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Original investigation

Does Extended Pre Quit Bupropion Aid in Extinguishing Smoking Behavior?

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Abstract

Introduction: Understanding the mechanisms by which bupropion promotes smoking cessation may lead to more effective treatment. To the extent that reduced smoking reinforcement is one such mechanism, a longer duration of pre quit bupropion treatment should promote extinction of smoking behavior. We evaluated whether 4 weeks of pre quit bupropion (extended run-in) results in greater pre quit reductions in smoking rate and cotinine and, secondarily, greater short-term abstinence, than standard 1 week of pre quit bupropion (standard run-in).

Methods: Adult smokers (n = 95; 48 females) were randomized to a standard run-in group (n = 48; 3-week placebo, then 1-week bupropion pre quit) or an extended run-in group (4-week pre quit bupropion; n = 47). Both groups received group behavioral counseling and 7 weeks of post quit bupropion. Smoking rate (and craving, withdrawal, and subjective effects) was collected daily during the pre quit period; biochemical data (cotinine and carbon monoxide) were collected at study visits.

Results: During the pre quit period, the extended run-in group exhibited a greater decrease in smoking rate, compared to the standard run-in group, interaction p = .03. Cigarette craving and salivary cotinine followed a similar pattern, though the latter was evident only among women. Biochemically verified 4-week continuous abstinence rates were higher in the extended run-in group (53%) than the standard run-in group (31%), p = .033.

Conclusions: The extended use of bupropion prior to a quit attempt reduces smoking behavior during the pre quit period and improved short-term abstinence rates. The data are consistent with an extinction-of-reinforcement model and support further investigation of extended run-in bupropion therapy for smoking cessation.

Introduction

In 1997, bupropion became the first non-nicotine pharmacotherapy approved by the U.S. Food and Drug Administration for smoking cessation.[1,2] While bupropion approximately doubles the odds of cessation relative to placebo, cessation rates at 6 months are modest with an average of 25% of participants in randomized clinical trials remaining smoke-free.[3,4] These results are comparable to quit rates with nicotine replacement therapy and somewhat lower than quit rates with varenicline.[5]

An improved understanding of the mechanisms by which bupropion works may lead to more targeted and effective use of bupropion for smoking cessation.[6–8] Most clinical studies to date have focused on bupropion's ability to attenuate post cessation increases in withdrawal, craving, or general negative affect. Although each of

these effects is robust, evidence that they actually mediate bupropion's efficacy for smoking cessation is mixed.[9,10]

The neurobiological actions of bupropion suggest that smoking reinforcement should be evaluated as a treatment mechanism. Bupropion is a stimulator and weak reuptake inhibitor of both norepinephrine and dopamine, as well as a nicotinic acetylcholine receptor antagonist.[11] These effects may reduce positive reinforcement from smoking.[12,13] Indeed, preclinical data suggest that chronic bupropion reduces nicotine self-administration in rats[14–16] and responding for stimuli associated with nicotine,[17] but see Paterson and colleagues.[18] As noted by Cryan and colleagues,[19] these findings "give neurobiological credence to the clinical practice of initiating bupropion therapy prior to nicotine cessation…bupropion may act…to attenuate the rewarding effects of nicotine, thus increasing the likelihood of cessation" (p.355).

In humans, there is surprisingly little research on the effect of bupropion on smoking reinforcement.[20] Post quit data from clinical trials demonstrate that bupropion reduces subjective reward and satisfaction during smoking lapses.[21] However, to more fully determine the effect of bupropion on smoking reinforcement, it is important to examine the pre quit period, paralleling the animal literature on self-administration. This also makes sense clinically, as bupropion is typically administered for a week prior to quitting,[1] offering a window for bupropion to attenuate reinforcement during typical smoking.[22]

From a learning perspective, the blockade of reinforcement should result in extinction, a decrease in the frequency of smoking. Although acute bupropion increased the *ad libitum* smoking among non-treatment-seeking smokers,[23] this increase could reflect an extinction burst, a temporary increase in behavior in the context of reinforcement blockade, that is followed by a reduction in behavior over time.[24,25] For extinction to occur, participants must continue smoking in order to learn that the reinforcing effects are attenuated.

In this study, we extend the typical 1 week of pre quit bupropion for two reasons. First, extinction is greatest when numerous "trials" are conducted over a prolonged period of time.[26–30] Given that bupropion and the metabolite hydroxybupropion do not reach steady-state concentrations until 5–8 days, a longer duration of bupropion pre quit treatment is likely necessary to adequately test the extinction mechanism. Second, and relatedly, extinction is context-specific. Simply changing the physical environment renews previously extinguished behavior[26,28] and craving.[31] It may be critical to extinguish smoking across a range of physical, social, and affective contexts.[29] Because learning theory predicts that extinction in smokers does not generalize from one trigger situation (e.g., while driving or on the phone) to another (e.g., while drinking coffee or alcohol or under stress), it is important that smokers take bupropion and continue smoking long enough to allow repeated exposures to a variety of contexts.

Given the target population, we recruited smokers motivated to quit[32,33] and randomized them to the standard pre quit run-in of 1 week or an extended pre quit run-in of 4 weeks (following prior extinction work).[24,34–37] Based on an extinction-of-reinforcement framework, we predicted that the extended bupropion run-in group would exhibit greater pre quit reductions in smoking rate and salivary cotinine compared with the standard bupropion run-in group. We also examined pre quit changes in overnight withdrawal and craving and in the subjective effects of smoking the first cigarette of the day. Though the study was under-powered to detect group differences in cessation, we provide preliminary data on short-term (4-week) continuous abstinence from smoking.

Methods

Participants

Radio, television, newspaper ads, and flyers in the community were used to recruit 95 adult (18–65 years old) treatment-seeking heavy cigarette smokers (at least 15 cigarettes per day) motivated to quit in the next 3 months. Exclusion criteria included self reported bupropion allergy, chronic renal or hepatic disease, history of head trauma or seizures, central nervous system tumor, insulin-treated diabetes, or uncontrolled hypertension; active cancer treatment; current use of St. John's Wart, antipsychotics, antidepressants, theophylline, systemic steroids, over-the-counter stimulants and anorectics, L-Dopa, or recent discontinuation of a benzodiazepine; currently pregnant (confirmed with urine screen) or lactating; history of bulimia or anorexia nervosa; and current substance dependence or abuse, psychosis, or depression per MINI International Neuropsychiatric Interview (MINI).[38] Participants received remuneration for attending study visits and adherence to study procedures, as detailed below.

Study Design and Medication

All procedures were approved by the Roswell Park Cancer Institute IRB. This experiment was designed and powered to evaluate the effects of extended pre quit bupropion treatment on changes in smoking behavior before participants tried to cut down or quit smoking. Thus, participants were randomized (double-blind) to either 4 weeks of bupropion SR (purchased from GlaxoSmithKline) prior to the target quit day (TQD) (extended run-in group) or to 3 weeks of placebo (visually identical to bupropion, purchased from the University of Pennsylvania), followed by 1 week of bupropion SR prior to TQD (standard run-in group). The initial week of treatment followed GSK guidelines and Phase III clinical trials[1,2,39]: 1 tablet (150 mg by mouth) once daily for 3 days, then 1 tablet (150 mg by mouth) twice daily. Both groups received a standard 7-week course of post-TQD bupropion. Prior quit attempts using bupropion were uncommon (n = 3 and 2 in the standard and extended run-in groups, respectively).

Procedures

During an orientation/baseline session (Visit 1) participants were given a study overview and provided informed consent, after which they completed assessments of smoking behavior (e.g., nicotine dependence[40], smoking history), demographics, personality, psychiatric disorders (MINI), and met with the study physician. Eligible participants received instruction regarding daily smoking diary procedures and a visit schedule.

At Visit 2 (Day 8), participants were randomized to either the standard run-in group (n = 48) or the extended run-in group (n = 47). During Visit 2 and subsequent visits (Visit 3 [Day 15], Visit 4 [Day 29], Visit 5 [Day 36; target quit date], Visit 6 [Day 50], Visit 7 [Day 64]), participants received medication and group counseling[39]; assessments included collection and review of daily smoking diary data, vital signs, side effects, carbon monoxide (CO), and saliva for assessment of cotinine.

Counseling groups included participants in both run-in conditions. Thus, counseling focused on standard smoking cessation topics,[39] including honing motivation and social support for quitting, identifying smoking triggers and developing coping strategies, and relapse prevention. Participants were not informed of the extinction rationale or hypothesis. Therefore, participants were not advised to smoke in a manner that might facilitate extinction, except that during the pre quit period, participants were asked to continue smoking

at least 25% of their baseline rate, following their urges to smoke, to allow their bodies time to adjust to the medication.[24,35]

Measures

Primary outcomes were self-reported cigarettes smoked per day and salivary cotinine during the pre quit period. Secondary outcomes were pre quit craving, withdrawal, and subjective effects, as well as short-term (4-week) continuous abstinence.

All pre quit measures except cotinine were collected via a daily diary, which began 1 week prior to the randomization visit and continued throughout the 4-week pre-TQD phase (daily data for the first 5 participants in the study were lost due to multiple data collection, upload, and integrity issues with the SmokeSignals Pro [MedSignals Inc.] electronic cigarette case; thereafter we moved to diary format). Timing of daily assessments was based on the first cigarette of the day. Prior to smoking, participants recorded the number of cigarettes smoked the previous day, indicated the time of waking and time of report, and completed a 5-item craving measure[41] and the Minnesota Nicotine Withdrawal Scale.[42] Participants then smoked the first cigarette of the day and completed the Subjective Effects of Smoking scale[43] (e.g., satisfying, good taste; scale = 0 "not at all" to 4 "extreme").

To prevent many of the issues inherent in diary data,[44] participants were required to document completion of the paper diary via voicemail each day within 1 hr of completing the assessments (participants dictated their responses, which were transcribed by a research assistant and later compared to physical diaries returned at each visit). To enhance compliance with daily assessments, a bonus was offered for reporting on more than the required minimum of 3 days per week (i.e., $5 for 4 days… $20 for all 7 days).

During the pre quit period, salivary cotinine obtained at the end of the baseline week (Visit 2) and the end of the 3-week drug manipulation phase (Visit 4) provided an additional measure of cigarette smoking.[34] (Budgetary constraints prohibited assaying cotinine at Visits 1, 3, and 6.) Saliva samples were stored at −80 °C until shipped to Salimetrics for duplicate enzyme immunoassay. Cotinine analyses were conducted on n = 78, after excluding participants for whom Visit 2 samples were not stored properly (n = 13) and participants with inadequate or contaminated samples (n = 4). Pre quit CO was not a reasonable alternative because logistical issues within the clinical research setting led to marked and variable delays between arrival and assessment of CO, particularly at Visits 1 and 2.

Continuous abstinence after the target quit day was a secondary outcome, as in other studies of extended pre quit medication.[45,46] Timeline follow-back interviews were conducted at each post quit follow-up and bio-verified with CO samples obtained at each visit, using a cut-off of 8 ppm.[47–49] Although we had planned to focus on 3-month continuous abstinence rates, compliance with study visits decreased markedly after the 4-week follow-up (Visit 7; the last visit in which counseling and study medication were provided). Given that the majority of relapse occurs within the first few weeks after quitting[6,50–52] and the exploratory nature of the abstinence data in this study, we focus on rates of 4-week continuous abstinence (not even a single puff, per self-report, and negative CO at all three in-person visits).[53]

Analyses

To evaluate pre quit changes in smoking rate (and secondary outcomes of craving, withdrawal, and subjective effects), piecewise linear mixed models were estimated (SPSS MIXED) for the baseline week (days 1–7; base), the 3-week pre quit intervention period (days 8–28; drug manipulation), and the final week prior to the TQD (days 29–35; final pre-TQD).[35] Random intercept and slopes were included in the models and a first-order auto-regressive covariance structure was employed.[54] For all models, run-in group (standard vs. extended) was included as between-subjects factors. In addition, given that participant sex often moderates the behavioral pharmacology of nicotine and smoking,[55,56] as well as cessation,[57,58] we explored the moderating role of sex in the effects of pre quit duration.

To evaluate pre quit changes in salivary cotinine, a run-in group × sex × time repeated measures ANOVA examined change in cotinine from the end of the baseline week (day 8, Visit 2) to the end of the drug manipulation phase (day 29, Visit 4).

For 4-week continuous abstinence, logistic regression analyses were used to test the effect of treatment condition on cessation outcome. Run-in group (standard vs. extended) and sex were included as between-subjects factors and the 2-way interaction was tested. Odds ratios and 95% confidence intervals (CIs) are reported and all significance tests were 2-tailed and set at $\alpha = .05$. Participants lost to follow-up were assumed to be smoking (n = 9; 4 extended run-in).

Results

Participant Characteristics

As shown in Table 1, the run-in groups did not significantly differ on a range of demographic and smoking variables. Compliance with the daily diaries was excellent (approximately 33 out of 35 days, on

Table 1. Demographic and Tobacco Use Characteristics at Baseline

	Run-in group		
	Standard (n = 48)	Extended (n = 47)	p value
Age, years	46.7 (9.3)	45.8 (10.1)	.68
Sex, female	54%	48%	.76
Racial/ethnic minority	10%	8%	.75
Education beyond high school	45%	43%	.84
Married, n (%)	27 (55%)	22 (45%)	.36
Income	40K–55K	25K–39K	.06
Cigarettes per day	22.0 (6.0)	23.4 (7.9)	.33
FTND	5.8 (1.7)	6.0 (1.9)	.50
Years smoking	28.8 (9.0)	26.7 (11)	.34
Daily assessment compliance[a]	96%	94%	.46

FTND = Fagerström Test of Nicotine Dependence. Values are mean (*SD*) unless otherwise noted.
[a]n = 90 (46 standard run-in group) for daily assessments.

average) and the number of days of daily data completed did not differ between groups, $F < 1$.

Pre quit Cigarettes Smoked Per Day

During the baseline week, cigarette smoking rate was comparable between run-in groups and across days, Fs < 1. During the drug manipulation phase, the critical run-in group × time interaction was significant, $F(1,86) = 4.7$, $p = .03$; follow-up tests were consistent with a greater average decrease in cigarettes smoked per day (CPD) over time in the extended run-in group, $b = -0.26$, $p = 1.1 \times 10^{-9}$ compared to the standard run-in group, $b = -0.16$, $p = 1.4 \times 10^{-6}$ (Figure 1). CPD continued to decrease across the final pre-TQD week when all participants were taking bupropion, time $F(1,86) = 10.3$, $p = .002$, but the rate of decline did not vary by run-in group or sex, Fs < 1. None of the run-in group × sex × time interactions were significant, Fs < 1.

Pre quit Salivary Cotinine

Cotinine levels did not differ by group and/or sex at the end of the baseline week, Fs < 1. As can be seen in Figure 2, the predicted pattern of a greater reduction in cotinine from the end of the baseline week to the end of the 3-week drug manipulation phase was observed among women, run-in group × time $F(1,41) = 5.3$, $p = .027$, but not men, $F < 1$, run-in group × sex × time $F(1,74) = 4.4$, $p = .039$. Women in the extended run-in group exhibited a significant reduction across the drug manipulation phase, $p = .001$; ps > .21 in all other run-in group × sex cells.

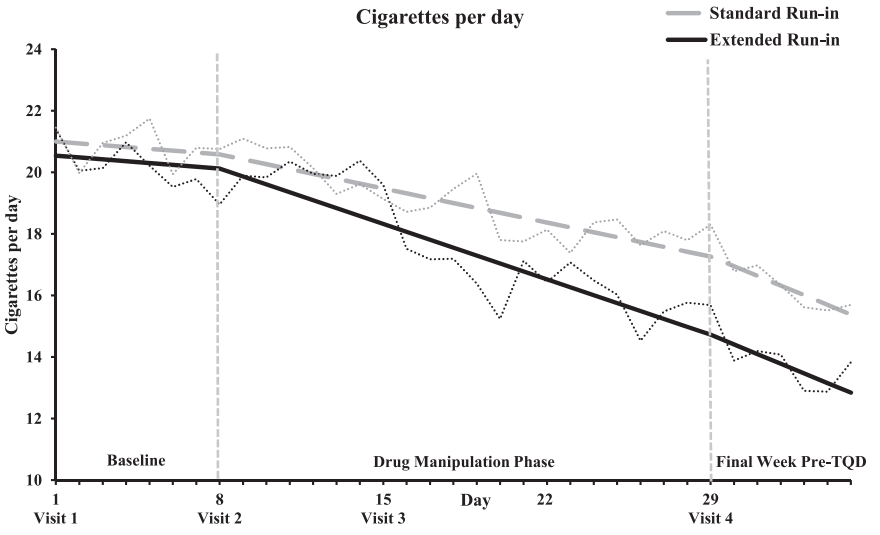

Figure 1. Cigarettes smoked per day across the 35-day pre quit period for each run-in group. *Note.* Solid lines represent predicted values based on parameter estimates from mixed models. Dotted lines represent raw values. Vertical dashed lines denote the three phases of the pre quit period: baseline (days 1–7), drug manipulation phase (days 8–28), final week pre target quit day (days 29–35).

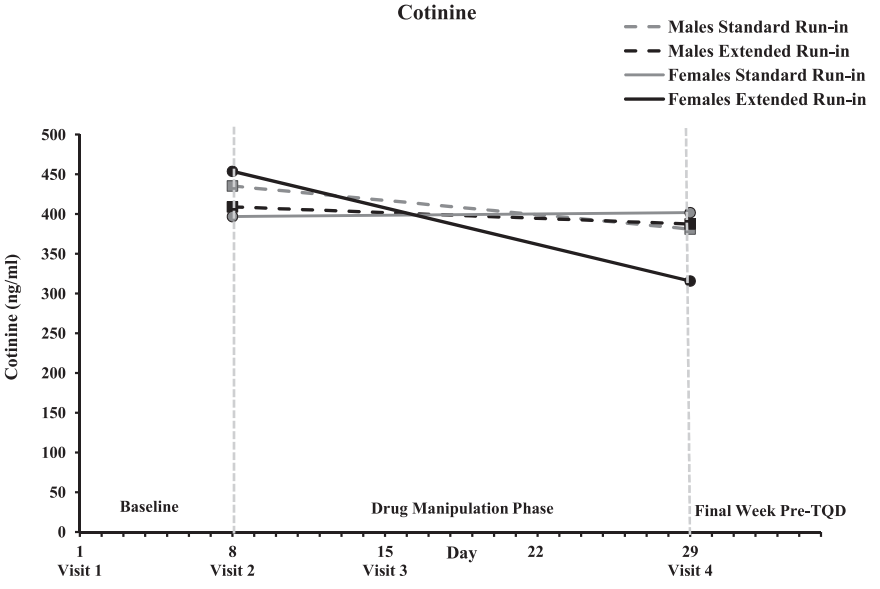

Figure 2. Mean salivary cotinine at the end of the baseline week (Visit 2) and end of the drug manipulation phase (Visit 4) for all run-in group × sex conditions.

Secondary Pre quit Subjective Measures

At the beginning of the baseline week (Day 1), mean morning craving was just above the midpoint of the 0–4 scale (mean[*SD*] = 2.4[1.0]), satisfaction with the first cigarette of the day was just below the scale midpoint (mean[*SD*] = 1.7[0.7]), and morning withdrawal was minimal (mean[*SD*] = 0.3[0.4]). During the baseline week, there were significant decreases in morning craving and satisfaction with the first cigarette of the day, *Fs*(1,84 and 1,86) = 28.8 and 129.6, *b*s = –0.05 and –0.07, *p*s < .001, but not morning withdrawal symptoms, $p = .41$. Changes during the baseline week were unrelated to run-in group and sex, *F*s < 1.

Across the critical 3-week drug manipulation phase, the modest further decreases in craving tended to be greater in the extended run-in group, $t(42) = -6.5$, $b = -0.033$, $p = .3 \times 10^{-7}$, compared to the standard run-in group, $t(45) = -4.5$, $b = -0.02$, $p = .0001$, but the run-in group × time interaction was marginal $F(1,85) = 3.6$, $p = .06$. Smoking satisfaction and withdrawal symptoms declined across the drug manipulation phase, *Fs* = 48.6 and 11.4, *b*s = –0.01 and –0.004, *p*s < .001 (with the decrease in withdrawal driven primarily by men, sex × time $F(1,84) = 4.4$, $p = .04$), but these effects were not moderated by run-in group, *F*s < 1.

During the final week pre-TQD, when all participants were taking bupropion, there were no further declines in smoking satisfaction or craving, *F*s < 1. Withdrawal symptoms increased across the week leading up to the TQD, but remained near the floor of the scale, Day 34 (mean[*SD*] = 0.5[0.6]), $F(1,81) = 32.1$, $b = 0.06$, $p < .001$, independent of run-in group and sex, *F*s < 1.

Secondary Clinical Endpoint—Short-Term Abstinence

Biochemically verified 4-week continuous abstinence rates were higher in the extended run-in group (53%) than the standard run-in group (31%), $p = .033$, $OR = 2.5$, 95% CI = 1.1–6.0). Although females were less likely to be abstinent compared to males (32% and 53%, respectively, $p = .039$, $OR = 0.40$, 95% CI = 0.17–0.95), there was no indication of a meaningful run-in group × sex interaction, $p = .57$. At the request of an anonymous reviewer, we also examined CO-verified 7-day point prevalence of abstinence at 4 weeks post-TQD: point prevalence abstinence rates were higher in the extended run-in group (72%) than the standard run-in group (44%), $p = .006$, and tended to be lower among females (50%) than males (67%), $p = .10$; interaction $p = .53$.

Discussion

The present study evaluated the hypothesis that extending the pre quit run-in period for bupropion from 1 to 4 weeks would alter smoking behavior in a manner consistent with an extinction-of-reinforcement mechanism. Consistent with our primary hypothesis, the extended run-in group exhibited greater pre quit reductions in self-reported smoking rate than did the standard run-in group. Importantly, self-report was captured daily, minimizing retrospective biases.[59]

Craving followed a pattern similar to CPD; the decrease in craving across the 3-week drug manipulation phase tended to be greater among the extended run-in group compared to the standard run-in group. Neither satisfaction with the first cigarette of the day nor morning withdrawal exhibited the predicted group differences across the pre quit period. Although these null findings may appear inconsistent with the extinction hypothesis, two aspects of the data mitigate this concern. First, smoking satisfaction and withdrawal were low, on average, prior to the drug manipulation phase. Thus, there was restricted range in which to observe further decreases on these measures. Second, as Rose and others have noted,[35,60] run-in group differences in smoking satisfaction would be most evident if smoking rate remained comparable between the two groups. However, when pre quit treatment results in a greater decrease in smoking rate (CPD)—as in the present study—such decreases in smoking behavior likely attenuate differences in self-reported smoking satisfaction.

As noted in the introduction, the best measure of extinction is the behavior of interest, smoking rate, which was obtained through daily self-report. To assuage concerns about reliance on self-report, cotinine provided a biochemical index of changes in pre quit smoking behavior. For women, cotinine analyses were consistent with the extinction hypothesis, decreasing across the drug manipulation phase in the extended run-in group but not the standard run-in group. However, men in the extended run-in group did not exhibit the predicted decrease in cotinine during the drug manipulation phase. There is some evidence that extended pre quit pharmacotherapy may have more powerful or rapid effects on smoking behavior and abstinence among women compared to men.[35,61] However, in the present study, sex did not moderate any other effect of extended run-in bupropion, suggesting the sex effect was specific to cotinine. Interestingly, emerging evidence suggests the cotinine clearance rate is substantially slower among men compared to women (likely due to estrogen-induced increases in CYP2A6 activity in women), resulting in weaker relationships between cotinine and other indicators of tobacco exposure (including urinary total nicotine equivalents) among men.[62] In the current study, sex differences in cotinine clearance could have attenuated the degree to which cotinine reflected run-in group differences in smoking rate among men.[63] Future large-scale studies of extended pre quit treatment should evaluate moderation by sex and include biomarkers of tobacco exposure that are less sensitive to individual differences in metabolism, such as urinary total nicotine equivalents.[62]

Although the focus of this study was on evaluating extinction-based predictions during the pre quit period, the participants were treatment-seeking smokers and we examined short-term abstinence rates as a secondary outcome. Consistent with the extinction framework, bio-verified continuous abstinence at 4 weeks post quit was significantly greater among the extended run-in group compared to the standard run-in group. These preliminary outcome data are particularly notable when one considers that the "control" group condition in the present study received standard bupropion therapy (and intensive group behavioral counseling), an evidence-based frontline treatment for smoking cessation.[3] Of course, longer-term follow-up in substantially larger samples would be necessary to evaluate the clinical efficacy and cost-effectiveness of extending the duration of pre quit bupropion therapy.

The results of the present study can be integrated within a broader reinforcement and extinction framework.[34,37,45,64] For extinction to occur, people must continue smoking in order to learn that the reinforcing effects are attenuated. Extinction is maximized when numerous "trials" are conducted over a long period of time and across a range of contexts.[30,65–68] Though there are promising data with as little as 2 weeks of pre quit NRT therapy, the pre quit CPD data (Figure 2) suggests that the effect of pre quit treatment grows over the 3-week drug manipulation phase,

as has also been found for varenicline.[34,35] Future work might consider whether pre quit therapy might optimally be combined with a flexible quit date[69] determined in part by a target reduction in smoking behavior. In the absence of such a reduction, it may be advisable to alter the treatment prior to attempting to quit.[70] Alternatively, reinforcing continued smoking near one's baseline rate during an extended period of pre quit pharmacotherapy, in combination with counseling that facilitates repeated exposure to a range of smoking-associated cues and contexts, would maximize the number of extinction trials. In that case, changes in pre quit craving or smoking satisfaction could guide selecting a quit date or switching therapies.

Extending the duration of pre quit pharmacotherapy is a practical approach to facilitating extinction of smoking behavior across a range of contexts (or "trigger" situations). However, the number of exposures to any particular context is limited, and low base-rate "triggers" or contexts may have relatively few, unsystematic exposures. Preclinical research on extinction of operant behavior has advanced markedly in recent years, demonstrating not only the ease with which extinction can be undone by changes in context (renewal), by subsequent extinction of a behavior that was paired with the original extinction (resurgence), or by rapid reacquisition upon a lapse, but also methods that can attenuate these effects.[71] Human behavioral pharmacology studies of these principles and effects are rare,[31] but are sorely needed to translate this promising animal literature on extinction and inform large-scale clinical trials.

Pre clinical work also provides clues to the aspects of reinforcement that are altered or extinguished by pre quit treatment. Bupropion increases the bioavailability of dopamine and norepinephrine and is a nicotinic acetylcholine receptor antagonist.[11] These effects may block or attenuate positive reinforcement from smoking.[12,13,19] Alternatively, the ability of pre quit bupropion to reduce smoking may result from substitution of reinforcement, as bupropion shares many of the effects of nicotine in pre clinical studies.[13,17] Interestingly, the ability of nicotine to enhance responding for even weak sensory reinforcers that are not drug-related cues may be critical in understanding the maintenance of smoking.[72–74] Bupropion appears to have similar reinforcement-enhancing effects, though perhaps through different neurotransmitter systems.[75] Although research extending this work to humans is surprisingly scarce, Perkins and colleagues[20] provided initial evidence that bupropion reverses the abstinence-induced decrease in responding for non-drug-related sensory stimuli (music) in human smokers. Further work on understanding the reinforcement-altering mechanisms of pre quit pharmacotherapy may allow tailoring of treatment and provide precise targets for treatment development.

In summary, the present data demonstrate that extended use of bupropion during the weeks leading up to a quit attempt reduces smoking behavior during the pre quit period, without increasing craving, withdrawal or smoking satisfaction. This pattern is consistent with an extinction framework. The outcome data, though exploratory, suggest that extending the duration of pre quit bupropion improves short-term abstinence rates above that obtained with standard bupropion treatment, at least in smokers similar to those studied here. The combination of a strong theoretical foundation, straightforward change in dosing strategy, and encouraging data on both process and outcome support further investigation of extended run-in bupropion therapy for smoking cessation.

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Declaration of Interests

LWH has served as a consultant on investigator-initiated smoking studies sponsored by Pfizer and the state of Florida. KMC provides expert testimony in litigation against cigarette manufacturers provides consulting advice and has received grants from Pfizer, and previously served as a co-investigator on a multicenter trial evaluating a nicotine vaccine from Nabi Biopharmaceuticals. MCM has served on the Speaker's Bureau for Pfizer and as the medical director of the New York State Smokers Quit Line. All other authors indicate that they have no competing interests.

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