

# Experimenter-defined quit dates for smoking cessation: adherence improves outcomes for women but not for men

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Submitted 8 May 2003;  
initial review completed 19 August 2003;  
final version accepted 15 October 2003

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## ABSTRACT

**Aims** Smoking cessation treatment trials often require that smokers quit on or before a protocol-defined date. The goals of this paper were to: (1) identify factors associated with adherence to a protocol-defined quit date and (2) determine whether such adherence predicts cessation outcome (relapse).

**Design** A quasi-experimental secondary analysis of data collected from a randomized placebo-controlled trial of fluoxetine (60 mg or 30 mg) versus placebo for smoking cessation.

**Setting and participants** Clinic-based smoking cessation treatment program comprising 989 non-depressed smokers.

**Intervention** Participants received cognitive behavioral therapy for smoking cessation and either study medication or placebo for 10 weeks. They were required to set a quit date within 2 weeks of their second study visit (by visit 4).

**Findings** Significant predictors of quit date adherence were low nicotine dependence and active drug treatment. High-dose fluoxetine (60 mg) and male gender were protective against relapse. Adherence to quit date was not an independent predictor of relapse; instead there was a significant interaction between quit date adherence and gender. Among non-adherers to the quit date, women were more than 2.5 times as likely as men to relapse; among adherers to the quit date, women were only 1.3 times as likely as men to relapse.

**Conclusions** Although women were more likely than men to relapse regardless of quit date adherence, adherence was strongly protective against relapse for women.

**KEYWORDS** Fluoxetine, quit attempts, relapse, smoking cessation.

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## INTRODUCTION

Approximately 46% of the 50 million smokers in the United States attempt quitting each year, but only 7% remain abstinent for 1 year (Fiore *et al.* 2000). Smoking cessation programs and research trials typically recruit self-selected smokers who are motivated to quit. These programs or clinical trials usually have a predetermined quit date and require all participants to try to quit on or before that date. Participants are informed of the quit date prior to their participation in treatment, so that their

acceptance or non-acceptance of this date becomes part of the eligibility criteria for entry into the trial.

While experimenter or provider-determined quit dates are common practice in smoking cessation treatment, it is not known whether the variability in the *actual* quit date predicts outcome at the end of treatment. For example, many experimental protocols require participants to quit within 2 weeks of study entry. It is not known whether participants who quit after the specified time range are more or less likely to remain quit than those who adhered to the externally imposed quit date.

Furthermore, it is unclear whether certain groups (e.g. women versus men) may benefit differentially from externally imposed quit dates.

Few studies have assessed whether or not adherence to a previously set quit date is predictive of smoking cessation outcomes. Rather, most have assessed the prediction of 6-month smoking outcomes from smoking behavior within the first 2 weeks of quitting (Russell *et al.* 1993; Richmond *et al.* Almeida 1994). In two pharmacological treatment studies, Westman *et al.* (1997) examined the achievement of quit date abstinence as a predictor of abstinence at a 6-month follow-up. Across both studies, the authors found that lower levels of nicotine dependence and achievement of abstinence on the quit date predicted a greater likelihood of abstinence at 6 months post-treatment, over and above other baseline characteristics, smoking behavior and smoking withdrawal. Quit date abstinence was found to have a 90% sensitivity in detecting those smokers who would achieve 6-month smoking abstinence. This study, however, did not examine predictors of quitting on the protocol-defined quit day, nor did they examine gender as a moderator of the effect of quit day abstinence on outcome.

The goals of our study were to: (1) determine the predictors of quit date adherence in a protocol which required participants to quit by an experimenter-determined quit date (typical of most randomized clinical trials) and (2) determine if adherence to the experimenter-imposed quit date would be associated with subsequent relapse, over and above other predictors known to be related to relapse. Based on previous literature that has shown that male gender, lower levels of nicotine dependence and active fluoxetine treatment are protective against relapse (Westman *et al.* 1997; Wetter *et al.* 1999; Borrelli *et al.* 2001; Niaura *et al.* 2002), we hypothesized that these variables would not only predict a lower likelihood of relapse, but also predict a greater likelihood of adherence to quitting by the target quit date. Consistent with Westman *et al.*'s (1997) work above, we hypothesized further that those who were adherent to their quit date would be more likely to be quit at the end of treatment. We decided to explore the interaction between gender and quit date adherence to provide some insight into treatment outcome findings suggesting gender disparities in quitting smoking in favor of men (e.g. Bjornson *et al.* 1995; Wetter *et al.* 1999).

## METHOD

### Participants

Participants were smokers involved in a double-blind, placebo-controlled multi-center trial investigating the effect of fluoxetine on smoking cessation (Eli Lilly Co.,

unpublished data; Niaura *et al.* 2002). Sixteen sites screened a total of 1137 subjects, of whom 989 met eligibility criteria and were randomized. Entry criteria required that subjects be 18–65 years old, have smoked daily for at least 1 year, exhibit a baseline expired carbon monoxide level  $\geq 8$  p.p.m. and agree to declare a quit date within 2 weeks after the second study visit (on or before visit 4). Exclusion criteria were a Hamilton Depression Rating Scale (Hamilton 1960; Endicott *et al.* 1981) score  $>14$ , pregnancy, hypertension, use of psychotropic medication or current psychiatric illness, alcohol or drug abuse in the past year, current use of nicotine replacement, unstable medical condition or major health event in the last 6 months, use of smokeless tobacco, pipes or cigars, recent experience of a major life event (e.g. divorce, major job change), suicidal ideation and history of bipolar disorder.

The sample composition was 60.4% female, with an average age of 41.8 years (SD = 9.3). Subjects smoked an average of 27.6 (SD = 11.2) cigarettes per day at baseline and were moderately dependent on cigarettes, as indicated by scores on the Fagerstrom Tolerance Questionnaire (FTQ) (M = 6.4, SD = 1.8; Fagerstrom 1978). The average body mass indices (BMI; weight in kg/M<sup>2</sup>) for women and men prior to medication were 24.5 kg (SD = 4.4) and 26.6 (SD = 4.3). The average baseline weight was 65.9 kg (SD = 12.9) for women and 84.4 kg (SD = 14.7) for men. There were no significant differences between treatment groups on any of the baseline variables.

## Measures

### Nicotine dependence

The Fagerstrom Tolerance Questionnaire, an eight-item scale (FTQ; Fagerstrom 1978) was used to assess nicotine dependence. The FTQ has been found to have good reliability and validity (Pomerleau *et al.* 1994).

### Smoking status

Smoking status was assessed at each visit. A quit attempt was defined as self-reported abstinence for 24 hours that was validated by expired air carbon monoxide test reading  $<10$  p.p.m. Participants were required to quit prior to visit 4 (the latest possible quit date was 24 hours prior to visit 4). Therefore, those who self-reported abstinence for 24 hours and who had a expired air carbon monoxide test reading of  $\leq 10$  p.p.m. at the time of visit 4 were considered quit by the target date ('adherers'). For the relapse analyses, participants who were quit by the target quit day and reported smoking at any of the subsequent visits were considered relapsers.

## BMI

Weight in kilograms was measured with shoes off at each visit using a balance beam scale. BMI was calculated as weight in kg/m<sup>2</sup>. BMI change was calculated by subtracting baseline BMI (before the start of medication) from the BMI at each visit during the treatment phase.

## Procedure

After a screening period, patients underwent a physical examination, chest X-ray, blood tests (complete blood count and differential) and medical history. Smokers fulfilling eligibility criteria were assigned randomly to placebo, 30 mg or 60 mg fluoxetine conditions. At visit 1, participants began the first of nine sessions of individual cognitive behavioral treatment aimed at achieving and maintaining smoking cessation through the development of coping skills, stimulus control and relapse prevention. Beginning at visit 2 and continuing to visit 9, participants received either study medication or placebo and were instructed to take one capsule every morning. This double-blind treatment phase was 10 weeks in duration and began at visit 2 (approximately 2 weeks prior to quit day) and continued through visits representing treatment sessions 3–9 (2 weeks prior to quit day and days 1–3 post quit, and weeks 1, 2, 4, 6 and 8 postquit day, with the final visit representing the end of treatment). At visit 2, participants were required to set a quit date within the subsequent 2 weeks (prior to visit 4). The latest possible quit date was 24 hours prior to visit 4. Participants paid a \$25.00 deposit that was refunded at their last visit non-contingent upon completion of the study or smoking status.

## Data analyses

Two separate regression models were constructed: one that modeled the predictors of time to first quit attempt and one that modeled the predictors of relapse. In the model for first quit attempt, the covariates predict the actual visit at which a successful quit attempt first occurred, whereas in the second they predict the time in days that elapsed between the first successful quit attempt and subsequent relapse, if any. Unlike the model for relapse, which operates on a continuous time scale, the model for quitting operates on a discrete time scale of visits since randomization. This was because the study protocol defined the required quit date in terms of visits, not days since randomization, and there was some between-subject variability in the timing of these visits.

In order to predict time to first quit attempt, we fit a discrete time analog of the proportional hazards (PH) regression model to the data. As shown by Prentice &

Gloeckler (1978) and Allison (1982), the model can be fit in PROC LOGISTIC of SAS 7.0 (SAS Institute Inc. 1999) and yields regression coefficients that correspond to log-hazard ratios, when the PH assumption holds in the underlying continuous scale.

Time to first relapse was analyzed using extensions of the Cox (Cox 1972) PH model for survival data available in PROC PHREG of SAS 7.0 (SAS Institute Inc. 1999). The basic premise of the Cox PH model is that the relapse hazard for two subjects whose covariates differ by a fixed amount remains constant over time at some fixed ratio, i.e. that the hazards are 'proportional'. For example, if active treatment lowered the relapse hazard substantially the first 2 weeks after it was administered, but its effects then wore off over time, the PH assumption would fail to hold. Accommodating such time-varying of time-invariant covariates (between-site differences that diminish over time) requires that the standard Cox PH model be extended to one with non-proportional hazards.

Violations of the PH assumption can be assessed graphically in PROC PHREG of SAS 7.0 using the martingale residuals approach of Therneau *et al.* (1990). In cases where a time-invariant stratification factor is found to fail the PH assumption, it is dropped from the list of predictors and the model is refitted, with time-invariant coefficients for all the remaining variables and a separate baseline hazard function for all subjects in a particular stratum. A common baseline survivor function is then no longer estimable, and even stratum-specific relapse probabilities require a sufficient number of events in each stratum before they can be estimated using the approach described in Kalbfleisch & Prentice (1980). However, to the extent that the remaining covariates do not interact with the stratification factor, informative statements about their effect on relapse can still be made in terms of their impact on the hazard function alone.

## RESULTS

### Predictors of time to first quit

As seen in Table 1, among those who made at least one quit attempt during treatment ( $n = 684$ ), 56% had quit by the recommended quit date (visit 4). We fitted a discrete-time PH regression model to the data with treatment site, Fagerstrom score, age, gender and BMI as main effects, and gender  $\times$  BMI and treatment  $\times$  BMI interactions. All continuous variables were standardized by subtracting the mean and dividing by the standard deviation. A backward elimination procedure based on the likelihood ratio test indicated that only the main effects of site, Fagerstrom score and treatment group were significant predictors of time to first quit attempt. Tests of time-dependent effects of these covariates were not significant,

**Table 1** Absolute probabilities of a first successful quit attempt: all 989 participants.

Visit	2	3	4	5	6	7	8	9	Total
First quit attempt	0.00	0.02	0.54	0.10	0.02	0.01	0.01	0.00	0.70
Censored*	0.03	0.06	0.03	0.04	0.02	0.03	0.03	0.06	0.30

\*Censoring before visit 9 indicates loss to follow-up.

**Table 2** Covariate effects on likelihood of a quit attempt.\*

	Coefficient	Standard error	Z-score	P-value
Fagerstrom	-0.17	0.04	-4.12	0.000
Active Tx	0.11	0.04	2.48	0.013
Site 1	-0.39	0.20	-1.94	0.053
Site 2	0.40	0.14	2.89	0.004
Site 3	0.25	0.15	1.70	0.090
Site 4	-0.13	0.16	-0.81	0.420
Site 5	-0.10	0.17	-0.61	0.543
Site 6	-0.46	0.18	-2.60	0.009
Site 7	-0.02	0.15	-0.10	0.920
Site 8	0.45	0.15	3.03	0.002
Site 9	0.85	0.16	5.24	0.000
Site 10	-0.05	0.15	-0.31	0.755
Site 11	-0.04	0.14	-0.27	0.788
Site 12	-0.16	0.16	-0.97	0.332
Site 13	-0.09	0.16	-0.58	0.560
Site 14	-0.49	0.14	-3.38	0.001
Site 15	-0.13	0.15	-0.86	0.390
Site 16	0.02	0.16	0.63	0.529

\*A test of the effect of between-site variability had value  $\chi^2_{15} = 63.06$ , with  $P = 0.001$ .

indicating that the effects of these variables did not change significantly over time, although there was a trend for gradual diminution in the effect of baseline nicotine dependence over time ( $P = 0.10$ ). In addition, there was no evidence of between-site heterogeneity in the effect of either Fagerstrom score ( $\chi^2 = 10.83$  on 15 df,  $P = 0.76$ ) or treatment ( $\chi^2 = 15.68$  on 15 df,  $P = 0.40$ ) or of Fagerstrom score by treatment interaction ( $P = 0.64$ ). Finally, there was no statistically significant difference in the main effects of the 30 mg and 60 mg dose groups ( $P = 0.34$ ) on time to first quit, so the two active treatment groups were combined and compared jointly against the placebo group.

The final regression model (Table 2) indicated that significant predictors of an earlier quit attempt were low Fagerstrom score ( $P = 0.001$ ) and active treatment dose ( $P = 0.013$ ). There was also evidence of significant between-site variability in the quit rates ( $\chi^2 = 63.06$  on 15 df,  $P = 0.001$ ). Because the 16 sites were coded as using sum-to-zero contrasts, the average size effect was zero overall and participants in sites with negative coefficients were likely to have a later quit attempt than subjects in sites with positive coefficients. Two sites had

**Table 3** Cumulative probability of a first quit successful quit attempt: reference group.\*

Visit	2	3	4	5	6	7	8	9
PE <sup>1</sup>	0.00	0.02	0.58	0.71	0.74	0.75	0.77	0.77
LCL <sup>2</sup>	0.00	0.01	0.52	0.65	0.69	0.70	0.71	0.71
UCL <sup>3</sup>	0.00	0.03	0.63	0.76	0.79	0.80	0.81	0.81

\*Placebo subjects with mean FTQ = 6.4 at a 'typical' site. <sup>1</sup>PE: point estimate. <sup>2</sup>LCL: 95% lower confidence limit. <sup>3</sup>UCL: 95% upper confidence limit.

coefficients very close to zero, and therefore the quit rates they achieved can be considered 'typical' among sites enrolled in the present study. Based on the results of Table 2, we derived maximum likelihood estimates and 95% upper and lower confidence limits for the probability that subjects in the reference group (i.e. placebo subjects with mean Fagerstrom score at a 'typical' site) would experience a first quit attempt at any particular visit. Because we are modeling not 'any quit attempts', but rather only the first quit attempt, the events being modeled are mutually exclusive and exhaustive, with the probability of a first quit attempt by a particular visit being the sum of the probabilities that the reference group will have made a first quit attempt at all visits up to and including that visit. As seen in Table 3, 58% of subjects in the reference group made a quit attempt by visit 4 (95% CI 0.52–0.63), with their proportion rising to 77% by visit 9 (95% CI 0.71–0.81) [58% of the reference group (those in the placebo group with a mean Fagerstrom score or 6.4 at a typical site) quit by visit 4 (Table 1)]. The absolute probability of a first quit attempt by visit 4 among all participants is 56%. Thus, 19% made a quit attempt after the designated quit date (visit 4), but before the end of treatment (visit 9) and 23% did not make a quit attempt at all between visit 4 and visit 9.

Whereas Table 3 focuses on the reference group alone, Table 4 allows for predictions regarding the rate of quit attempts for other subgroups of interest. In particular, we were interested in evaluating the impact of varying Fagerstrom score over its interquartile range for both the placebo and active treatment groups at a 'typical' site. Increasing the level of nicotine dependence from the 25th sample percentile (Fagerstrom = 5) to the 75th percentile (Fagerstrom = 8) resulted in a 10% decrease in the predicted probability of a quit attempt by the

**Table 4** Cumulative probability of a quit attempt: subgroups.

Treatment	Fagerstrom	Visit 4		Visit 9	
		PE <sup>1</sup>	95% CI	PE <sup>1</sup>	95% CI
Placebo	5	0.62	(0.56, 0.68)	0.80	(0.75, 0.85)
	8	0.52	(0.47, 0.58)	0.72	(0.65, 0.77)
Active	5	0.70	(0.66, 0.74)	0.87	(0.83, 0.90)
	8	0.60	(0.55, 0.65)	0.79	(0.74, 0.83)

<sup>1</sup>PE: point estimate.

suggested quit date (visit 4) and a 8% decrease by the end of the medication period (visit 9), regardless of treatment group. The effect of fluoxetine on time to first quit was such that those on active treatment attempted to quit earlier than those on placebo at both low (Fagerstrom = 5) and high (Fagerstrom = 8) levels of nicotine dependence. Specifically, the probability of a first quit attempt by visit 4 was 9% higher among the active dose group than the placebo group regardless of Fagerstrom score; this differential in favor of the active treatment retained its clinical significance throughout the medication period, changing slightly from 9% at visit 4 to 7% at visit 9.

#### Quitting on quit day as a predictor of relapse

A continuous-time proportional-hazards regression model was tested to assess the impact of adherence to the prescribed quit date (visit 4) on subsequent relapse and, more specifically, whether quitting by the prescribed quit day moderated differences in outcome by gender and by treatment group. The model controlled for Fagerstrom, age, gender, BMI and treatment group (placebo, 30 mg, 60 mg). Site was used as a stratification factor because the proportional hazards failed to hold for this latter variable. In addition, interactions of adherence to the prescribed quit date with gender and treatment were also entered into the model. All continuous variables were standardized by subtracting their mean and dividing by their standard deviation. Contrasts between each active drug treatment condition and placebo were computed.

The placebo and 30-mg doses were not significantly different in terms of their impact on relapse hazard and were merged subsequently into a single group and contrasted with the 60 mg group. Main effects of Fagerstrom score ( $P = 0.072$ ), 60 mg dose treatment ( $P = 0.037$ ), gender ( $P = 0.001$ ) and adherence to the quit date ( $P = 0.110$ ) as well as a gender  $\times$  quit date interaction ( $P = 0.034$ ) were the only terms retained in the final model. This final model utilized a backwards-elimination procedure which employed an  $\alpha = 0.10$  level of

**Table 5** Covariate effects on likelihood of relapse.

Visit	PE <sup>1</sup>	LCL <sup>2</sup>	UCL <sup>3</sup>	P-value
Fagerstrom	1.10	0.99	1.23	0.072
60 mg dose Tx	0.78	0.82	0.99	0.037
Male gender	0.75	0.58	0.96	0.025
Quit after visit 4	1.36	0.94	1.97	0.110
Males, quit after visit 4	0.50	0.27	0.95	0.034

<sup>1</sup>PE: point estimate. <sup>2</sup>LCL: 95% lower confidence limit. <sup>3</sup>UCL: 95% upper confidence limit.**Table 6** Gender by quit date interaction.

Female : male hazard ratio	PE <sup>1</sup>	LCL <sup>2</sup>	UCL <sup>3</sup>	P-value
Adherers	1.33	1.04	1.72	0.025
Non-adherers	2.63	1.47	4.76	0.001

<sup>1</sup>PE: point estimate. <sup>2</sup>LCL: 95% lower confidence limit. <sup>3</sup>UCL: 95% upper confidence limit.

significance as a retention cut-off and proceeded in a hierarchical fashion, starting with the second-order terms first and retaining all main effects associated with a significant interaction.

Point estimates (PE) and 95% lower (LCL) and upper (UCL) confidence limits for the relapse hazards are shown in Table 5. As expected, high-dose treatment (60 mg) was protective against relapse: it reduced the hazard of relapse by 22% relative to the placebo or low-dose (30 mg) treatment groups (PE = 0.78, 95% CI 0.62–0.99). Although not significant ( $P < 0.072$ ), participants with high levels of nicotine dependence tended to be more prone to relapse, such that as an individual's Fagerstrom scores increased from 6.4 to 8.2 (i.e. one standard unit away from the mean), the associated relapse hazard increased by 10% (PE = 1.10, 95% CI 0.99–1.23).

In order to understand better how adherence to the prescribed quit date may moderate the effect of gender on relapse, we used the coefficients of Table 5 to calculate the simple effects of gender separately by adherence group for our reference group of subjects with mean FTQ = 6.4 who were in the placebo or low-dose arms of the trial. We found that, among non-adherers to the quit date, women were more than 2.5 times as likely than men to relapse (PE = 2.63, 95% CI 1.47–4.76), whereas among adherers to the quit date, women were only 1.3 times as likely to relapse than men (PE = 1.33, 95% CI 1.04 to 1.72; Table 6). Therefore, although women were more likely than men to relapse regardless of whether they adhered to the prescribed quit date ( $P = 0.025$ ) or not ( $P = 0.001$ ), women's greater risk of relapse was more than twice as strong among non-adherers.

## DISCUSSION

Clinical trials in smoking cessation require typically that subjects quit on a particular date, or within a narrow time frame. Although an externally imposed quit date facilitates research objectives, no studies have examined the association between participant characteristics, adherence to quit date and abstinence outcomes. The goals of this study were to identify predictors of adherence to an externally imposed quit date and, in turn, to determine the effect of such adherence on the maintenance of abstinence. The results revealed that those on active treatment (30 mg or 60 mg fluoxetine) and those with low levels of nicotine dependence were more likely to adhere to the externally imposed quit date specified by the study protocol. In a separate model examining the predictors of relapse, high dose treatment (60 mg fluoxetine) significantly predicted a lower likelihood of relapse. There was also an interaction between quit date adherence and gender such that, although women were more likely to relapse than men whether or not they adhered to the quit date, women's risk of relapse was disproportionately heightened if they were non-adherent to the quit date.

Only 56% of participants quit within the time-frame required by study protocol (by visit 4). Thus, a large number of participants were non-adherent to the study protocol. The findings raise the possibility that providing participants with a narrow window of time in which they must quit might be too restrictive and unrealistic for a sizeable number of smokers. Of course, smokers assigned themselves to be adherent versus non-adherent to the quit date: they could not be randomly assigned. As such, we are unable to comment on any causal effects on relapse of being adherent versus non-adherent to the quit date, as distinct from those involved in possessing whatever personal attributes led smokers to behave adherently or not. Nevertheless, in light of new recommendations to impose grace periods on quitting, it may be worth reconsidering the merits of client-determined fixed quit dates given client-centered methods to motivate smoking cessation (e.g. motivational interviewing, Miller & Rollnick 2002).

In our study, adherence to the quit date was predicted by active treatment dose (either 30 mg or 60 mg fluoxetine) and low levels of nicotine dependence. Antidepressants, such as fluoxetine, nortryptiline and bupropion, have been shown to produce dose-response increases in quit rates (Niaura *et al.* 2002; Spring *et al.* 1995; Hurt *et al.* 1997; Hall *et al.* 1998). Our study found evidence of an overall drug effect on adherence to quit date; both active treatments vs. placebo resulted in a significantly greater likelihood of quitting by the target quit date. In a separate model predicting relapse, only the high (60 mg) dose fluoxetine was protective against relapse. A differ-

ence between our study and previous ones is that we examined two outcomes: quitting by the target quit date and relapse to smoking, rather than 7-day point prevalence abstinence.

There are several possible reasons why fluoxetine treatment may have both helped to promote quitting by the required quit date and curtailed relapse. Fluoxetine treatment may have reduced the compulsion to smoke or diminished preoccupation with cigarettes via an action analogous to its reduction of obsessional ideation and behaviours in bulimics (Goldbloom & Olmsted 1993) and those with obsessive-compulsive disorder (Piccinelli *et al.* 1995). Indeed, other serotonergic agents, such as sertraline (Covey *et al.* 2002) and paroxetine (Killen *et al.* 2001), have been found to reduce craving for cigarettes. Fluoxetine might have enhanced quit date adherence via reduction of depressogenic ruminations (Richmond *et al.* 2001) or relief of negative affect (Dalack *et al.* 1995). Indeed, Dalack *et al.* (1995) found that fluoxetine, compared with placebo, improved depressed mood among treatment-motivated smokers prior to the quit date. An alternative explanation is that side-effects could have alerted participants that they were, indeed, taking active drug versus placebo, increasing their confidence or self-efficacy about being able to adhere to the designated quit date (Hitsman *et al.* 2001). Both neurobiological and cognitive accompaniments of pharmacological treatment of smoking warrant future exploration, as both could be important mediators of treatment effects.

Maintenance of abstinence was predicted by level of nicotine dependence, 60 mg fluoxetine, gender and the interaction of gender and adherence to quit date. Previous literature has found that not smoking on the quit date is strongly predictive of subsequent abstinence (Westman *et al.* 1997), such that those who adhere to their quit date are over 10 times less likely to relapse than those who do not adhere. In our study, adherence to the quit date was not an independent predictor of relapse; rather, its effect was moderated by gender. Among those who did not adhere to the quit date, women were more than 2.5 times as likely to relapse than men, whereas among those who did adhere to the quit date, women were only 1.3 times as likely as men to relapse. Thus, although women were more likely to relapse than men regardless of adherence to the prescribed quit date, adherence to the study protocol was strongly protective against relapse for women.

In a randomized trial, Flaxman (1978) compared 'gradual quitting' to two different types of 'abrupt' quitting: (1) immediate (quitting on the day following a 1.5-hour group session on self-control techniques) and (2) quitting on the target quit date, which occurred 2 weeks after the beginning of treatment. When the two 'abrupt'

groups were combined and contrasted with delayed quitting, there was an interaction of gender and treatment group, such that women who received the delayed treatment and men who were in either abrupt quitting group smoked significantly less than women who quit smoking immediately and men whose quit dates were delayed. However, when treatment that involved quitting on a targeted quit date was compared to delayed quitting, the targeted quit date group smoked significantly less than the delayed group, and this effect did not vary by gender. In our study, time of quitting did not significantly predict smoking outcome as an overall main effect, possibly because we focused on actual quitting, not reduction. Another difference was that, unlike Flaxman's study, our participants were not assigned randomly to differing quit dates. Although quit date adherence was not an independent predictor of relapse in our study, the effect of adherence on relapse was moderated by gender such that women who did not quit by the target date were at heightened risk of relapse. This suggests that, for women, non-adherence to the initial quit date followed by a period of abstinence may be a harbinger of eventual relapse.

What remains to be understood are the underlying psychological processes that explain why smoking on the quit date is associated with poor cessation outcomes for women. These women may be more ambivalent about quitting, perhaps needing greater support and motivational enhancement for quitting. Alternatively, women may simply need extra time to build the skills needed for cessation in the face of multiple barriers to quitting (e.g. depression, Borrelli *et al.* 1996). Further study of treatment processes is needed to select from among these and other possible explanations.

Our finding that men were significantly less likely to relapse than women is consistent with findings from several community and clinical trials that have shown women to be more likely to relapse than men (Bjornson *et al.* 1995; Wetter *et al.* 1999). Other studies have not, however, supported a gender disparity in smoking outcome (Gritz *et al.* 1998; Killen *et al.* 2002). Several explanations for gender differences in relapse have been proffered, including women's greater vulnerability to depression (Borrelli *et al.* 1996; Hall *et al.* 1998) and fear of weight gain (Borrelli & Mermelstein 1998; Pinto *et al.* 1999; Borrelli *et al.* 2001).

Our study has several limitations. It should be noted that the study sample was selective, comprised of smokers willing to visit a medical setting to seek multi-session smoking cessation treatment that included medications. It cannot be assumed that these results will generalize to smokers who do not volunteer for treatment or who would be unwilling to engage in such an intensive treatment program. Also, our study was not able to examine the reasons why women who quit later than the pre-

scribed quit date were at heightened vulnerability to relapse. Importantly, smokers in our study were not randomized to experimenter-defined versus participant-defined quit dates. Therefore, no inferences can be drawn from our findings regarding whether participant-chosen quit dates yield better or worse cessation outcomes than fixed quit dates. However, it is difficult to answer this question in a randomized design, given that participants will self-select into quitting by the quit date or quitting on their own timeline, regardless of the condition to which they are assigned.

Our findings supported the hypothesis that the time of the first quit is an important but often neglected predictor of maintenance of smoking abstinence, at least for women. These results suggest that the new guidelines on implementing a grace period following quit day, proffered by the current Society for Research on Nicotine and Tobacco (SRNT; Hughes *et al.* 2003), may need to be evaluated empirically for the effects on quitting and relapse prior to widespread adoption.

## ACKNOWLEDGEMENTS

This study was funded by Eli Lilly & Co. (Niaura & Spring), as well as by NIH grant HL59348, HL32318, a VA merit award (Spring), National Cancer Institute Grants P50 CA84719 (Niaura) and R01 CA74553 (Borrelli). Brian Hitsman was supported by a grant from the National Institute on Drug Abuse F31 DA05854. The opinions presented are those of the authors and may not reflect the opinions of Eli Lilly & Co.

## REFERENCES

- Allison, P. D. (1982) Discrete-time methods for the analysis of event histories. In: Leinhardt, S., ed. *Sociological Methods and Research*, pp. 61–98. San Francisco: Jossey-Bass.
- Bjornson, W., Rand, C., Connett, J., Lindgren, P., Nides, M., Pope, F., Buist, A. S., Hoppe-Ryan, C. & O'Hara, P. for the Lung Health Study Research Group (1995) Gender differences in smoking cessation after 3 years in the Lung Health Study. *American Journal of Public Health*, **85**, 223–230.
- Borrelli, B., Bock, B., King, T., Pinto, B. & Marcus, B. (1996) The impact of depression on smoking cessation in women. *American Journal of Preventive Medicine*, **12**, 378–387.
- Borrelli, B. & Mermelstein, R. M. (1998) The role of weight concern and self-efficacy in smoking cessation and weight gain among smokers in a clinic-based cessation program. *Addictive Behaviors*, **23**, 609–622.
- Borrelli, B., Spring, B., Niaura, R., Hitsman, B. & Papandonatos, G. (2001) Influences of gender and weight gain on short-term relapse to smoking in a cessation trial. *Journal of Consulting and Clinical Psychology*, **69**, 511–515.
- Covey, L. S., Glassman, A. H., Stetner, F., Rivelli, S. & Stage, K. (2002) A randomized trial of sertraline as a cessation aid for

- smokers with a history of major depression. *American Journal of Psychiatry*, **159**, 1731–1737.
- Cox, D. R. (1972) Regression Models and Life-Tables (with Discussion). *Journal of the Royal Statistical Society, Series B*, **34**, 187–220.
- Dalack, G. W., Glassman, A. H., Rivelli, S., Covey, L. & Stetner, F. (1995) Mood, major depression, and fluoxetine response in cigarette smokers. *American Journal of Psychiatry*, **152**, 398–403.
- Endicott, J., Cohen, J., Nee, J., Fleiss, J. & Sarantakos, S. (1981) Hamilton Depression Rating Scale: extracted from regular and change versions of the Schedule for Affective Disorders and Schizophrenia. *Archives of General Psychiatry*, **38**, 98–103.
- Fagerstrom, K. O. (1978) Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addictive Behavior*, **3**, 235–241.
- Fiore, M. C., Bailey, W. C., Cohen, S. J., Dorfman, S. F., Goldstein, M. G., Gritz, E. R., Heyman, R. B., Jaen, C. R., Kottke, T. E., Lando, H. A., Mecklenburg, R. E., Mullen, P. D., Nett, L. M., Robinson, L., Stitzer, M. L., Tommasello, A. C., Villejo, L. & Wewers, M. E. (2000) *Treating Tobacco Use and Dependence*. Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services, Public Health Service.
- Flaxman, J. (1978) Quitting smoking now or later: gradual, abrupt, immediate, and delayed quitting. *Behavior Therapy*, **9**, 260–270.
- Goldbloom, D. S. & Olmsted, M. P. (1993) Pharmacotherapy of bulimia nervosa with fluoxetine: assessment of clinically significant attitudinal change. *American Journal of Psychiatry*, **5**, 770–774.
- Gritz, E. R., Thompson, B., Emmons, K., Ockene, J. K., Judith, K., McLerran, D. F. & Nielsen, I. R. (1998) Gender differences among smokers and quitters in the Working Well Trial. *Preventive Medicine*, **4**, 553–561.
- Hall, S. M., Reus, V. L., Munoz, R. F., Sees, K. L., Humfleet, G., Hartz, D. T., Frederick, S. & Triffleman, E. (1998) Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Archives of General Psychiatry*, **8**, 683–690.
- Hamilton, M. A. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–61.
- Hitsman, B., Spring, B., Borrelli, B., Niaura, R. & Papandonatos, G. D. (2001) Influence of antidepressant pharmacotherapy on behavioral treatment adherence and smoking cessation outcome in a combined treatment involving fluoxetine. *Experimental and Clinical Psychopharmacology*, **9**, 355–362.
- Hughes, J. R., Keely, J. P., Niaura, R. S., Ossip-Klein, D. J., Richmond, R. L., & Swan, G. E. (2003) Measures of abstinence in clinical trials: issues and recommendations. *Nicotine and Tobacco Research*, **5**, 13–25.
- Hurt, R. D., Sachs, D. P., Glover, E. D., Offord, K. P., Johnston, J. A., Dale, L. C., Khayrallah, M. A., Schroeder, D. R., Glover, P. N., Sullivan, C. R., Croghan, I. T. & Sullivan, P. M. (1997) A comparison of sustained-release bupropion and placebo for smoking cessation. *New England Journal of Medicine*, **337**, 1195–1202.
- Kalbfleisch, J. D. & Prentice, R. L. (1980) *The Statistical Analysis of Failure Time Data*. New York: John Wiley & Sons.
- Killen, J. D., Fortmann, S. P., Schatzberg, A. F., Hayward, C., Sussman, L., Rothman, M., Strausberg, L. & Varady, A. (2001) Nicotine patch and paroxetine for smoking cessation. *Journal of Consulting and Clinical Psychology*, **68**, 883–889.
- Killen, J. D., Fortmann, S. P., Varady, A. & Kraemer, H. C. (2002) Do men outperform women in smoking cessation trials? Maybe, but not by much. *Experimental and Clinical Psychopharmacology*, **10**, 295–301.
- Miller, W. R. & Rollnick, S. (2002) *Motivational Interviewing: Preparing People for Change*, 2nd edn. New York: Guilford Press.
- Niaura, R., Spring, B., Borrelli, B., Goldstein, M., Keuthen, N., DePue, J., Kristeller, J., Ockene, J., Prochazka, A., Chiles, J. A., Abrams, D. B. & Hedeker, D. (2002) Multicenter trial of fluoxetine as an adjunct to behavioral treatment for smoking cessation. *Journal of Consulting and Clinical Psychology*, **70**, 887–896.
- Piccinelli, M., Pini, S., Bellantuono, C. & Wilkinson, G. (1995) Efficacy of drug in obsessive-compulsive disorder. A meta-analytic review. *British Journal of Psychiatry*, **4**, 424–443.
- Pinto, B. M., Borrelli, B., King, T. K., Bock, B. C., Clark, M. M., Robert, M. & Marcus, B. (1999) Weight control smoking among sedentary women. *Addictive Behaviors*, **24**, 75–86.
- Pomerleau, C. S., Carton, S. M., Lutzke, M. L., Flessland, K. A. & Pomerleau, O. (1994) Reliability of the Fagerstrom Tolerance Questionnaire and the Fagerstrom Test for Nicotine Dependence. *Addictive Behaviors*, **19**: 33–39.
- Prentice, R. L. & Gloeckler, L. A. (1978) Regression analysis of grouped survival data with application to breast cancer data. *Biometrics*, **34**, 57–67.
- Richmond, R. L., Harris, K. & de Almeida, N. A. (1994) The transdermal nicotine patch: results of a randomised placebo-controlled trial. *Medical Journal of Australia*, **161**, 130–135.
- Richmond, M., Spring, B., Sommerfeld, B. K. & McChargue, D. (2001) Rumination and cigarette smoking. A bad combination for depressive outcomes. *Journal of Consulting and Clinical Psychology*, **69**, 836–840.
- Russell, M. A. H., Stapleton, J. A., Feyerabend, C., Wiseman, S. M., Gustavsson, G., Sawe, U. & Connor, P. (1993) Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *British Medical Journal*, **306**, 1308–1312.
- SAS Institute Inc. (1999) *SAS/STAT User's Guide*, version 7. Cary, NC: SAS Institute Inc.
- Spring, B., Wurtman, J., Wurtman, R., Khoury, A., Goldberg, H., McDermott, J. & Pingitore, R. (1995) Efficacies of dexfenfluramine and fluoxetine in preventing weight gain after smoking cessation. *American Journal of Clinical Nutrition*, **6**, 1181–1187.
- Therneau, T. M., Grambsch, P. M. & Fleming, T. R. (1990) Martingale-based residuals and survival models. *Biometrika*, **77**, 147–160.
- Westman, E. C., Behm, F. M., Simel, D. L. & Rose, J. E. (1997) Smoking behavior on the day of a quit attempt predicts long-term abstinence. *Archives of International Medicine*, **3**, 335–340.
- Wetter, D. W., Kenford, S. L., Smith, S. S., Fiore, M. C., Michael, C., Douglas, E. & Baker, T. B. (1999) Gender differences in smoking cessation. *Journal of Consulting and Clinical Psychology*, **4**, 555–562.