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Fluoxetine, Smoking, and History of Major Depression: A Randomized Controlled Trial

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The study was a randomized placebo-controlled trial testing whether fluoxetine selectively enhances cessation for smokers with a history of depression. Euthymic smokers with (H+, $n = 109$) or without (H-, $n = 138$) a history of major depression received 60 mg fluoxetine or placebo plus group behavioral quit-smoking treatment for 12 weeks. Fluoxetine initially enhanced cessation for H+ smokers ($p = .02$) but subsequently impaired cessation regardless of depressive history. Six months after quit date, fluoxetine-treated participants were 3.3 times more likely to be smoking ($p = .02$). Further research is warranted to determine why high-dose fluoxetine produces continuing effects that oppose tobacco abstinence.

Keywords: tobacco, smoking cessation, depression, fluoxetine, randomized controlled trial

Serotonergic agents have been found generally ineffective for enhancing long-term (> 6 months) tobacco abstinence (Hughes, Stead, & Lancaster, 2005). More favorable short-term results have emerged in some trials (Bowen, Spring, & Fox, 1991; Cornelius, Perkins, Salloum, Thase, & Moss, 1999; Killen et al., 2000; Niaura et al., 2002; Spring et al., 1995; Spring, Wurtman, Gleason, Wurtman, & Kessler, 1991) but not others (Blondal et al., 1999; Covey, Glassman, Stetner, Rivelli, & Stage, 2002; Naranjo, Kadlec, Sanhueza, Woodley-Remus, & Sellers, 1990; Saules et al., 2004; Sellers, Naranjo, & Kadlec, 1987). Variability in outcome for fluoxetine might be explained if the drug has a selective effect,

primarily benefiting the many current smokers who are depression prone. A drug benefit for cessation might emerge chiefly in studies that included a high proportion of smokers with (H+) versus without (H-) a history of major depressive disorder (MDD). Other pharmacotherapies for smoking (bupropion and nortriptyline) have not shown differential efficacy for euthymic H+ versus H- smokers (Hughes et al., 2005). However, to our knowledge, no previously reported studies had been conducted to examine whether, as cessation aids, serotonergic agents selectively benefit smokers with a history of depression.

The influence of MDD history on cessation failure remains controversial (Covey, 2004; Hitsman, Borrelli, McChargue, Spring, & Niaura, 2003; Hitsman, Spring, Borrelli, McChargue, & Niaura, 2004). Pre-quit dysphoria (Hall, Munoz, & Reus, 1994; Killen et al., 1996; Rausch, Nicholson, Lamke, & Matloff, 1990; Swan, Ward, & Jack, 1996) and postquit depressive symptoms (Covey, Glassman, & Stetner, 1990; Killen, Fortmann, Schatzberg, Hayward, & Varady, 2003) have both been shown to predict relapse. Both are characteristic of H+ smokers (Borrelli et al., 1999; Hitsman et al., 2003; Pomerleau et al., 2004). Fluoxetine might plausibly benefit H+ smokers because it has been shown to reduce their depressive symptoms prior to a quit attempt (Dalack, Glassman, Rivelli, Covey, & Stetner, 1995) and to improve short-term abstinence (Hitsman et al., 1999; Blondal et al., 1999) among smokers who have elevated baseline depression but are subthreshold for MDD. Also, the drug displays increased efficacy relative to placebo as a cessation aid for smokers who exhibit mild pre-quit symptoms of depression (Blondal et al., 1999; Hitsman et al., 1999). Fluoxetine might especially benefit H+ smokers in the time

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frame shortly after quitting, when they exhibit heightened postquit mood disturbance (Hall et al., 1994) and increased risk of relapse into a depressive episode (Borrelli et al., 1996; Glassman, 1997; Killen et al., 2003; Tsoh et al., 2000).

Consequently, this double-blind, randomized, placebo-controlled clinical trial tested the effect of 60 mg fluoxetine plus cognitive-behavioral smoking cessation treatment on abstinence among euthymic H+ and H- smokers. We hypothesized that H+ smokers would show superior abstinence when treated with fluoxetine, whereas no drug effect would be evident for H- smokers.

Method

Recruitment and Entry Criteria

Interested smokers were recruited by newspaper and radio advertisements; screened initially via telephone; then mailed questionnaires about demographics, medical history, tobacco use (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), alcohol use (Selzer, 1973), and depression (Beck, Steer, & Brown, 1996). They returned these in person, provided informed consent, and were interviewed with the Hamilton Depression Rating Scale (Ham-D; Hamilton, 1960) and the Structured Clinical Interview for DSM-IV (SCID-IV), Non-Patient Version (Spitzer, Williams, & Gibbon, 1994; First, Gibbon, Spitzer, & Williams, 1996). Assessors were master's- and doctoral-level psychology trainees under the supervision of the principal investigator, a licensed, board-certified clinical psychologist. They received 11 hours of standardized videotape training on the SCID-IV (First et al., 1996). Then they conducted mock interviews, observed patient interviews conducted by an experienced assessor, and were observed during live interviews until they attained 100% interrater reliability on MDD symptoms and diagnosis. Throughout the study, all assessors attended weekly supervision meetings with the principal investigator to discuss each case. Diagnostic disagreements were resolved by consensus.

At a second screening visit, the study physician assessed exclusionary medical conditions. Entry criteria specified males or females ages 18–65 who smoked at least 10 cigarettes per day for the past year. They could be categorized either as lacking a lifetime history of MDD or as having at least one past episode of MDD. Participants could not be currently depressed, as evidenced by a Beck Depression Inventory (BDI) score > 15, a Ham-D score > 14, or an MDD episode within the past 6 months. Also ineligible were those meeting criteria for any current episode of Axis I disorder (other than nicotine dependence) assessed by the SCID, or having a history of seizures, psychosis, or bipolar disorder. Additional exclusion criteria were current use of nicotine replacement therapy, beta blockers, thiazide diuretics, guanethidine, reserpine, clonidine, Type IC antiarrhythmics, or highly protein-bound drugs; or use of psychotropic medication within the past month. Also screened out were those with medically unstable conditions, CBC values 10% outside normal limits, liver enzymes exceeding 40% of the upper limit of normal, severe allergies, or allergy to fluoxetine; and women who were pregnant, lactating, or trying to become pregnant.

The Institutional Review Boards of the University of Illinois at Chicago and Edward Hines Jr. Veterans Affairs Hospital provided ethical approval for the study.

Study Design and Participant Flow

Of 2,050 candidates, 247 were eligible (Figure 1). The main factors that resulted in failure to meet entry criteria were exclusionary medications (45.2% of ineligible candidates), unstable medical condition (17.4%), age (13.6%), smoking < 10 cigarettes/day (11.3%), and psychological disorder (4.2%). The study pharmacist stratified participants by depression history and used computer-generated random numbers to assign them to drug or placebo. Research staff and participants were blinded to medication status. Medications were distributed at each treatment visit, including the first. Treatment groups met nine times during the 12-week treatment: weekly for 6 weeks and bi-weekly thereafter. Assigned quit date was the evening prior to the fourth visit. Thus, there were three visits before and six after the scheduled quit.

BDI data were collected at baseline; on the target quit date; and at 4, 8, 16, and 24 weeks postquit. Participants completed the Ham-D at baseline; on quit day; and at 4, 8, 12, 16, 20, and 24 weeks after the quit day. Blood and urine samples, collected 1 and 8 weeks postquit, were assayed to assess medication adherence. Following treatment, participants attended four paid (\$10/visit) monthly follow-up visits.

Intervention Through Cognitive-Behavioral Cessation Treatment

Manualized group treatment incorporated cognitive-behavioral and motivational interviewing techniques (Spring, 2002, in press). Treatment after quit date focused on coping with cravings, preventing relapse, and recycling relapsed participants toward another quit attempt.

Pharmacotherapy

At each visit, fluoxetine (D+) and placebo (D-) were dispensed in identical capsules and unused medication was returned. Additional pills, to be taken with each drug dose, were also prescribed to all participants. These pills, described as containing a cofactor necessary for making the medication work, actually supplied a 50-mg riboflavin tracer detectable in urine, enabling assessment of medication adherence for both placebo and drug. Drug dosage increased gradually over 2 weeks: 20 mg for 4 days; then 30 mg for 3 days, 40 mg for 3 days, 50 mg for 5 days, and 60 mg for the remainder of the treatment. Treatment group leaders elicited information about side effects at each group session and were available by pager between sessions to address clinical concerns. The study physician delayed an increased or lowered dosage for participants reporting severe side effects. Drug was discontinued abruptly at the end of the treatment phase.

Measures

Point prevalence abstinence was determined for each visit through the end of follow-up. Smoking status was assessed by self-report, expired carbon monoxide (CO), and salivary cotinine. CO was measured at all visits; cotinine samples were collected at 4 and 8 weeks postquit, and at the 4- and 6-month postquit follow-ups. Participants were considered *smoking* if they self-reported any smoking since the prior visit, had CO value ≥ 10

Figure 1. Participant flow through the trial. Participants were considered to have completed treatment if they attended at least one of the final two treatment visits, and to have completed follow-up if they attended at least one of the final two follow-up visits.

parts per million, or had cotinine value ≥ 20 ng/ml. Prolonged abstinence was coded as *continuous abstinence* from a grace period ending 2 weeks after quit date (Hughes et al., 2003) through end of treatment or end of follow-up.

When participants could not attend a session, they self-reported smoking status by telephone. To appraise the validity of self-report-only smoking status, we examined concordance between self-report and bioverification for each participant. Of the 181 participants who self-reported only abstinence, 15 had their data recoded as smoking because their self-reported abstinence at another timepoint was contradicted by CO or cotinine. What we judged to be dishonest claims of abstinence did not vary by drug, but varied by depression history, $\chi^2(1) = 3.89, p = .049$; 12 out of 15 dishonest reporters were MDD–history negative.

We measured pill-taking adherence for both treatment groups by grading urine samples according to riboflavin fluorescence (Kapur, 1992). Plasma fluoxetine and norfluoxetine levels for drug-treated participants were measured using gas-liquid chromatography (Nash, Bopp, Carmichael, Farid, & Lemberger, 1982).

Statistical Analyses

Smoking status (abstinent vs. smoking) was measured at multiple time points from 2 weeks to 6 months postquit. Power was estimated using Hsieh's formula (Hsieh, 1988) for dichotomous data over time. Based on the primary study hypothesis, the study was powered to detect a clinically meaningful drug effect on abstinence, if one was present, for H+ smokers and for H– smokers separately. Specifically, the study was powered to detect a 20% difference in abstinence between drug and placebo, separately for H+ and H– smokers, with power set at .80 and a two-sided alpha of .05. The assumed abstinence rate for the placebo group was set between 0 and 10% for H+ smokers and between 20 and 30% for H– smokers. The sample sizes of H+ and H– smokers were set so as to ensure that the drug versus placebo comparison had power of at least .80 for a 20% drug benefit, under any of these placebo base rates. Sample acquisition was discontinued when analyses conducted after accrual of the H+ sample

showed a negative drug effect on long-term abstinence in both history groups.

Data were analyzed by intent-to-treat: All randomized participants were included in the analyses under their original group assignments. Smoking status at eight time points (Postquit Weeks 2, 4, 6, and 8 of treatment, and follow-up visits 3, 4, 5, and 6 months after the quit date) was analyzed longitudinally using logistic regression for correlated dichotomous responses estimated by the generalized estimating equations (GEE) method (Liang & Zeger, 1986), implemented via SAS PROC GENMOD. The GEE method uses all available data to estimate model parameters, rather than excluding cases with missing data or requiring deterministic imputations (e.g., missing data are equivalent to smoking). With GEE, it is assumed that the missing data are random, after adjusting for model covariates. For example, if missing data increase across time, but are unrelated to variables other than time, and time is included as a model covariate, then the GEE assumption is reasonable. To better account for the missing data and satisfy this assumption that missingness is random after adjusting for covariates, the model included the following covariates: weeks until dropout (the visit after which no further smoking data were obtained), percentage rate of attendance for visits prior to dropout, and percentage of missed visits where smoking was reported by telephone. Finally, GEE models are robust to misspecification of the dependency structure that results from repeated assessments of an individual over time (Diggle, Heagerty, Liang, & Zeger, 2002). We chose an m-dependent (Toeplitz) correlation structure based on the observed correlations of smoking status across time.

The GEE model characterized the repeated dichotomous classifications in terms of initial (Postquit Week 2) cessation and time-related changes in cessation. All analyses included time and time-squared terms to allow for curvilinear trends in cessation across time. Tests determined the effects of drug (fluoxetine vs. placebo), depression history (present vs. absent), and their interactions with each other and with time. Nonsignificant interaction terms were removed from the model in a backwards manner (i.e., three-way interactions first, followed by two-way and then main effects; Drug $\times$ Time-Squared first, then Drug $\times$ Time), and the model was refitted. Full sample analysis was followed by planned stratified analyses within each history group, and by per protocol analyses that considered only treatment-adherent participants. Moderator analyses tested whether drug and history effects varied

by gender. For comparability with other trials of smoking medications, we also analyzed prolonged abstinence at end of treatment and end of follow-up via binary logistic regression, assuming that all missing data signified smoking. Finally, the effects of drug and history on symptoms of depression over time were assessed, in a manner analogous to the longitudinal analysis of smoking, with mixed-effects regression models for continuous variables (Verbeke & Molenberghs, 2000).

Results

Participant Characteristics

Participants ($N = 247$; 54% female) were 62% Caucasian, 26% African American, 4% Latino, 3% Asian, 5% multiethnic (Table 1). Groups did not differ with respect to age, race, cigarettes smoked per day, nicotine dependence, baseline depression, weeks until dropout, percentage of visits attended, or percentage of missed visits at which participants reported smoking status by telephone. A marginal difference in sex distribution, $\chi^2(1) = 3.12$, $p = .08$, suggested that H+ smokers (60%) were more likely than H- smokers (50%) to be female. Of the 44% of study participants who reported a history of MDD, 30% reported multiple episodes.

Smoking Outcome

Table 2 shows all covariate, history, and drug main effects, and statistically significant interactions in the GEE analysis predicting smoking status for the full sample. Here we note only significant findings. Overall, the probability of smoking increased across time in a curvilinear manner. Participants who dropped out earlier were more likely to be smoking. Also, greater nicotine dependence predicted an increased likelihood of smoking.

In regard to the main study question, the *a priori* analyses partially supported the primary hypotheses. Planned GEE analyses stratified by depression history yielded a Drug $\times$ Time interaction among H+ smokers ($z = 2.14$, $p = .032$, Figure 2). Supplemental GEE analyses stratified by history and study period (treatment vs. follow-up) showed that for H+ smokers, fluoxetine, relative to placebo, enhanced abstinence during the treatment period, $z = -2.27$, odds ratio [OR] = 0.28 (.09, .84), $p = .023$. During follow-up after treatment, however, fluoxetine impaired abstinence.

Table 1
Characteristics by Group

Characteristic	History – placebo ($n = 72$)			History – fluoxetine ($n = 66$)			History + placebo ($n = 51$)			History + fluoxetine ($n = 58$)		
	<i>M</i>	<i>SD</i>	%	<i>M</i>	<i>SD</i>	%	<i>M</i>	<i>SD</i>	%	<i>M</i>	<i>SD</i>	%
Age (years)	43.5	8.7		44.6	10.3		41.6	9.5		44.0	10.0	
Sex (no. and % female)	35		48.6	33		50.0	31		60.8	35		60.3
Race (no. and % White)	47		65.3	41		62.1	32		62.7	39		67.2
Cigarettes per day	22.5	10.6		23.3	11.4		21.6	7.9		24.0	10.2	
FTND score	5.9	2.1		6.0	2.1		6.0	2.05		6.70	2.03	
BDI score	6.6	5.9		6.1	7.9		10.7	7.2		10.9	7.4	
Weeks until dropout	12.3	10.2		12.4	9.9		11.8	9.66		14.81	10.49	
Attendance at visits predropout			75.24			76.43			82.8			71.5
Missed visits, smoking reported by telephone			49.11			53.53			55.3			65.4

Note. FTND = Fagerstrom Test for Nicotine Dependence; BDI = Beck Depression Inventory.

Table 2
Generalized Estimating Equations (GEE) Model Predicting Smoking Status

Variable	Regression coefficient	SE	z	95% confidence interval
Covariates				
FTND score	0.16	0.07	2.17*	0.21, 4.13
Weeks until dropout	-0.10	0.02	-5.23**	-7.20, -3.28
Attendance pre-dropout	-1.43	1.43	-1.00	-2.96, 0.96
Smoking status called in	0.09	0.42	0.21	-1.75, 2.17
Gender	-0.13	0.28	-0.46	-2.42, 1.50
Time effects				
Time	0.32	0.15	2.10*	0.14, 4.06
Time ²	-0.05	0.02	-2.42*	-4.38, -0.46
Group and Group × Time effects				
Depression History	0.12	0.31	0.38	-1.58, 2.34
Depression History × Time	-0.27	0.21	-1.24	-3.20, 0.72
Depression History × Time ²	0.07	0.03	2.03*	0.07, 3.98
Drug	-0.13	0.30	-0.43	-2.39, 1.53
Drug × Time	0.16	0.07	2.24*	0.28, 4.19

Note. 0 = abstinent, 1 = smoking. FTND = Fagerstrom Test for Nicotine Dependence.

* $p < .05$. ** $p < .01$.

nence, $z = 2.95$, OR = 7.00 (1.99, 24.70), $p = .003$ (Figure 2). For H- smokers, fluoxetine effects were nonsignificant but directionally negative.

Analysis of the full sample also yielded a Drug × Linear Time interaction ($z = 2.24$, $p = .025$). Drug had no significant effect on abstinence during the treatment period; but, subsequently, a par-

ticipant's having been treated with fluoxetine predicted increased risk of smoking during follow-up (Figure 3). Assuming missing data = smoking did not alter these results. Supplementary logistic regression analyses showed that at end of treatment (i.e., postquit Week 8 in Figure 3), drug did not significantly affect smoking status ($z = 1.58$, OR = 2.02, $p = .114$). However, at end of

Figure 2. Abstinence rates by drug status for those with a history of depression (left panel) and for those with no history of depression (right panel). Shading indicates on-drug phase (available data).

Figure 3. Abstinence rates by drug status for complete sample using all available data. Shading indicates on-drug phase.

follow-up (i.e., 6 months postquit in Figure 3), participants previously treated with fluoxetine were 3.3 times more likely to be smoking, $z = 2.32$, $OR = 3.33$ (1.21, 9.20), $p = .020$.

Additionally, the GEE full sample analysis yielded a Depression History $\times$ Quadratic Time interaction ($z = 2.03$, $p = .043$, Figure 4). During the treatment phase, H- smokers, in comparison to H+ smokers, showed an initial marginal cessation advantage that reversed over time ($z = -1.94$, $p = .052$). During follow-up, they showed an initial relative cessation advantage that tended to increase ($z = 1.72$, $p = .086$). Stated differently, H+ showed a relative cessation disadvantage 2 weeks postquit, followed by a cessation advantage during the remainder of treatment. Then, during follow-up, H+ consistently showed worse cessation than H-, and their disadvantage increased across time.

Logistic regression analyses of prolonged abstinence showed no significant effects of history, drug or their interaction. Equating missing data to smoking yielded an overall end-of-treatment prolonged abstinence rate of 21.1% (52/247): H- D- 20.8% (15/72); H+ D- 21.6% (11/51); H- D+ 16.7% (11/66); H+ D+ 25.9% (15/58). The comparable end-of-follow-up prolonged abstinence rate was 10.5% (26/247): H- D- 13.9% (10/72); H+ D- 9.8% (5/51); H- D+ 7.6% (5/66); H+ D+ 10.3% (6/58).

Treatment Moderators and Processes

Gender. Our GEE analysis explored whether the effects of drug and depression history were comparable for both genders (Table 3). Results showing a significant Gender $\times$ Drug $\times$ Linear Time interaction ($z = -2.38$, $p = .017$) were interpreted by stratifying the sample on gender and testing the separate interactive effects of drug assignment with time. The Drug $\times$ Linear Time interaction was significant for men ($z = 3.32$, $p = .001$) but not women ($z = 0.22$, $p = .829$). By final follow-up, men previously treated with fluoxetine were more than 4 times as likely to be smoking as placebo-treated men ($z = 2.19$, $OR = 4.17$, $p = .028$).

Moderator analysis also revealed a significant Gender $\times$ Depressive History $\times$ Linear Time interaction ($z = 2.60$, $p = .009$). Stratifying the sample by gender yielded significant History $\times$

Time interactions in opposite directions for both men ($z = -2.28$, $p = .023$) and women ($z = 2.53$, $p = .012$). For women, the disproportionate negative effect of depression history on abstinence increased progressively over time. By 6 months postquit, H+ women were nearly 3 times more likely to be smoking than H- women ($z = 2.21$, $OR = 2.86$, $p = .027$). H+ males were also disadvantaged relative to H-, but the differences decreased over time and were nonsignificant during follow-up.

Blinding. When asked to guess drug assignment after 3 weeks of treatment (i.e., 1 week before the quit date), neither participants' accuracy, $\chi^2(1) = 0.47$, $p = .493$, nor facilitators' accuracy, $\chi^2(1) = 1.46$, $p = .23$, varied by treatment group. Drug assignment was guessed correctly by 59.8% of placebo and 64.6% of fluoxetine participants. Facilitators guessed correctly for 65.3% of placebo and 55.6% of fluoxetine participants. Participants' accuracy did not predict smoking status over time ($z = 0.11$, $p = .912$) but was greater than chance for both participant guesses, $\chi^2(1) = 11.22$, $p = .0008$, and facilitator guesses, $\chi^2(1) = 9.42$, $p = .002$.

Medication adherence. Freezer malfunction caused some loss of urine and plasma samples. Urine samples were available from 73 placebo and 71 fluoxetine participants 1 week after the quit date, and from 41 placebo and 46 fluoxetine participants at 8 weeks postquit. Plasma samples were available from 65 and 39 fluoxetine participants at Postquit Weeks 1 and 8, respectively.

Riboflavin analyses collapsed across drug showed 83.3% compliance at Week 1 and 79.3% at Week 8. Adherence varied by drug group at Week 1, $\chi^2(1) = 5.34$, $p = .021$: More placebo participants (90.4%) than fluoxetine participants (76.1%) were compliant. The drug groups no longer differed at Week 8, $\chi^2(1) = 0.07$, $p = .798$: 80.5% of placebo and 78.3% of fluoxetine patients were adherent.

For the drug group, fluoxetine and norfluoxetine values were added and log-transformed to create a single outcome variable. Mixed effects regression modeling showed that metabolite level did not vary by time, nicotine dependence, history of depression, attendance, or time until dropout. Metabolite level was positively

Figure 4. Abstinence rates by history of depression (available data). Shading indicates on-drug phase. H+ = history of depression; H- = no history of depression.

Table 3
Generalized Estimating Equations (GEE) Moderator Analysis Predicting Smoking Status
Including Gender Interaction Terms

Variable	Regression coefficient	SE	z	95% confidence interval
Covariates				
FTND score	0.14	0.07	1.99*	0.03, 3.95
Weeks until dropout	-0.11	0.02	-5.40**	-7.38, -3.46
Attendance predropout	-1.40	1.41	-0.99	-2.94, 0.98
Smoking status called in	0.10	0.41	0.23	-1.75, 2.17
Gender	-0.05	0.50	-0.11	-1.89, 2.03
Time effects				
Time	0.28	0.15	1.84	0.08, 4.00
Time ²	-0.05	0.02	-2.06*	-3.94, -0.02
Group and Group × Time effects				
Depression History	0.62	0.45	1.39	-0.53, 3.39
Depression History × Time	-0.51	0.22	-2.31*	-4.34, -0.42
Depression History × Time ²	0.06	0.03	1.98*	-0.07, 3.85
Drug	-0.47	0.44	-1.07	-2.92, 1.00
Drug × Time	0.44	0.12	3.73**	1.50, 5.42
Gender interaction effects				
Gender × Time	-0.06	0.12	-0.47	-2.43, 1.49
Gender × History	-0.84	0.58	-1.44	-3.40, 0.52
Gender × History × Time	0.41	0.16	2.60**	0.64, 4.56
Gender × Drug	0.46	0.58	0.79	-1.17, 2.75
Gender × Drug × Time	-0.37	0.16	-2.38*	-4.35, -0.42

Note. 0 = abstinent, 1 = smoking. FTND = Fagerstrom Test for Nicotine Dependence.

* $p < .05$. ** $p < .01$.

associated with riboflavin compliance, $F(1, 67) = 7.61, p = .008$. At the 1st week postquit, the mean fluoxetine + norfluoxetine blood level was 427.95 ng/ml, $SD = 352.62$ (men: $M = 392.10, SD = 371.28$; women: $M = 457.03, SD = 339.08$). Eight weeks after the quit date, the mean level was 412.78 ($SD = 348.90$; men: $M = 397.02, SD = 320.84$; women: $M = 420.00, SD = 367.45$). Values were comparable to average fluoxetine + norfluoxetine blood level reported elsewhere (60 mg = 421.95; Koran, Cain, Dominguez, Rush, & Thiemann, 1996).

Per protocol analysis. In this study, 155 participants were adherent with behavioral treatment, operationalized as having attended six of the nine treatment sessions. The Drug × Linear Time interaction remained significant in the adherent subsample ($z = 2.27, p = .023$). Again, fluoxetine produced a negative effect on abstinence that increased over time. Although the Depression History × Quadratic Time interaction became marginal ($z = 1.92, p = .055$), its direction again suggested that H+ smokers were initially less and subsequently more likely to be smoking.

For participants randomized to placebo, medication compliance was operationalized as all assays having tested positive for riboflavin and no assays having tested nonzero for fluoxetine or norfluoxetine. For those randomized to fluoxetine, compliance was defined as all assays having tested positive for riboflavin and for nonzero values of fluoxetine and norfluoxetine. We found 72% ($n = 88$) of placebo and 80% ($n = 99$) of fluoxetine participants to be medication compliant. GEE analysis of the adherent subsample replicated the significant interactions found using all available data: Drug × Linear Time ($z = 2.51, p = .012$); History × Quadratic Time ($z = 2.17, p = .030$).

Depressive symptoms. Random effects regression modeling of BDI and Ham-D data over time indicated that H+ smokers had higher Ham-D scores than H- smokers at baseline, and the differ-

ence persisted throughout the treatment and follow-up periods, $t(667) = 4.06, p = .001$. Similarly, H+ smokers had elevated BDI scores at baseline, but there was a significant Depression History × Linear Time interaction indicating that the difference diminished somewhat over time, $t(500) = -2.62, p = .009$. Fluoxetine treatment had no effect on either BDI scores, $t(500) = 0.70, p = .486$, or Ham-D scores, $t(667) = 1.38, p = .168$. There was also no evidence that discontinuing fluoxetine increased depressive symptoms.

Clinical significance. To evaluate whether fluoxetine's negative long-term effect on abstinence was clinically significant, we calculated number needed to harm (NNH) (Kraemer & Kupfer, 2006; McQuay & Moore, 1997). At the end of the follow-up phase, NNH for the drug effect was 5 (95% confidence interval 40, 3), indicating a clinically meaningful adverse drug effect. An NNH of 5 means that if 5 patients were treated with fluoxetine, 1 would be more likely to be smoking at end of follow-up than if all had received placebo. To evaluate whether fluoxetine's initial enhancement of cessation among H+ smokers was clinically meaningful, we calculated number needed to treat (NNT). Six weeks after quit date, NNT for H+ smokers treated with fluoxetine was 13, meaning that 13 H+ smokers would need to be treated with fluoxetine in order to produce 1 case of abstinence not seen with placebo treatment. However, by 8 weeks after quit date, when treatment ended, there was no longer a drug benefit, but rather there was an NNH of 44. Thus, there was not evidence of a clinically important, sustained, short-term benefit of fluoxetine for smokers with a history of depression.

Discussion

We tested whether fluoxetine selectively aids smoking cessation for H+ smokers, relative to H- smokers. As predicted, fluoxetine,

compared to placebo, improved initial cessation outcome for H+ but not H- smokers during most of the period through which smokers remained in treatment. Regardless of depression history, however, smokers treated with fluoxetine were more likely to be smoking during follow-up. Six months postquit, formerly fluoxetine-treated participants were 3.3 times more likely to be smoking than formerly placebo-treated participants.

Our finding of an initial drug benefit confined to H+ smokers is consistent with other observations of a short-term improvement in abstinence due to fluoxetine among H+ smokers (cf. Cornelius, Perkins, Salloum, Thase, & Moss, 1999). Results also resemble other prior findings showing a short-term benefit of fluoxetine for smokers who show some depressive symptoms (Blondal et al., 1999; Hitsman et al., 1999). The drug benefit we observed for H+ smokers was only short-term. It lasted for much of the 2-month period that immediately followed the quit date (during which participants remained on medication), but it had dissipated by the end of treatment.

We expected that a beneficial effect of fluoxetine on H+ abstinence would be mediated by an antidepressant action of fluoxetine at baseline or during the immediate postquit period. However, no drug effect on depressive symptoms was observed, nor were there interactions between drug, time, and depressive history. Hence, we cannot attribute fluoxetine's transient cessation advantage for H+ smokers to an alleviation of depressive symptoms. We have insufficient data on other nicotine withdrawal symptoms to comment on whether drug effects on withdrawal might offer an alternative explanation.

Having a history of depression and exhibiting pre- or postquit depressive symptoms are individual differences that tend to co-occur (Borrelli et al., 1999; Hitsman et al., 2003; Pomerleau et al., 2004). This constellation of attributes may signify the presence of an underlying vulnerability to depression that accompanies heightened sensitivity to serotonergic intervention. In the current study, depressive vulnerability, indexed by a participant's having a history of MDD, predicted heightened positive responsiveness (albeit on a short-lived basis) to a serotonin-enhancing drug. In a different, opposite intervention context, we found that having a history of depression plus being a smoker predicted heightened negative responsiveness to a tryptophan-depleting dietary challenge that transiently lowers serotonin (Spring et al., 2007). Variation in the degree to which smokers vulnerable to depression are represented in study samples may help to explain inconsistent short-term findings from trials testing serotonergic agents as cessation aids.

Fluoxetine's more long-lasting and more clinically important influence was a negative effect on cessation. A negative effect on abstinence has been observed in three prior fluoxetine studies (Naranjo et al., 1990; Niaura et al., 2002; Spring et al., 1995). Current results parallel the findings of Covey et al. (2002) from a trial of the selective serotonin reuptake inhibitor (SSRI) sertraline for H+ smokers. Although neither effect was significant in that study, Covey et al. (2002) reported the pattern observed in the current study: increased abstinence associated with SSRI treatment while on medication, reversing to reduced abstinence during follow-up.

The reversal of a fluoxetine-related abstinence advantage for H+ smokers began toward the end of treatment and continued throughout follow-up. That transition from a beneficial to a detrimental drug effect warrants comment, as does the drug's more consistently adverse effect on cessation for H- smokers. We con-

sidered two mechanisms that might explain the negative effect: one related to a fluoxetine discontinuation syndrome and the other related to neurobiological changes triggered by chronic fluoxetine exposure. Consistent with other evidence that fluoxetine's slow clearance from the body precludes a discontinuation syndrome (Judge, Parry, Quail, & Jacobson, 2002), smokers in this study did not report fluoxetine withdrawal symptoms. Fluoxetine lacked an effect on depressive symptoms during follow-up, just as it had during treatment. Thus, fluoxetine's negative effect on abstinence among H+ smokers during the follow-up period does not appear to reflect a fluoxetine discontinuation syndrome.

An alternative, biological explanation of the negative drug effect derives from animal studies showing that chronic fluoxetine use suppresses dopamine (DA) in the nucleus accumbens system, which modulates reward (Ichikawa, Kuroki, & Meltzer, 1998; Ichikawa & Meltzer, 1995; Korsgaard, Gerlach, & Christensson, 1985). Nicotine's rewarding effects are partially mediated through activation of DA release in the nucleus accumbens (Corrigall, 1991; Gamberino & Gold, 1999). Conversely, removal of nicotine suppresses dopaminergic neurotransmission and elevates brain reward threshold, signifying decreased reward sensitivity or anhedonia (Epping-Jordan, Watkins, Koob, & Markou, 1998; Harrison, Liem & Markou, 2001; Markou, Kosten, & Koob, 1998). Although coadministration of fluoxetine in the short-term prevents this reward decrement (Harrison et al., 2001), continuing to administer fluoxetine chronically, as was done in the current study, decreases extracellular DA in the nucleus accumbens (Ichikawa et al., 1998; Ichikawa & Meltzer, 1995; Korsgaard et al., 1985).

To the extent that these animal data can be extrapolated to humans, chronic fluoxetine administration may augment a functional DA deficiency state already triggered by nicotine deprivation. Consequently, drug-treated smokers in the present study may have found cigarettes increasingly tempting. They may have resumed smoking in order to restore reward functioning. The observation that abstinence began to decline for fluoxetine-treated cases even before drug treatment ended is consistent with the possibility that chronic fluoxetine treatment heightened the reward value of nicotine. That fluoxetine's adverse effect on abstinence continued, and among H+ smokers worsened, after the drug was discontinued might reflect progressive central nervous system adaptation to fluoxetine withdrawal. However, it is also plausible that neurophysiological changes undermining abstinence were initiated during drug exposure, developed gradually, and became evident clinically only after an incubation phase that just happened to conclude after drug treatment ended. The present study was not designed to distinguish between these two scenarios experimentally, and they are very challenging to differentiate analytically after the fact. Relevant interpretive issues have been discussed recently in the context of late-appearing serious thrombotic events that became evident after rofecoxib (Vioxx) discontinuation, leading to the drug's withdrawal from the market (Lagakos, 2006).

We also observed two post hoc moderator effects related to gender. One suggested that the adverse effect of fluoxetine on abstinence was heightened for men. The other suggested that a negative effect on abstinence of a history of depression grew stronger over time for women. Because we made no gender-related predictions for this study, both moderator effects were unanticipated. Those findings would need to be replicated by others before being considered meaningful.

Our findings have some limitations. First, as is typical of smoking cessation trials (Ahluwalia, Harris, Catley, Okuyemi, & Mayo, 2002; Jorenby et al., 1999), study attrition was substantial: 63–78% completed treatment; 55–67% completed follow-up. Second, as is customary for an efficacy trial, the sample was highly selected, which may limit generalizability. Approximately 12% of those who expressed interest were randomized, comparable to the 9% randomized in other studies of antidepressant pharmacotherapy plus behavioral cessation counseling (Hall et al., 2002; Hall, Humfleet, Reus, Munoz & Cullen, 2004). Third, we were only partially successful in keeping the study blind. Facilitators and patients were not very successful at guessing their drug assignments (65.3% and 55.6% accuracy, respectively), but their guesses exceeded chance (50%). Importantly, though, successful guessing did not appear to undermine the internal validity of the trial, because accuracy was comparable across drug and placebo conditions. Fourth, because follow-up extended only to 6 months postquit date, it is unknown whether effects persist over the longer term. Fifth, because all participants received cognitive-behavioral group therapy in addition to fluoxetine or placebo, effects of pharmacotherapy alone cannot be discerned.

Study results extend and clarify previous findings regarding influences of SSRIs and depressive history on smoking cessation. Past research has yielded mixed findings as to whether serotonergic agents benefit tobacco abstinence in the short-term. The current findings suggest that such benefit does occur initially among smokers with a history of depression. In the present study, the on-drug advantage for H+ smokers lasted for the first 6 weeks postquit. However, such a drug benefit is too transient to be clinically useful, especially since fluoxetine has a clinically significant adverse impact on abstinence in the long-term. Fluoxetine's longer-term suppression of abstinence contraindicates using the drug as a cessation treatment regardless of a patient's depressive vulnerability, particularly since there are available other, more effective smoking pharmacotherapies with antidepressant properties (bupropion, nortriptyline). Further study of psychological mechanisms is warranted to determine why high-dose SSRI treatment apparently produces a continuing effect that opposes tobacco abstinence.

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