The Effects of Extended Pre-Quit Varenicline Treatment on Smoking Behavior and Short-Term Abstinence: A Randomized Clinical Trial

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Preclinical research and learning theory suggest that a longer duration of varenicline treatment prior to the target quit date (TQD) would reduce smoking rates before cessation and improve abstinence outcomes. A double-blind randomized controlled trial tested this hypothesis in 60 smokers randomized to either an Extended run-in group (4 weeks of pre-TQD varenicline) or a Standard run-in group (3 weeks of placebo, 1 week of pre-TQD varenicline); all the participants received 11 weeks of post-TQD varenicline and brief counseling. During the pre-quit run-in, the reduction in smoking rates was greater in the Extended run-in group than in the Standard run-in group (42% vs. 24%, *P* < 0.01), and this effect was greater in women than in men (57% vs. 26%, *P* = 0.001). The rate of continuous abstinence during the final 4 weeks of treatment was higher among women in the Extended group compared to women in the Standard run-in group (67% vs. 35%). Although these data suggest that extension of varenicline treatment reduces smoking during the pre-quit period and may further enhance cessation rates, confirmatory evidence is needed from phase III clinical trials.

Cigarette smoking remains the single largest preventable cause of death in the United States.[1] Despite the fact that the vast majority of the 45 million smokers in the United States today want to stop smoking, most are unable to do so easily with the currently available therapies for nicotine addiction.[1]

The 2008 update on smoking cessation issued by the Public Health Service[2] added varenicline to the limited list of first-line pharmacotherapies for smoking cessation. The results of trials published since then have continued to support the use of varenicline because they show that it produces outcomes comparable to or better than those with any other cessation agent.[3] Nevertheless, long-term abstinence rates remain disappointing; by the end of 12 weeks of treatment with varenicline, <50% of smokers in clinical trials remain abstinent, and abstinence rates generally drop to around 25% within the first year.[3] However, there is good reason to believe that a better understanding of the mechanisms through which varenicline works can lead to improved outcomes.[4,5]

Varenicline binds to the α-4 β-2 receptor subunit of nicotinic acetylcholine receptors and exerts effects both as a partial nicotine agonist (by stimulating dopamine release) and as

an antagonist (by blocking the binding of nicotine to this site). Preclinical studies suggest that varenicline is also a full agonist at the α-7 nicotinic acetylcholine receptors subunit.[6] In two clinical trials, postcessation smoking urges and cravings, as well as the level of satisfaction obtained from cigarette smoking during lapses, were robustly reduced with varenicline.[7,8]

Although post-quit abstinence mechanisms are certainly important, it is also important to examine the effects of medication *prior* to actual cessation.[2,9,10] This is especially important in the case of an agent such as varenicline that is typically administered for 1 week prior to quitting and that is believed to work, in part, by reducing the reinforcing or desirable effects of smoking. From a learning perspective, when the favorable consequences are removed, the behavior decreases in frequency or is extinguished. In this respect, and in line with the results of the preclinical work of Coe and Rollema, we hypothesize that varenicline reduces the reinforcing effects of smoking, thereby promoting the extinction of smoking behavior.[11,12]

Building on the pioneering work of Rose and colleagues,[13] a small body of literature is developing that deals with the
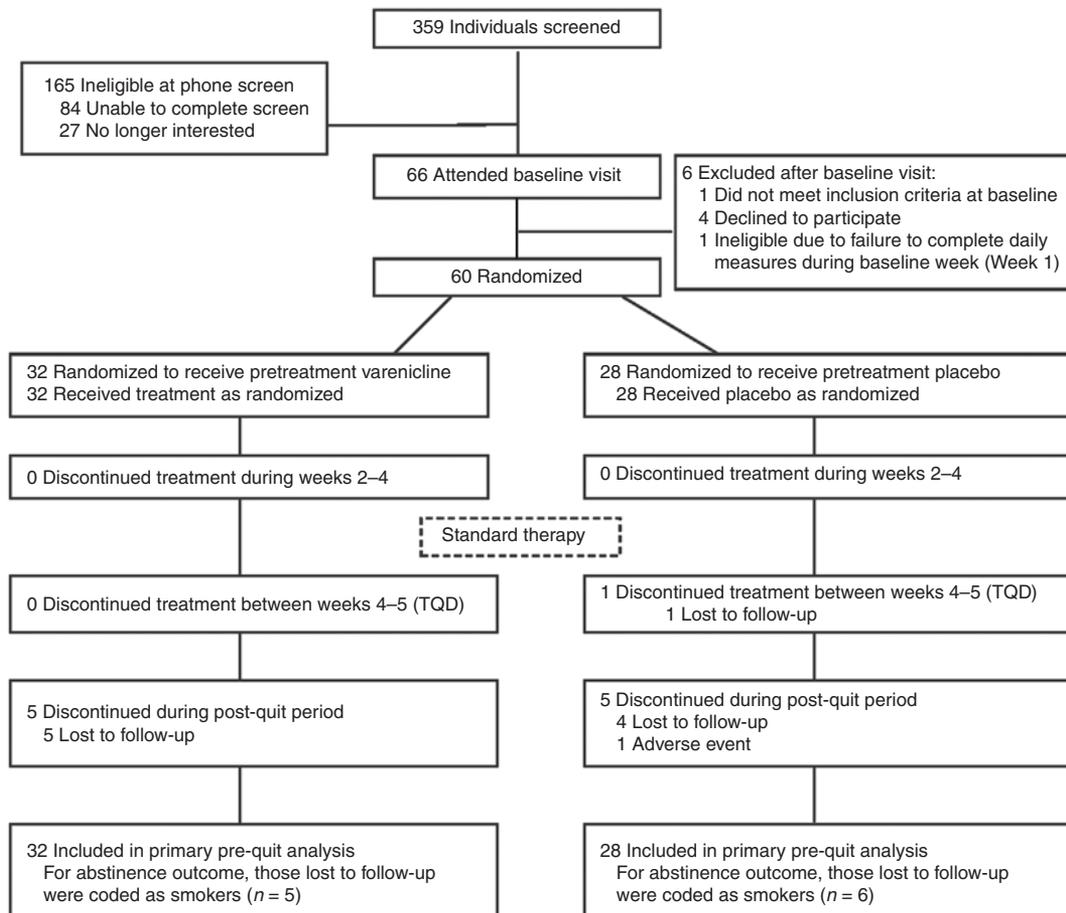
Figure 1 Disposition of participants. TQD, target quit date.

potential impact of extending pretreatment pharmacotherapy. A meta-analysis of four studies using nicotine patch therapy prior to quitting concluded that pretreatment patch use resulted in a doubling of 6-week and 6-month quit rates.[14] Consistent with a framework predicated on extinction of smoking behavior, the three studies that assessed this parameter reported reductions in cigarettes smoked per day. Similarly, we (L.W. Hawk, M.C. Mahoney, R.L. Ashare, J.D. Rhodes, J. Oliver, K.M. Cummings *et al.*, unpublished data) recently observed that 4 weeks of pre-quit bupropion reduced both smoking rates and subjects' self-reported ratings of how good cigarettes tasted during the pre-quit period, relative to bupropion treatment that began 1 week prior to cessation. This regimen of extended pre-quit bupropion also increased the time to first lapse and approximately doubled the duration of short-term cessation.

This paper presents data from a randomized clinical trial designed to test whether extending the duration of pre-quit varenicline from 1 week (Standard run-in) to 4 weeks (extended run-in) would lead to greater pre-quit reductions in smoking rate, expired-air breath carbon monoxide (CO), and lower ratings from the participants with respect to cigarette taste and smoking satisfaction. We also conducted exploratory analyses of smoking abstinence measured 3 months after the target quit date (TQD). In addition, given that gender is often a parameter that moderates the behavioral pharmacology of nicotine and

smoking[15,16] as well as cessation outcomes,[17,18] we explored whether there were gender-based differences in participants' responses to the extension of pre-quit run-in with varenicline.

RESULTS

Participant characteristics

The 60 participants eligible for the study were randomly assigned to the study groups and included in the primary analysis (see **Figure 1** for participant flow). **Table 1** provides demographic information and baseline smoking characteristics for all run-in group × gender conditions. There were no statistically significant main effects or interactions for any baseline characteristic. On average, participants were 48 years old, reported smoking 21 cigarettes per day (CPD), and were moderately nicotine-dependent (mean score of the Fagerström Test for Nicotine Dependence (FTND) = 5.2).

Pre-quit changes in smoking behavior

Cigarettes smoked per day. **Figure 2a** presents the mean (SE) CPD for each run-in group × gender condition across the 5-week pre-quit period. The predicted run-in group × time interaction was significant, $P = 0.004$. The reduction in CPD from week 2 to week 5 was greater in the Extended run-in group (mean difference = 6.3, $P = 0.0001$) than in the Standard run-in group (mean difference = 3.2, $P = 0.0003$). The results

Table 1 Selected demographic and tobacco-use characteristics at baseline

	Run-in group				P value		
	Extended		Standard				
	Male	Female	Male	Female	Run-in group	Gender	G × S
n	14	18	11	17	—	—	0.73
Age, years	46.3 (10.7)	48.8 (7.5)	49.0 (7.5)	48.7 (11.7)	0.61	0.67	0.57
Nonwhite, n (%)	1 (7%)	2 (11%)	1 (9%)	4 (24%)	0.34	0.30	—
Income (% below 40K)	50%	33%	18%	41%	0.50	0.93	—
Education (% greater than high school education)	21%	39%	28%	53%	0.35	0.09	—
Weight (kg)	85.6 (19.4)	76.4 (17.6)	85.9 (10.8)	81.0 (18.1)	0.59	0.12	0.63
Years smoking	27.1 (11.5)	26.8 (10.8)	25.3 (10.4)	28.2 (13.8)	0.94	0.68	0.60
Baseline CPD	21.4 (5.6)	21.4 (5.7)	23.6 (7.2)	19.4 (3.4)	0.94	0.15	0.15
FTND	5.4 (2.2)	5.4 (1.8)	5.4 (2.7)	4.5 (1.6)	0.37	0.45	0.43
≥One prior quit, n (%)	11 (79%)	16 (89%)	10 (91%)	15 (88%)	0.58	0.61	—

Except where indicated, all the values represent mean and standard deviation (SD).

CPD, cigarettes per day; FTND, Fagerström Test for Nicotine Dependence; G × S, run-in group (G) × gender (S) interaction.
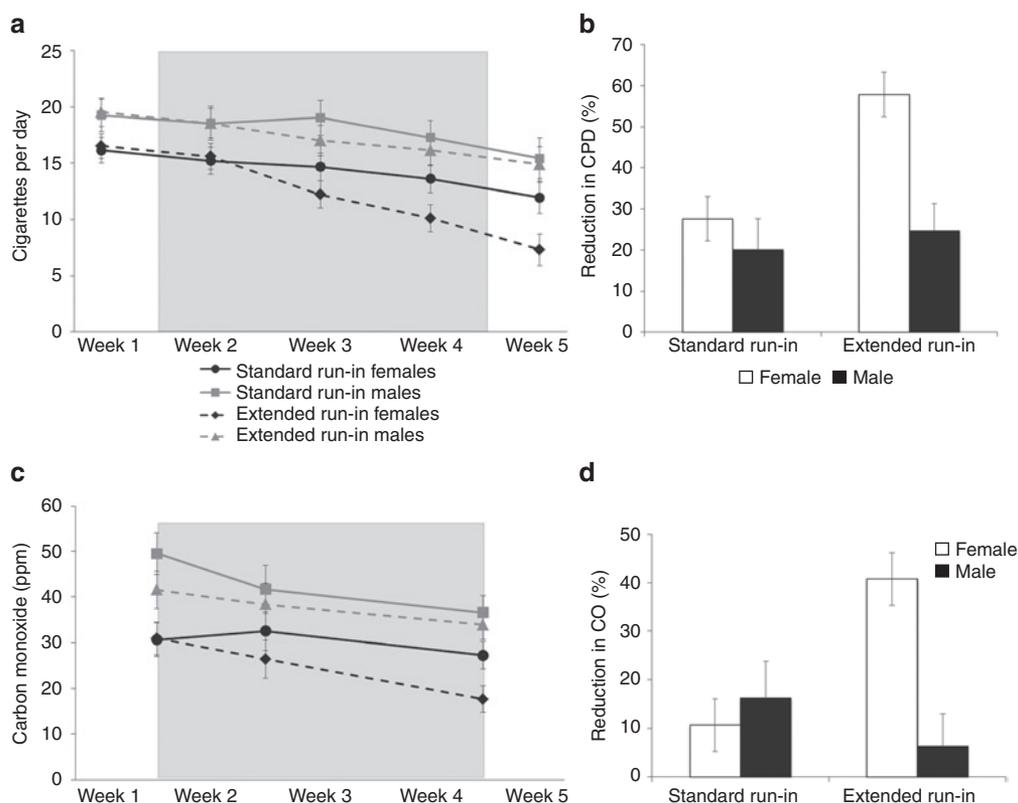

Figure 2 Pre-quit smoking rate and expired-air carbon monoxide. (**a**) Unadjusted mean and standard error (SE) cigarettes per day for all run-in group × gender conditions during the 5-week pre-quit period. Shaded region reflects the 3-week drug-manipulation phase. Baseline (week 1) was used as a covariate in repeated measures ANOVA. (**b**) Mean (SE) percent reduction in CPD during the pre-quit phase (final week pre-TQD; week 5 vs. baseline week; week 1) in all run-in group × gender conditions. (**c**) Mean (SE) expired-air CO measurements for all run-in group × gender conditions during the 5-week pre-quit period. Analyses included baseline (end of week 1) and drug-manipulation phase (end of weeks 2 and 4). During the 3-week drug manipulation phase, the Extended run-in group received varenicline, and the Standard run-in group received placebo. (**d**) Mean (SE) percent reduction in CO during the pre-quit phase (end of week 4 vs. end of week 1) in all run-in group × gender conditions.

also suggested that the group × time interaction differed by gender, $P = 0.029$. Women in the Extended group showed a greater reduction in CPD than women in the Standard group (mean difference = 4.9 CPD), $P = 0.003$. There was no treat-ment-group effect for the men (mean difference = 0.78 CPD, $P = 0.98$). The same pattern was evident for percentage reduc-tion in CPD during the pre-quit period (**Figure 2b**), for which run-in group × gender $P = 0.045$. Women in the Extended
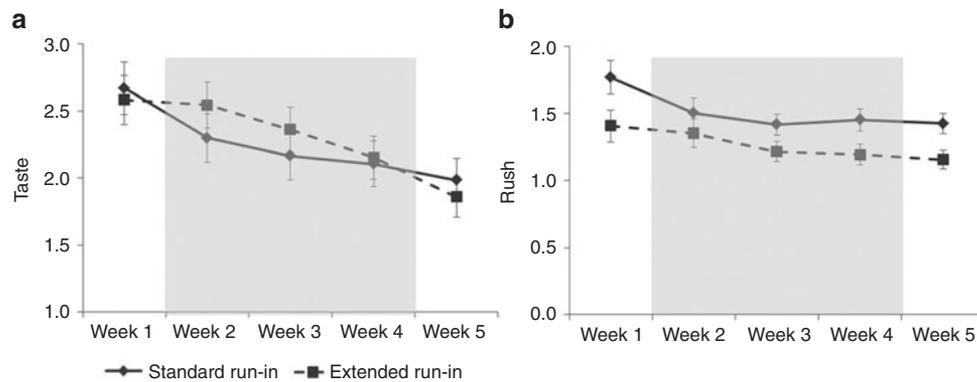
Figure 3 Unadjusted means (SE) for (**a**) single CEQ item "Did it taste good?" and (**b**) CEQ rush scale in reference to the first cigarette of the day by run-in group during the 5-week pre-quit period. Shaded region reflects the 3-week drug-manipulation phase. Baseline (week 1) was used as a covariate in repeated measures ANOVA. CEQ, cigarette-effect questionnaire.

group exhibited a greater reduction in smoking than those in each of the other run-in group × gender combinations, all pairwise, all values of p being < 0.01. All these other combinations showed comparable reductions across the pre-quit period, all values of p being > 0.6.

CO levels. **Figure 2c** presents the mean (SE) CO levels for each run-in group × gender condition across the pre-quit period. The predicted run-in group × time interaction was not significant for CO levels, $P = 0.22$. However, the run-in group × gender interaction was again significant, $P = 0.005$. During the 3-week drug manipulation period of the run-in (when one group was on varenicline treatment and the other on placebo), women in the Extended group had lower CO levels than women in the Standard group (mean difference = 8.1 ppm, $P = 0.002$); there was no run-in group effect for men (mean difference = 3.3 ppm, $P = 0.28$). The percentage reduction in CO levels during the pre-quit period (**Figure 2d**) exhibited a similar pattern, with a significant run-in group × gender interaction, $P = 0.015$; women in the Extended group showed a greater percentage reduction in CO than each of the other run-in × gender combinations (all P's < 0.01), all of which showed CO reductions comparable to one another (all P's > 0.65).

Pre-quit changes in craving, withdrawal symptoms, and cigarette effects
Craving and withdrawal. There were no significant group-dependent differences with respect to self-reported morning craving and withdrawal symptoms during the pre-quit period, all P's > 0.21.

Cigarette effects. There was a marginal run-in group × time interaction with respect to satisfaction per the cigarette-effect questionnaire (CEQ), $P = 0.08$. This interaction appeared to be driven by reduction in scores for a single item, "How good did it taste?" Therefore, we examined the cigarette taste item separately and found that the run-in group × time interaction was significant, $P = 0.032$. As predicted, the Extended run-in group reported greater reductions in scores for cigarette taste,

$P = 0.0001$ than did the Standard run-in group, $P = 0.08$ (see **Figure 3a**).

For the CEQ "rush" scale (light-headedness and head rush items; generally aversive to nonsmokers), there was a significant run-in group × time interaction, $P = 0.009$. Simple main-effects tests revealed that the Extended group reported significant decreases in the rush provided by the first cigarette of the day across the pre-quit period, $P = 0.004$; the Standard group showed no change in their experience of this rush, $P = 0.95$ (see **Figure 3b**).

In the other CEQ subscales, there were no significant changes over time, group differences, or interactions, all P's > 0.14.

Abstinence
Although continuous abstinence during the final 4 weeks of treatment was higher in the Extended run-in group (53%) than in the Standard run-in group (40%), OR = 1.8, this run-in group effect was not significant, $P = 0.27$. However, the treatment effect tended to be moderated by gender (run-in group × gender $P = 0.08$, OR = 5.50, 95% CI, 0.65–46.5). Follow-up tests revealed that, in women, continuous abstinence rates were higher in the Extended group (67%) than in the Standard group (35%) (OR = 4.3, 95% CI, 0.978–18.65, $P = 0.05$). By contrast, there were no differences in continuous abstinence rates between the Extended (36%) and Standard (46%) groups in men (OR = 0.60, 95% CI, 0.114–3.17, $P = 0.5$) (see **Figure 4**).

Adherence to medication
Overall, medication adherence was excellent, with mean values being >96% at each clinic visit. There were no group differences in adherence (all P's > 0.21). Although men tended to be less compliant in taking medication during weeks 2–4 as compared with women, this was only a 2% absolute difference, ($P = 0.05$) and it did not vary by run-in group ($P = 0.88$). There were no gender-related differences in adherence rates at subsequent time points (all P's > 0.19).

Evaluation of treatment blinding
Whereas only 39% of the participants taking placebo during this period believed they were taking varenicline, 75% of those

actually taking varenicline believed they were taking varenicline ($P = 0.008$). This effect was virtually identical for men (36% and 71%, respectively) and women (41% and 78%).

Adverse events

Table 2 presents a systematic assessment of adverse events by group during both the 3-week drug-manipulation phase (that is, weeks 2–4) and the subsequent 3-week period during which all the participants were taking varenicline (weeks 5–7). During

Figure 4 CO-verified 4-week continuous abstinence (not even a puff during the final 4 weeks of treatment; post-quit weeks 8 through 11) for all run-in group × gender conditions. CO, carbon monoxide. *$P = 0.05$.

weeks 2–4, nausea, constipation, bloating, and indigestion were significantly more common in the Extended run-in group than in the Standard group, but none of these side effects reliably differentiated the run-in groups in weeks 5–7. Relative to the Extended group, the standard group tended to report more problems with dry mouth during weeks 2–4 (when they were not receiving active medication) and increases in headaches and skin problems during weeks 5–7. No other side effects reliably differentiated the two run-in groups in either of these 3-week periods. The majority of all the side effects were rated as "mild."

Given that gender was a moderating factor in run-in group effects on multiple outcomes, we examined the most common side effect—nausea—separately in men and women. As seen in the data for CPD and CO, run-in group differences were evident in the women, but not in the men. During the drug-manipulation phase, nausea was more common in women in the Extended group (78%) than in women in the Standard group (24%), $P = 0.001$. This difference tended to persist during weeks 5–7 (50% vs. 24%, $P = 0.11$). The effect of run-in group on the incidence of nausea in men was not statistically significant (29% vs. 18% during weeks 2–4 and 21% vs. 10% during weeks 5–7), $P = 0.55$ and $P = 0.46$, respectively.

During the 3-week drug-manipulation phase, no participant discontinued treatment. One participant in the Standard run-in group discontinued pharmacotherapy during the final pre-TQD
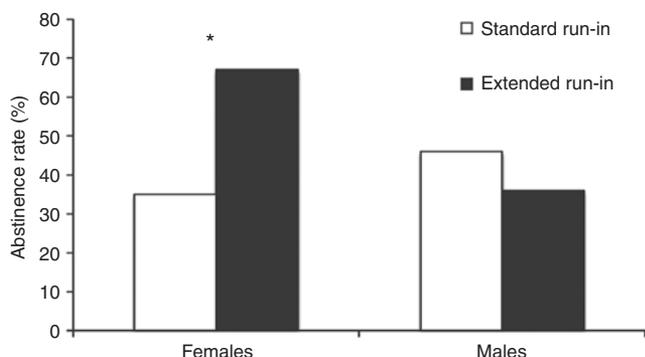
Table 2 Self-reported side effects by run-in group, separately for weeks 2–4 and weeks 5–7

	Weeks 2–4			Weeks 5–7		
	Extended (%)	Standard (%)	*P* value	Extended (%)	Standard (%)	*P* value
Nausea	56	21	0.006	38	18	0.11
Constipation	25	4	0.02	22	11	0.27
Bloating	25	7	0.06	22	15	0.49
Indigestion	19	4	0.07	12	11	0.87
Dry mouth	16	36	0.07	12	26	0.19
Headache	28	21	0.55	13	37	0.03
Skin problems	3	7	0.48	0	11	0.05
Insomnia	34	21	0.27	34	15	0.09
Flatulence	22	14	0.44	28	30	0.90
Vomiting	9	7	0.76	3	4	0.90
Decreased appetite	25	18	0.50	16	19	0.77
Taste problems	25	11	0.15	9	15	0.52
Abnormal dreams	34	21	0.27	34	26	0.48
Forgetfulness	12	14	0.84	12	15	0.80
Fatigue	22	18	0.70	25	26	0.94
Muscle aches	19	11	0.38	12	4	0.23
Dizziness	9	11	0.86	9	7	0.79
Ringing in ears	16	11	0.58	12	15	0.80
Mood	12	7	0.49	12	15	0.80
Suicidal thoughts	0	0	—	0	4	0.27

For each side effect, values represent % of participants reporting an increase from baseline. Weeks 2–4 were the drug manipulation phase, during which the Extended run-in group received varenicline and the Standard run-in group received placebo. Weeks 5–7 included the target-quit-date visit and the 2-week follow-up visit and represent the first 3 weeks during which the Standard run-in group received varenicline.

week. During the period when all participants were receiving standard varenicline therapy, five participants in each arm discontinued use of medication, including one participant in the Standard run-in arm who reported feelings of hostility and irritability 3 weeks after being started on varenicline. Medication was stopped immediately, and all symptoms resolved within several days. No serious adverse events were observed.

DISCUSSION

The present study evaluated the hypothesis that extending the pre-quit run-in period for varenicline from 1 to 4 weeks would alter smoking behavior and subjective effects in a manner consistent with the theorized reduction-of-reinforcement mechanism.[12,19] Consistent with our primary hypothesis, the Extended run-in group exhibited greater pre-quit reductions in smoking rate, as well as greater decreases in the taste and "buzz" from the first cigarette of the day, as compared with the Standard run-in group. Although the pattern of pre-quit expired-air CO was not as clear, CO-verified continuous abstinence (an exploratory outcome) during the final 4 weeks of the 3-month postquit period were encouraging. The odds ratio for quitting with extended (4-week) precessation varenicline was 1.8, relative to the Standard run-in of 1 week. The preliminary outcome data are particularly notable when one considers that the "control" condition in the study is at least as effective as any other frontline cessation strategy[2] and produced a 3-month abstinence rate of 40% in the present study.

A recently published clinical trial with a nearly identical research design[20] also found that pre-quit reductions in CPD, CO, and cigarette enjoyment as well as 3-month abstinence rates were enhanced with 4 weeks of pre-quit varenicline as compared with 1 week. Important limitations of that study, including missing pre-quit data for 15–30% of participants on each key pre-quit measure and the absence of bioverification of 3-month abstinence, are addressed in the present study. For example, the daily PDA-based assessment method employed in this study minimized retrospective biases[21] and resulted in complete time series data for every participant, ruling out possible selection biases or differences due to attrition. More generally, the replication of key results across both studies bolsters confidence in suggesting that the strategy of increasing the duration of pre-quit varenicline treatment is a strong candidate for further study in larger trials with longer follow-up periods.

Together with data from other studies that examined pre-quit strategies to enhance tobacco cessation,[14,20,22,23] the present findings can be integrated within a broader framework predicated on reinforcement and extinction of smoking behavior.[24] For extinction to occur, people must continue smoking in order to learn that the reinforcing effects are attenuated. Extinction is maximized when numerous instances of the behavior occur in the absence of reinforcement over a long period of time and across a range of contexts.[25–29] Although there are promising data based on as little as 2 weeks of pre-quit nicotine-replacement therapy (NRT), the pre-quit CPD data (**Figure 2**) suggest that the effect of pre-quit treatment increases over the 3-week manipulation phase (see also ref. 20).

Indeed, the results of one study of smokers who were not trying to quit suggest that the decline in smoking seen with varenicline may continue gradually over a period of weeks or even months.[30,31] Future work might consider whether pre-quit therapy might optimally be combined with a flexible quit date[31] so that the date would not precede attainment of a preset level of reduction in smoking behavior—some studies suggest 50% (refs. 10,20).

The above discussion implicitly assumes that varenicline reduces the *positively reinforcing* aspects of smoking. However, the marked increase in nausea prompted by extended pre-quit varenicline raises the possibility that the changes in subjective effects and smoking behavior develop because smoking at one's normal rate during varenicline treatment is aversive. Nausea is the most common side effect of varenicline and is also a relatively common reason for discontinuation of the treatment.[32] However, in both the present study and one by Hajek *et al.*,[20] the increased nausea during extended pre-quit varenicline did not lead to discontinuation. Perhaps the nausea that develops with standard varenicline therapy, typically around and shortly after cessation, is more readily attributed by the patient to varenicline, thereby increasing the likelihood of stopping medication; conversely, nausea that occurs in the pre-quit period with an extended run-in may be most proximally associated with smoking, leading to reductions in smoking rates. Evaluating the respective contributions of mechanisms of positive reinforcement (reduction in smoking due to reduced reward from smoking) and negative reinforcement (e.g., reduction in smoking in an attempt to limit nausea) will require adequate sampling of both processes over time in a large sample of smokers. Such data could provide valuable data regarding causal processes that might aid in setting a quit date or suggest a target for the development of new therapies.

No treatment helps everyone, and it is important to consider potential moderators of treatment.[33] In the present work, the effects of extended pre-quit treatment were consistently, albeit unexpectedly, moderated by gender across behavioral, biochemical, and subjective measures. In the women, extended pre-quit varenicline prompted greater reductions in self-reported smoking rate and biochemical evidence of smoking exposure (expired-air CO) prior to the TQD, caused more nausea pre-TQD, and doubled the rates of bioverified abstinence at 3-month follow-up. In the men, none of these effects was statistically significant. However, consistent with data from other clinical trials of varenicline that reported equivalent abstinence rates for men and women,[7,8] we observed no gender-related differences between those receiving standard treatment, and abstinence rates were solidly within the range typically observed with standard varenicline treatment.

These data raise the possibility that gender specifically moderates pre-quit processes that are the focus of the extended run-in period. The results of the largest trial to date of extended pre-quit treatment are broadly consistent with this hypothesis. Specifically, the beneficial effects of a pre-quit regimen of transdermal nicotine and denicotinized cigarettes on short-term abstinence were driven primarily by women.[34]

It is important to consider whether the seemingly gender-related differences observed here are in fact reflective of a more proximal variable, such as differences in drug concentrations. Indeed, steady-state varenicline levels are predictive of cessation outcome.[35] Although the lack of robust evidence of gender-related differences in weight or medication adherence in our study fails to support the hypothesis that varenicline concentrations were markedly gender-dependent, future work should include direct measures of varenicline concentrations over time (see also ref. 36).

However, we are not suggesting that extended pre-quit treatment is ineffective for men. The results of one recent study raise the possibility that, on average, the beneficial effects of pre-quit varenicline may emerge more slowly in men.[30] More generally, rather than propose that gender is *the* critical factor to examine, we suggest that future studies of extended pre-quit treatment explicitly consider individual differences in a range of parameters, including baseline smoking rate,[37] nicotine metabolism,[33] and varenicline concentration.[35]

In summary, the present data demonstrate that extended use of varenicline during the weeks leading up to a quit attempt reduces smoking behavior and subjective effects of smoking during the pre-quit period. The data are consistent with an extinction model of the mechanism of varenicline. The outcome data suggest that extending the duration of pre-quit varenicline increases short-term abstinence rates above the already notable rates obtained with standard varenicline dosing, at least for a subset of smokers. The combination of a strong theoretical foundation, straightforward treatment modification, and encouraging data on both process and outcome suggest that phase III trials of extended run-in varenicline therapy for smoking cessation are warranted.

METHODS

Study design. This study used a two-group, balanced, randomized, double-blind, placebo-controlled parallel-group design. The groups are identified on the basis of the run-in period, that is, the duration of varenicline treatment prior to the TQD. The Standard run-in group received 3 weeks of placebo, followed by standard dosing: 1-week pre-TQD varenicline and 11-week post-TQD varenicline, totaling 12 weeks. The Extended run-in group received 4 weeks of varenicline pre-TQD, then continued with standard (11 weeks) post-quit treatment. Both groups received brief cognitive-behavioral counseling. All visits took place at Roswell Park Cancer Institute (RPCI). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki,[38] and all procedures were approved by the institutional review board of the Roswell Park Cancer Institute. The trial was registered with ClinicalTrials.gov (NCT00835900).

Participants. Adult smokers were recruited through advertisements in newspapers and television and through Web posting and e-mail. Inclusion criteria included age 18–65 years, smoking at least 10 CPD for the past year, and willingness to refrain from additional treatments for smoking cessation during the study period. Exclusion criteria included serious medical condition(s) (e.g., diabetes, renal impairment, uncontrolled hypertension); depression requiring treatment in the past year; a history of panic disorder, psychosis, or bipolar disorder; a history of alcohol or drug abuse in the past year; use of tobacco products other than cigarettes; current use of other cessation pharmacotherapies; and pregnancy/planned pregnancy. Participant disposition is summarized in

Figure 1, and demographics and smoking characteristics are presented in Table 1.

Study procedures

Randomization: A study statistician provided the research pharmacist with a randomization scheme designating small-block (2:2) randomization within gender. The other study personnel and all the participants were blinded as to group membership; however, the participants were asked to guess their treatment group at the end of the 3-week drug-manipulation phase, a week prior to the TQD.

Interventions: Pfizer provided the required supply of varenicline and placebo of identical appearance for the trial. Participants were dispensed an initial 1-week supply of study medication (either varenicline or placebo to be taken orally) at the randomization visit (end of week 1) and instructed on its use (0.5 mg daily × 3 days, 0.5 mg twice daily × 4 days, then 1.0 mg twice daily, beginning on day 8). One week prior to the TQD, participants assigned to the placebo arm were switched over to varenicline in a blinded fashion with titration to standard dose during this initial week, using 0.5 mg tablets during the transition phase. During both titration weeks (week 2 and week 5), multiple pill bottles were provided, along with explicit instructions for their use. At each clinic visit, participants returned any unused pills and were dispensed only enough medication to last until the next visit plus two additional doses.

Brief (~15 min) behavioral counseling was provided at each contact visit. Until the end of the drug-manipulation phase, the participants were instructed to smoke as usual to allow their bodies to get used to the medication, as described by Rose *et al.*[13] At 1 week prior to TQD, the participants were also encouraged to sign up for the Pfizer Get-Quit program (http://www.chantix.com/support-plan.aspx).

Clinic visits: Each clinic visit included a review of adverse events, pill counts, assessment of vital signs, and expired-breath CO measurement. Participants completed weekly self-report measures (e.g., craving, withdrawal, side-effects checklist), returned any unused medication, and received new supplies of study medication and brief behavioral counseling. Through week 7, personal digital assistant (PDA) data (e.g., regarding CPD and cravings/withdrawal) were downloaded at each visit (reactivity to PDA-presented smoking and neutral cues during weeks 1–5 are considered in a separate paper). Participants were compensated up to $434 for attending visits and completing study measures.

Daily assessments: Daily assessments of smoking patterns and smoking satisfaction began 1 week prior to the randomization visit and continued throughout the pre-quit period and the first 2 weeks of the post-TQD period. For these assessments, participants were individually trained to use Palm Tungsten E2 PDAs and to complete these ecological momentary assessments (EMAs) before and after the first cigarette of the day, log the number of cigarettes smoked, and respond at four time points during the day (alerted by an alarm on the PDA) to record craving, withdrawal and reactivity to smoking, and neutral cues.

This article focuses on data relating to the morning assessment. Prior to smoking the first cigarette of the day, participants reported the previous day's CPD, craving, mood, and tobacco withdrawal. Craving, assessed with a four-item craving questionnaire,[39] was rated on a 5-point scale from 1 (strongly disagree) to 5 (strongly agree). Mood items (not reported here) consisted of a single positive-mood item and a single negative-mood item rated on a 5-point scale from 1 (strongly disagree) to 5 (strongly agree). Withdrawal symptoms were assessed using eight items from the Minnesota Nicotine Withdrawal Scale (MNWS)[40] rated on a 5-point scale from 1 (none) to 5 (severe). Within 15 min after smoking the first cigarette of the day, participants completed a modified version of the CEQ.[41,42] Ten items were rated on a 5-point scale from 1 (not at all) to 5 (extremely).

In studies such as this one, it is critical to accurately capture changes over days and weeks. EMAs offer important advantages over retrospective recall at each visit or traditional paper diaries.[43] To enhance compliance and encourage high rates of EMA completion the participants were

remunerated (up to a maximum weekly payment of $66); on average, participants completed the morning assessment on 33 of the 35 mornings during the pre-quit period.

Adverse events: Adverse events were monitored throughout the trial with a structured checklist and open-ended queries at each visit. An independent Data Safety and Monitoring Board provided review and oversight but did not issue any actions or directives.

Primary outcomes: The primary outcome measure was the number of cigarettes smoked per day during the pre-quit period, as recorded daily through EMAs (see description above). Participant error with the PDA led to invalid data in two cases (5 weeks for one participant; 1 week for another); these data were replaced with self-report data based on Time Line Follow Back (TLFB) interviews conducted at each visit. Problems with the remaining EMA data were rare, with only 1.1% of EMA data excluded on account of isolated inconsistencies with (i) the rest of the EMA time series, (ii) EMA cigarette logs, and/or (iii) TLFB. Expired-breath CO levels were measured during the pre-quit phase to biologically verify changes in self-reported CPD. On the basis of previous findings suggesting that varenicline may reduce satisfaction from smoking,[44] pre-quit changes in the CEQ satisfaction scale were also set as a coprimary outcome.

Secondary outcomes: Because the trial was not powered (see below) to detect effects on dichotomous cessation outcomes, analyses of cessation outcomes are considered exploratory. To parallel most clinical trials of varenicline,[3] we focused on CO-verified (<11 parts per million) continuous abstinence (not even one puff) during the final 4 weeks of treatment (i.e., post-quit weeks 8 through 11). Participants lost to follow-up were coded as smokers.

Sample size: Prior published work with nicotine-replacement therapy[14] and preliminary work with bupropion (Hawk *et al.*, unpublished data) suggested that the effect of extended pretreatment on our primary outcome, reduction in pre-quit smoking rate, was ~$d = 0.7$ (50% vs. 25%, with SD = 35%). A sample size of 30 participants per group was chosen to provide a power of 0.8, with two-tailed $\alpha = 0.05$, to detect such an effect.

Statistical analyses. Pre-quit changes in CPD and cigarette satisfaction were analyzed in 2 run-in groups × 2 genders × 4 time (weeks 2, 3, 4, and 5) ANOVAs, using the Huynh–Feldt (H-F) correction for violations of sphericity.[45] Parallel analyses examined secondary pre-quit measures (craving, withdrawal, and the other subjective effects of smoking scales (psychological reward, craving reduction, aversion, and respiratory sensations)). The baseline (week 1) value for each variable was included as a covariate. A parallel analysis of pre-quit changes in CO levels targeted the levels measured at the ends of weeks 2 and 4, with baseline CO (end of week 1) as a covariate. To further characterize pre-quit changes in smoking patterns, we analyzed the percentage reduction in pre-quit CPD ((week 1 − week 5)/week 1 × 100) and CO level ((end of week 1 − end of week 4)/end of week 1 × 100) in parallel ANOVAs.

During the post-quit period, an intention-to-treat approach was utilized, with participants lost to follow-up and those for whom CO-level verification was missing coded as smokers (see **Figure 1**). Abstinence measures were analyzed with logistic regression models that examined the separate and combined effects of run-in group and gender. Odds ratios and 95% confidence intervals (CIs) are reported, and all significance tests were two-tailed.

Group-related differences in study blinding at the end of the 3-week drug manipulation phase (guesses by participants as to their treatment assignment), as well as percentage adherence to medication and the rate of increase in adverse events relative to baseline (end of week 1), were analyzed using X^2. Because both run-in groups received varenicline but started medication at different times, side-effect data and percentage adherence were examined separately for the 3-week drug-manipulation phase (maximum reported at weeks 2, 4), when only the Extended group was taking varenicline, and the subsequent 3-week period (maximum at weeks 5, 7), which were the first 3 weeks of varenicline for the Standard run-in group.

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