 mg q.d. for 3 days, followed by 0.5 mg b.i.d. for 4 days and then the full dose of 1.0 mg b.i.d. The same number of placebo tablets was taken during the weeks of the placebo condition. Compliance during run-up and quit week (weeks 2 and 3 of each phase) was 98%, assessed by pill counts at every visit. Pfizer also provided open-label varenicline for those accepting medication for the optional poststudy quit attempt.

Self-report measures. Craving and withdrawal were assessed at every visit using the 11-item Brief Questionnaire of Smoking Urges[18] and the Minnesota Nicotine Withdrawal Scale,[19] respectively, with each item scored on a 0–100 visual analog scale. The Questionnaire of Smoking Urges provides two separate craving factors: one reflecting a strong intention and desire to smoke (factor 1) and the other reflecting anticipation of relief from negative affect (factor 2). Medication blinding was assessed on the Monday of the quit-assessment week, with subjects choosing from among three response options—"Chantix" (varenicline), "no medication," or "don't know"—to indicate what they perceived to be the contents of the capsule they were taking. Side effects were rated on a 0–3 scale (none, mild, moderate, and severe, respectively).

Experimental protocol. The design of this crossover study was a mix of one within-subject factor, varenicline (1.0 mg b.i.d.) vs. placebo, and two between-subject factors, namely, current intrinsic quit interest (either high or low) and reinforcement for abstinence (either payment of $12 for each day of abstinence or no payment). The duration of the study was 6 weeks, consisting of two 3-week phases. Each phase involved the following: (i) 1 week of *ad libitum* smoking (baseline, week 1), (ii) 1 week on the medication regimen (varenicline or placebo) while continuing to smoke (dose run-up, week 2), and (iii) 1 week of trying to abstain while continuing on the medication (varenicline or placebo) (quit assessment, week 3). The second 3-week phase began after the completion of the first phase. During washout (week 4 of the protocol), there was no medication, and subjects were required to smoke *ad libitum*. Subjects who had abstained during week 3 were therefore required to resume smoking during week 4, the baseline week for the next medication condition. (All the subjects were told that they did not have to resume smoking after week 3 if they wanted to remain abstinent, although they would not be able to continue in the study. All the subjects opted to resume smoking during week 4 and stay in the study.) The order of administration of varenicline and placebo between phases was counterbalanced between subjects. The participants visited the clinic 3 days per week during each baseline and dose run-up week (e.g., Mondays, Wednesdays, and Fridays) and all 5 weekdays (Mondays to Fridays) during each quit-assessment week. Daily assessments included levels of carbon monoxide, withdrawal, and craving.

During the in-person screening session prior to week 1, all subjects provided written informed consent for participation after the nature and consequences of the study were explained. All of them also agreed in writing that they would try hard to quit during the two quit-assessment weeks (weeks 3 and 6). The subjects were then given a physical examination by a physician to confirm eligibility. Those entered into the study were randomized to either the abstinence reinforcement or the no reinforcement condition, stratified by intrinsic quit interest group and sex.

Data analyses. Preliminary analyses of variance were used to examine the effects of sex and medication order between phases. No significant main or interaction effects of sex were found, but the effect of medication order was significant, as noted in the Results section. The primary analysis was an analysis of variance of days of abstinence per quit-assessment week (range of 0–5, not necessarily consecutive), with intrinsic quit interest and abstinence reinforcement as the between-subject factors, and medication (varenicline or placebo) as the within-subject factor. Of most interest were the interactions of medication condition with intrinsic quit interest and/or abstinence reinforcement. We hypothesized that medication would interact with intrinsic quit interest but not with abstinence reinforcement, consistent with our previous study of the nicotine patch.[5] We also used nonparametric tests to determine the effects of varenicline relative to placebo (Wilcoxon signed ranks) and of quit interest and monetary reinforcement, and the interactions of varenicline with quit interest or reinforcement (χ^2), with respect to the following: (i) ability to quit on the target quit day of each quit-assessment week (i.e., meeting the abstinence criteria on the first full day of abstinence assessment, Monday); (ii) ability to quit at all during each quit-assessment week (i.e., meeting abstinence criteria on at least 1 day that week); (iii) ability to avoid relapse during the quit-assessment week after initiating abstinence (i.e., no relapse at any point before the end of the week); and (iv) continuous abstinence throughout the week (i.e., 5 quit days). In analyses of craving and withdrawal, we used repeated-measures linear mixed-effects models with residual maximum-likelihood estimation to determine effects of varenicline, quit interest, and monetary reinforcement. Only data from abstinent days were included, to avoid confounding medication effects with relief from continuing to smoke. All models assumed a compound symmetric covariance structure between repeated measurements.

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CONFLICT OF INTEREST

K.A.P. has served as a consultant for GlaxoSmithKline. C.L. has served as a consultant for GlaxoSmithKline, Pfizer, and AstraZeneca. She has research funding, unrelated to this study, from Pfizer and AstraZeneca. M.L.S. serves Aradigm Corporation in an advisory capacity in connection with potential development of a new nicotine replacement medication. K.N.R.C. has served

as a consultant for AstraZeneca and has research funding from Janssen Pharmaceuticals, both unrelated to smoking cessation. The other authors declared no conflict of interest.

1. Kola, I. The state of innovation in drug development. *Clin. Pharmacol. Ther.* **83**, 227–230 (2008).
2. Perkins, K.A., Stitzer, M. & Lerman, C. Medication screening for smoking cessation: a proposal for new methodologies. *Psychopharmacology (Berl.)* **184**, 628–636 (2006).
3. Lerman, C. *et al*. Translational research in medication development for nicotine dependence. *Nat. Rev. Drug Discov.* **6**, 746–762 (2007).
4. Butz, R.F. & Morelli, G. Innovative strategies for early clinical R&D. *IDrugs* **11**, 36–41 (2008).
5. Perkins, K.A. *et al*. Development of procedures for early human screening of smoking cessation medications. *Clin. Pharmacol. Ther.* **84**, 216–221 (2008).
6. Cleophas, T.J. Crossover studies: a modified analysis with more power. *Clin. Pharmacol. Ther.* **53**, 515–520 (1993).
7. Fleiss, J.L. The Design and Analysis of Clinical Experiments (Wiley, New York, 1986).
8. Stitzer, M.L., Rand, C.S., Bigelow, G.E. & Mead, A.M. Contingent payment procedures for smoking reduction and cessation. *J. Appl. Behav. Anal.* **19**, 197–202 (1986).
9. Rollema, H. *et al*. Pharmacological profile of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology* **52**, 985–994 (2007).
10. Picciotto, M.R. *et al*. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. *Nature* **391**, 173–177 (1998).
11. Gonzales, D. *et al*.; Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* **296**, 47–55 (2006).
12. Heatherton, T.F., Kozlowski, L.T., Frecker, R.C. & Fagerström, K.O. The Fagerström test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. *Br. J. Addict.* **86**, 1119–1127 (1991).
13. Jorenby, D.E. *et al*.; Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* **296**, 56–63 (2006).
14. West, R., Baker, C.L., Cappelleri, J.C. & Bushmakin, A.G. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology (Berl.)* **197**, 371–377 (2008).
15. Patterson, F. *et al*. Varenicline improves mood and cognition during smoking abstinence. *Biol. Psychiatry* **65**, 144–149 (2009).
16. Aubin, H.J. *et al*. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax* **63**, 717–724 (2008).
17. Jupp, B. & Lawrence, A.J. New horizons for therapeutics in drug and alcohol abuse. *Pharmacol. Ther.* **125**, 138–168 (2010).
18. Cox, L.S., Tiffany, S.T. & Christen, A.G. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob. Res.* **3**, 7–16 (2001).
19. Hughes, J.R., Gust, S.W., Skoog, K., Keenan, R.M. & Fenwick, J.W. Symptoms of tobacco withdrawal. *Arch. Gen. Psychiatr.* **48**, 52–59 (1991).