

## **Antidepressant Pharmacotherapy Helps Some Cigarette Smokers More Than Others**

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### **ABSTRACT**

Adult smokers ( $N = 253$ ) without clinically significant depression were randomized on a double-blind basis to receive fluoxetine (30 or 60 mg daily) or a placebo for 10 weeks in combination with cognitive—behavioral therapy (CBT). It was predicted that fluoxetine would selectively benefit smokers with higher baseline depression, nicotine dependence, and weight concern and lower self-efficacy about quitting smoking. Among those who completed the prescribed treatment regimen, baseline depression scores moderated the treatment response. Logistic regression analyses showed that 1 and 3 months after the quit date, fluoxetine increased the likelihood of abstinence, as compared with placebo, among smokers with minor depression but not among those with little or no depression. Results suggest that, as an adjunct to CBT, fluoxetine enhances cessation by selectively benefiting medication-compliant smokers who display even subclinical levels of depression.

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After declining steadily over the past several decades, smoking rates have recently leveled off ( [Centers for Disease Control and Prevention, 1994](#) ). Many researchers believe that the residual pool of smokers may have specific attributes that are associated with difficulty in quitting ( [Coombs, Kozlowski, & Ferrence, 1989](#) ; [Hughes & Glaser, 1993](#) ). These attributes include depression, nicotine dependence, fear about weight gain related to quitting smoking, and low self-efficacy about resisting the urge to smoke.

Antidepressant agents have recently been studied as adjuncts to cognitive—behavioral treatment to promote smoking cessation. Several promising compounds have been identified, including bupropion, nortriptyline, and fluoxetine ( [Bowen, Spring, & Fox, 1991](#) ; [Hall et al., 1998](#) ; [Hurt et al., 1997](#) ; [Niaura et al., 1997](#) ; [Spring, Wurtman, Gleason, Wurtman, & Kessler, 1991](#) ; [Spring et al., 1995](#) ). Although many smokers have achieved abstinence with the use of adjunctive antidepressant pharmacotherapy, it is unclear who are the best candidates for such combined treatment. Accordingly, this study aimed to identify individual differences that predict cessation when fluoxetine is combined with cognitive—behavioral treatment.

Adding antidepressant pharmacotherapy to cognitive—behavioral treatment may blunt the negative impact of several personal attributes that usually predict relapse. Proneness to depression, for example, is consistently associated with cessation failure. The presence of even low levels of depression prior to a quit attempt predicts early relapse in cognitive—behavioral smoking cessation treatment ( [Mermelstein, Henry, Hedeker, & Wong, 1995](#) ; [Zelman, Brandon, Jorenby, & Baker, 1992](#) ). Treatment with fluoxetine has been shown to lessen precessation depressive symptoms in depression-prone smokers ( [Dalack, Glassman, Rivelli, Covey, & Stetner, 1995](#) ). If depression-prone smokers exhibit habitual depressive symptoms that interfere with cessation, they should selectively benefit from a drug treatment that alleviates those symptoms.

A high degree of nicotine dependence also predicts cessation failure in cognitive—behavioral treatment, presumably because highly nicotine-dependent smokers experience prominent withdrawal symptoms that prompt them to resume smoking ( [Killen, Fortmann, Kraemer, Varady, & Newman, 1992](#) ; [Nides et al., 1995](#) ). Symptoms of nicotine withdrawal include depressed mood, irritability, anxiety, insomnia, difficulty concentrating, restlessness, and increased appetite or weight gain ( [American Psychiatric Association, 1994](#) ), many of which resemble signs of depression. Because depression is the withdrawal symptom most predictive of cessation failure ( [Hughes, Higgins, & Hatsukami, 1990](#) ), we examined whether nicotine dependence and depression might explain overlapping variance in cessation outcome. The two variables have been found to be significantly correlated in some ( [Breslau, Kilbey, & Andreski, 1991](#) ; [W. R. Yates, Cadoret, & Troughton, 1997](#) ), although not all, studies ( [Glassman et al., 1993](#) ). Treatment with nortriptyline diminished nicotine withdrawal symptoms during cessation ( [Hall et al., 1998](#) ), suggesting that nicotine-dependent smokers who are prone to withdrawal might benefit from an antidepressant when quitting.

Some evidence suggests that exaggerated weight concerns also reduce the likelihood of successful cessation in cognitive—behavioral treatment ( [French & Jeffery, 1995](#) ). A possible mechanism is that highly weight-conscious individuals drop out of treatment or resume smoking if they gain any weight ( [Swan, Ward, Carmelli, & Jack, 1993](#) ). Interestingly, actual weight gain after quitting smoking has, in some studies, predicted continued abstinence rather than relapse ( [Hall, Ginsberg, & Jones, 1986](#) ). Although seemingly

opposite, these findings may actually be complementary in the respect that less weight-concerned individuals may be able to tolerate greater amounts of weight gain before feeling compelled to resume smoking. Because serotonergic agents minimize increased calorie intake and weight gain triggered by cessation ( [Borrelli et al., 1999](#) ; [Spring et al., 1991, 1995](#) ), they provide a tool to allay the weight-conscious smoker's concerns about gaining weight. Consequently, we predicted that smokers with high levels of weight concern would benefit selectively from fluoxetine versus a placebo.

Low self-efficacy is another barrier to quitting smoking in cognitive—behavioral smoking cessation treatment ( [Motherstill, McDowell, & Rosser, 1988](#) ; [Stuart, Borland, & McMurray, 1994](#) ). Much evidence suggests that pretreatment self-efficacy predicts short-term abstinence, although its ability to predict longer term abstinence is less certain ( [DiClemente, 1985](#) ). How much low self-efficacy and depression explain overlapping causal variance in cessation failure remains to be understood. If low self-efficacy and depression are interrelated constructs in the context of cessation, then fluoxetine should selectively benefit smokers with low self-efficacy. A plausible mechanism may be that antidepressant pharmacotherapy prevents dysphoria from undermining the smoker's confidence about being able to resist cigarette cravings.

In summary, this study examined whether individual differences in depression symptomatology, nicotine dependence, weight concerns, and self-efficacy would moderate the likelihood that fluoxetine enhances success at quitting smoking. Because serotonergic agents reduce dysphoria and weight gain after quitting smoking, we hypothesized that smokers with greater depressive symptoms and those with elevated weight concerns would be more likely to achieve abstinence when assigned to fluoxetine versus a placebo. Because antidepressant agents alleviate some nicotine withdrawal symptoms, we also hypothesized that highly nicotine-dependent smokers might benefit disproportionately from fluoxetine. Finally, to the extent that depressive symptoms undermine confidence in quitting smoking, we expected that fluoxetine would selectively benefit smokers with low self-efficacy.

## Method

### Participants

Participants were 253 male and female smokers between the ages of 18 and 65 years recruited for a double-blind, placebo-controlled study to determine whether fluoxetine would prevent postcessation weight gain while not jeopardizing success in quitting smoking. About three fourths of our sample (  $n = 186$  ) also provided data for the 16-site Eli Lilly—sponsored trial of fluoxetine's effect on smoking cessation. This included 64 of the 131 participants seen at our North Chicago site, 53 from the Cleveland site, and 69 from the Worcester site. Participants' mean age was 41.5 years (  $SD = 9.5$  ). Most were female (59%), Caucasian (97%), married (65%), and college educated (62%). Participants averaged 28.3 cigarettes per day (  $SD = 11.9$  ) for a mean of 23.2 years (  $SD = 9.3$  ) prior to treatment. Participant eligibility criteria, as well as the cessation and weight-control outcomes of the multicenter trial, are reported elsewhere ( [Borrelli et al., 1999](#) ; [Niaura et al., 1997](#) ).

### Procedure

After screening and baseline assessments, participants began the first of nine, 1-hr individual cognitive—behavioral treatment sessions. Participants were randomized on a double-blind basis to receive 10 weeks of treatment with fluoxetine (30 mg or 60 mg) or a placebo, which began at the second session. Participants were required to set a quit date within 2 weeks after drug treatment began. Medication was started about 2

weeks prior to cessation so that a therapeutic drug level would be achieved before quitting smoking. At the third session, participants quit smoking. The ninth session coincided with the end of medication. The final phase of the study involved a 6-month follow-up period that began when medication was discontinued. For participants enrolled in Eli Lilly's multicenter trial, the follow-up included only those who were abstinent at the end of treatment because the company wished to learn whether drug discontinuation adversely affected cessation among participants who had already demonstrated responsiveness to treatment.

### **Medication compliance.**

Compliance was verified by weekly self-report (verified by pill count) and assays of plasma concentrations of fluoxetine metabolites at Visits 5 (3 weeks after starting drug) and 9 (end of medication). Assays were performed after study completion using gas chromatography ( [Nash, Bopp, Carmichael, Farid, & Lemberger, 1982](#) ). Participants randomized to a 30-mg dose of fluoxetine were classified as compliant if their fluoxetine or norfluoxetine blood levels were less than or equal to 150 ng/ml. Those randomized to a 60-mg dose were classified as compliant if their levels were less than or equal to 300 ng/ml ( [Bergstrom, Beasley, Levy, Blumenfield, & Lemberger, 1993](#) ).

### **Smoking status.**

Smoking status was operationalized by a composite of three measures—self-report of smoking, expired carbon monoxide (CO), and saliva cotinine—which were collected at baseline and at the beginning of each treatment session. To be classified as abstinent, participants had to report all of the following: zero cigarettes smoked, expired CO less than or equal to 8 ppm, and cotinine values less than or equal to 10 ng/ml. Participants exceeding any of these criteria were classified as smokers.

### **Dependent Measures Depression.**

We assessed depressive symptoms using the Hamilton Rating Scale for Depression (HRSD; [Hamilton, 1967](#) ). The HRSD is a clinician-rated, semistructured interview that evaluates 21 depressive signs (e.g., psychomotor retardation) and symptoms (e.g., feelings of worthlessness), each rated on a 3-point or 5-point scale. Scores range from 0 to 84, with higher scores representing greater levels of depression. The HRSD has been shown to have acceptable levels of reliability and validity ( [Knesevich, Biggs, Clayton, & Ziegler, 1977](#) ).

### **Nicotine dependence.**

We administered the eight-item Fagerstrom Tolerance Questionnaire (FTQ; [Fagerstrom, 1978](#) ) to measure degree of behavioral responses suggestive of nicotine dependence (e.g., smoking many cigarettes and smokes early in the morning). Scores range from 0 to 11, with values of 7 or greater suggesting nicotine dependence.

### **Weight concerns.**

We assessed weight concern with the Dietary Restraint subscale of the Three-Factor Eating Questionnaire ( [Stunkard & Messick, 1985](#) ). The Dietary Restraint subscale measures the tendency to monitor and restrict food intake to control body weight. Scores range from 0 to 20, with higher scores reflecting greater degrees of weight concern.

## Self-efficacy.

We measured self-efficacy about quitting smoking by using the Self-Efficacy Questionnaire (SEQ; [A. J. Yates & Thain, 1985](#)). The SEQ assesses a smoker's degree of confidence about being able to resist urges to smoke in 14 challenging situations (e.g., when feeling impatient, when wanting to cheer up, and when being offered a cigarette). Scores range from 14 to 98, with higher scores indicative of greater self-efficacy.

## Analytic Approach

To assess whether fluoxetine benefits some smokers more than others, we first performed an intent-to-treat analysis of all participants randomized to treatment. The intent-to-treat analyses attempt to answer the following question: Before an interventionist knows whether a smoker will adhere to cessation treatment, can she or he predict who benefits from adjunctive treatment with fluoxetine? Results of intent-to-treat analyses are generalizable to the average smoker who enters clinic-based cessation treatment. This approach is also based on the overly conservative assumption that study dropouts can legitimately be considered as treatment failures. Interpretive validity is compromised to the degree that this assumption is false. To overcome the impossibility of knowing the treatment response of those who dropped out, we also performed analyses of participants who completed and adhered to treatment through Visit 9. The analysis of completers answers a different question—namely, among smokers who adhere to treatment, who benefits from fluoxetine? Results of completer analyses have more limited generalizability because nearly 50% of the participants were noncompliant at the later stages of treatment. Nevertheless, completer analyses provide the most valid test of the ability to predict outcomes among those who fully participate in treatment. Finally, in an effort to determine the kind of smoker who would be likely to adhere to this treatment, we constructed analyses predicting treatment adherence.

Logistic regression analyses were used to determine whether the individual difference factors assessed at baseline interacted with drug treatment to predict abstinence at three separate time points: 1 week, 1 month, and 3 months after the quit date, with the 3-month point corresponding to the end of treatment. We were only able to examine 6-month follow-up data in the intent-to-treat analyses because the sample of treatment-compliant participants who were not smoking at Visit 9, and therefore allowed to enter Eli Lilly's follow-up protocol, was too small to produce a stable predictive model. The criterion variable at each assessment point was smoking status (0 = *abstinent*, 1 = *smoking*). As predictors, we tested the main effects of treatment site, gender, the HRSD, the FTQ, the Dietary Restraint subscale, the SEQ, and drug treatment, as well as the interactions between drug treatment and each of the predictors. Before conducting the analyses, we tested the assumption of linearity in the logit for each continuously scaled predictor variable. This assessment was made by breaking the range of each predictor variable into quartiles, finding its average, and then plotting the log odds of smoking status by the average value for each quartile. Examination of the data plots supported treating the predictor variables as linear in the logit.

To select variables that resulted in the best fitting, most parsimonious model of smoking status at each time point, we used a hierarchical approach to variable selection ([Hosmer & Lemeshow, 1989](#)). The main effect of treatment site was entered first. We then entered main effects and interaction terms on the basis of theoretical priority; attributes with a presumed partial physiological basis (i.e., gender, nicotine dependence, and depression) were entered before cognitive variables (i.e., dietary restraint and self-efficacy). Drug treatment was entered on the 7th step. Next, the interaction of treatment site and gender was entered. To test our hypothesized interactions, we entered the terms for HRSD  $\times$  Drug Treatment and Dietary Restraint Subscale  $\times$  Drug Treatment on the 9th and 10th steps, respectively. The FTQ  $\times$  Drug Treatment and the

SEQ  $\times$  Drug Treatment interactions were entered in the final steps because we considered these interactions to be more speculative. At each step, we assessed the importance of each term included in the equation by examining the Wald statistic and its associated significance level. Starting with the hypothesized interactions and progressing to main effects, we temporarily eliminated from the equation the variable with the smallest chi-square value. We then tested the fit of the new, adjusted model by comparing it to the full model using the likelihood ratio test. The variable was eliminated from the full model permanently if the likelihood ratio test of the difference between the two models was not significant. If the likelihood ratio test was significant ( $p < .05$ ), we reentered the variable into the model and then tested the importance of the variable with the next smallest chi-square value. We also reentered the variable into the model if the magnitude of the coefficients of the variables in the equation changed significantly between the adjusted model and the full model.

During this model-building process, we observed that when drug treatment was entered into the model, it had an odds ratio (OR) of infinity. Closer examination of the  $2 \times 3$  contingency table of Drug Dose  $\times$  Smoking Status revealed cells with fewer than 10 participants because most participants on fluoxetine had achieved abstinence at 1 week. Examination of this pattern at later time points showed similar cell counts. To eliminate small cell sizes, we collapsed across the 30- and 60-mg doses of fluoxetine, creating two drug levels (0 = *placebo*, 1 = *fluoxetine*). This strategy increased the variability in smoking status, resulting in a more stable predictive model, although it prevented us from assessing individual differences in response to varying drug dosage.

Finally, to evaluate the strength of the predictive models produced by the hierarchical approach, we performed parallel analyses using a stepwise selection procedure. Instead of entering variables into the equation on the basis of theoretical priority, the stepwise procedure selects and orders predictor variables on the basis of statistical explanatory power using the likelihood ratio chi-square test. For the stepwise analyses, we set the criterion for variable selection at  $p = .25$  because more traditional significance levels (such as  $p = .05$ ) often fail to identify important predictors (cf. [Hosmer & Lemeshow, 1989](#)).

## Results

### Pretreatment Characteristics

We used chi-square analyses and analyses of variance to test whether the three treatment groups differed on age; gender; education; smoking history; or baseline level of nicotine dependence, depression, weight concern, and self-efficacy. There were no significant differences among the treatment groups on any of these variables. For the individual difference predictors, the mean scores were as follows: HRSD = 3.0 ( $SD = 2.5$ ), FTQ = 6.6 ( $SD = 1.8$ ), Dietary Restraint subscale = 6.6 ( $SD = 4.9$ ), and SEQ = 57.7 ( $SD = 13.6$ ).

### Relationships Among Baseline Predictors

Pearson product—moment correlations were computed to examine the relationships among baseline predictor variables. A small but statistically significant negative correlation was observed between FTQ and Dietary Restraint subscale scores ( $r = -.16, p < .05$ ), suggesting that higher levels of nicotine dependence were associated with lower levels of weight concerns. HRSD scores were not associated with either FTQ or SEQ scores, suggesting that, at least within this restricted range of depression scores, nicotine dependence and self-efficacy beliefs about quitting smoking bear little direct relationship to depression.

## Intent-to-Treat Analyses

Using hierarchical logistic regression, we tested the prediction that smokers exhibiting greater depressive symptoms, weight concerns, nicotine dependence, and lower self-efficacy would benefit disproportionately from treatment with fluoxetine as compared with a placebo. To perform the intent-to-treat analyses, it was necessary to make an assumption about the smoking status of participants who discontinued the study prematurely. We classified participants as smoking if they were smoking at the visit just prior to attrition. Participants who moved ( $n = 4$ ) or discontinued medication prior to completing the study ( $n = 35$ ) were assigned the smoking status from their last valid assessment (i.e., smoking status from the last valid visit was carried forward to later visits) if they remained in treatment and reported not smoking. In most cases, however, participants who did not complete the study were smoking at the time of attrition.

The results of separate hierarchical logistic regression models constructed for smoking status at 1 week and at 1, 3, and 6 months after the quit date generally failed to yield any stable predictive model of smoking cessation. The only significant predictor of outcome was a main effect of HRSD scores 1 week after the quit date, indicating that higher levels of depression predicted failure to achieve abstinence. At the 1-, 3-, and 6-month time points, no main effects or interactions with drug treatment were prognostic of outcome. The stepwise analyses produced the same results, as did plots of each Baseline Predictor  $\times$  Drug Treatment interaction at each assessment point, suggesting that none of the factors yielded a predictive pattern of abstinence.

## Analysis of Treatment-Compliant Participants

The analysis of treatment-compliant participants included only those individuals who attended every treatment session and who consistently complied with drug treatment. Of the 253 participants who continued through the quit date, 194 met these criteria at 1 week and 123 and 108 met these criteria at 1 month and 3 months, respectively. In parallel to the intent-to-treat analyses, we constructed separate regression models at each of the three assessment points.

### Abstinence 1 week postcessation.

[Table 1](#) shows the results of the final hierarchical logistic regression analysis. Contrary to expectations, the HRSD  $\times$  Drug Treatment, the FTQ  $\times$  Drug Treatment, the Dietary Restraint Subscale  $\times$  Drug Treatment, and the SEQ  $\times$  Drug Treatment interactions did not predict abstinence. However, the FTQ and HRSD main effects predicted abstinence. Increasing levels of nicotine dependence and depression were associated with a decreasing likelihood of abstinence. In addition, the main effect of drug treatment was marginally significant ( $p = .06$ ), indicating that the likelihood of abstinence for participants on fluoxetine tended to be higher than for those on a placebo. On the basis of the Hosmer—Lemeshow goodness-of-fit test, the final model fit the data well,  $\chi^2(8, N = 169) = 8.2, p = .41$ . The parallel stepwise analyses validated the results obtained using the hierarchical approach and confirmed that, during the initial stages of quitting, fluoxetine's effects on abstinence were not moderated by any of the individual differences we studied.

### Abstinence 1 month postcessation.

Results of the final hierarchical logistic regression analysis are shown in [Table 2](#). As expected, the HRSD  $\times$  Drug Treatment interaction was a significant predictor. Contrary to expectations that smokers with high

levels of nicotine dependence, weight concerns, and self-efficacy would selectively benefit from fluoxetine as compared with a placebo, the FTQ  $\times$  Drug Treatment, the Dietary Restraint Subscale  $\times$  Drug Treatment, and the SEQ  $\times$  Drug Treatment interactions failed to predict abstinence. In addition, the main effect of dietary restraint was significant, indicating the higher levels of weight concerns were associated with a decreased likelihood of abstinence. On the basis of the results of the Hosmer—Lemeshow test, the final model fit the data very well,  $\chi^2(8, N = 105) = 4.8, p = .78$ . Again, the results we obtained from the parallel stepwise analyses were comparable to those obtained using the hierarchical approach, in that dietary restraint, drug treatment, and the HRSD  $\times$  Drug Treatment interaction were selected as predictors of abstinence.

To interpret the HRSD  $\times$  Drug Treatment interaction, we plotted the log odds of abstinence computed from the full model against HRSD scores for fluoxetine versus a placebo. The log odds were calculated by setting the values of the other parameters at zero. As seen in [Figure 1](#) (left panel), increasing HRSD scores were associated with a decreasing likelihood of abstinence for participants treated with a placebo. In contrast, for participants treated with fluoxetine, there was a positive association between degree of depression and the likelihood of abstinence. This effect was more pronounced for individuals who scored in the upper quartile (HRSD = 3, OR = 2.00, 95% confidence interval [CI] = 0.85—4.70) than for those who scored in the lowest quartile (HRSD = 1, OR = 1.10, 95% CI = 0.38—3.19).

### **Abstinence 3 months postcessation.**

[Table 3](#) shows the results of the final hierarchical logistic regression analysis. As expected, the HRSD  $\times$  Drug Treatment interaction predicted abstinence at the end of drug treatment. Contrary to expectations, the FTQ  $\times$  Drug Treatment, the Dietary Restraint Subscale  $\times$  Drug Treatment, and the SEQ  $\times$  Drug Treatment interactions were not significant. The Hosmer—Lemeshow test showed that the final model fit the data well,  $\chi^2(8, N = 90) = 7.3, p = .51$ . The stepwise analysis substantiated these results.

To interpret the interaction between HRSD and drug treatment, we plotted the log odds of abstinence calculated from the final model results against HRSD scores for the placebo and fluoxetine conditions. The log-odds computations were again based on setting the values of the other parameters at zero. [Figure 1](#) (right panel) shows that, for placebo-treated participants, higher HRSD scores were associated with a decreased likelihood of abstinence. In contrast, for participants treated with fluoxetine, there was a positive relationship between HRSD scores and abstinence, such that higher scores were associated with an increased likelihood of abstinence. Again, this effect tended to be more pronounced for individuals who scored in the highest quartile (HRSD = 3, OR = 1.44, 95% CI = 0.53—3.91) than for those who scored in the lowest quartile (HRSD = 1, OR = 0.56, 95% CI = 0.17—1.84). Three months after the quit date, fluoxetine selectively benefited smokers with higher initial levels of depressive symptoms, as was the case at 1 month postquit.

### **Who Complied With Treatment?**

In an effort to understand the differing outcomes of the analyses based on randomized versus compliant participants, we examined how attrition might have affected the samples. We performed *t* tests comparing the randomized versus compliant subgroups within each drug condition on their demographic characteristics and baseline predictor variables. We detected no significant differences, suggesting that the participants who dropped out were similar to those who adhered to treatment on age, gender, and education, as well as baseline levels of depression, nicotine dependence, weight concern, and self-efficacy.

Finding no obvious differences between the groups, we attempted to develop a predictive model of treatment adherence. We conducted a stepwise logistic regression analysis to predict end of study treatment compliance. We evaluated the individual difference factors (i.e., the HRSD, the FTQ, the Dietary Restraint subscale, and the SEQ), as well as demographic (i.e., age, gender, and race) and smoking characteristics (i.e., baseline expired CO, salivary cotinine, number of cigarettes, and years smoked), for their utility in predicting adherence to drug treatment. None of the demographic or individual difference factors predicted treatment adherence. In contrast, smoking characteristics did predict treatment compliance. Specifically, both biological indicators of nicotine intake, saliva cotinine ( $\chi^2 = 11.4, p < .001$ ) and expired CO ( $\chi^2 = 5.3, p < .05$ ), were separate predictors of medication adherence. Lower baseline values (indicative of less nicotine intake) predicted an increased likelihood of complying with treatment.

## Discussion

Although several kinds of antidepressant pharmacotherapy have been shown to enhance the likelihood of smoking cessation when combined with cognitive—behavioral treatment ( [Bowen et al., 1991](#) ; [Hall et al., 1998](#) ; [Hurt et al., 1997](#) ; [Niaura et al., 1997](#) ; [Spring et al., 1991, 1995](#) ), it has been unclear who might benefit most from such treatment. This study aimed to identify which smokers would benefit most from receiving adjunctive treatment with the serotonin-reuptake-inhibiting antidepressant, fluoxetine. We examined whether individual differences in depression, nicotine dependence, weight concerns, or self-efficacy would moderate the likelihood of cessation among healthy adult male and female smokers who were treated with cognitive—behavioral therapy in conjunction with fluoxetine or a placebo. Because fluoxetine reduces dysphoria and weight gain after quitting smoking, we predicted that smokers with greater depression and elevated weight concerns would be more likely to achieve abstinence when treated with fluoxetine rather than with a placebo. Because antidepressants alleviate some nicotine withdrawal symptoms, we expected that highly nicotine-dependent smokers would benefit selectively from fluoxetine. Finally, because depression can undermine confidence about being able to quit, we predicted that fluoxetine would selectively bolster the efforts of smokers with low self-efficacy.

Using an intent-to-treat analysis of all smokers randomized to treatment and assuming that participants lost to follow-up were smoking, we were unable to predict cessation outcome on the basis of drug assignment, individual differences, or their interaction. Thus, we cannot suggest that an interventionist could simply use the personal attributes we studied to predict which smokers might benefit from adjunctive fluoxetine before knowing something about whether a smoker is likely to adhere to an intensive treatment regimen involving medication plus cognitive—behavioral therapy. For the approximately 50% of the participants who underwent the study intervention as prescribed, scores on the HRSD were predictive of end-of-treatment abstinence status. Higher pretreatment scores predicted a lower likelihood of abstinence among unmedicated smokers but a higher likelihood of abstinence among those treated with fluoxetine. This finding suggests that smokers with even minimal degrees of depression are likely to benefit from adjunctive treatment with an antidepressant like fluoxetine, if they adhere to treatment.

The interaction between initial depression scores and treatment response showed several interesting features. First, the relationship did not become evident until some time had elapsed after the quit date. Shortly (1 week) after the quit date, cessation outcome was poorer among smokers with higher HRSD scores, regardless of treatment. Because participants selected their own quit date within specified protocol guidelines, the duration on medication at the time of the 1-week follow-up ranged from several days to 2 weeks, with an average of 1 week, and may have been insufficient to establish a reliable antidepressant

response. By 1 month, however, and persisting through 3 months, having a higher initial HRSD score predicted a greater likelihood of abstinence among smokers treated with fluoxetine and a lesser likelihood of abstinence among smokers treated with placebo. The most remarkable aspect of these findings is the demonstration that baseline depression moderated subsequent treatment response, even after excluding all smokers with clinically obvious depression (HRSD >14).

Contrary to expectations, we found no evidence to suggest that the more nicotine-dependent smokers derived special benefit from fluoxetine. Also noteworthy was the observation that the moderating effect of depression on fluoxetine responsiveness was independent of the effect of nicotine dependence and, indeed, persisted even after the variance explained by nicotine dependence was removed. These findings suggest that adjunctive antidepressant treatment offers little selective benefit for highly nicotine-dependent smokers. A related observation was the finding that smokers with high baseline CO and cotinine scores were more likely to drop out of this particular treatment regimen. These observations suggest that, in order to remain in treatment, heavy smokers may require tools, like nicotine replacement, that directly address their physiological dependence. Also contrary to expectations, fluoxetine failed to selectively benefit smokers who expressed prominent weight concerns or low self-efficacy. Targeted cognitive—behavioral interventions to address these cognitive domains might prove more helpful to such smokers.

The present study had important limitations. First, we could not examine cessation outcomes longer than 3 months past the quit date, nor can we comment on the mechanism by which fluoxetine enhanced cessation outcomes among more depressed smokers. Fluoxetine may act like other agents that promote smoking cessation by curtailing dysphoria associated with acute nicotine withdrawal ( [Hall et al., 1998](#) ; [Spring et al., 1991](#) ). This interpretation remains speculative, however, in the absence of further data on treatment mechanisms. Another limitation is that we were unable to examine individual differences in the response to varying doses of fluoxetine. Finally, lacking data on whether participants had a prior history of depression, we cannot ascertain whether the empirically meaningful variations in depressive symptoms that we observed are explicable on the basis of differences in personal and familial history of depression.

The importance of the present research lies in investigating a vastly understudied problem: individual differences in responsiveness to tobacco interventions ( [Glassman, 1998](#) ). As the residual pool of continuing smokers becomes more difficult to reach, and as available treatments become more diverse, there is great need to learn which treatments address the specific needs of different kinds of recalcitrant smokers. Antidepressants represent an increasingly widely used tool in the armamentarium of quit-smoking aides, but efforts to predict who will benefit from them have been surprisingly unsuccessful (cf. [Hall et al., 1998](#) ). In this study, smokers with depressive symptoms even within a subclinical range benefited from receiving fluoxetine while quitting. Greater depression was associated with a better outcome on fluoxetine and with a worse outcome on a placebo only among smokers who adhered to a fairly intensive treatment regimen.

Research is needed to address several additional questions. First is whether the present findings with fluoxetine can be replicated, particularly in a sample that includes individuals with a broader score range of depression scores. A similar question is whether similar results will emerge with other antidepressant smoking cessation aides, like bupropion or nortriptyline. Another important question concerns how to retain in treatment the highly physiologically nicotine-dependent smokers who are most likely to drop out. That problem is especially pressing for the subset of smokers who are depression prone as well as nicotine dependent and who might benefit from adjuvant nicotine replacement in combination with antidepressant treatment.

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Table 1. Results of Hierarchical Logistic Regression Analysis Predicting Abstinence 1 Week After the Quit Date

**Table 1. Results of Hierarchical Logistic Regression Analysis Predicting Abstinence 1 Month After the Quit Date**

Step	Variable	Beta	SE	$\chi^2$	OR	95% CI
1	FHQ	-0.175	0.08	4.53*	0.84	0.68-1.04
2	MBQ	-0.14	0.07	4.15*	0.87	0.73-1.04
3	Stressor Reappraisal	0.38	0.17	5.01*	1.46	1.04-2.05
4	MBQ	-0.05	0.07	1.87	0.95	0.78-1.15
5	Drug Treatment	0.03	0.18	0.01	1.03	0.67-1.58

Note. Model  $\chi^2(4, N = 145) = 16.8, p < .01$ . The sample size for this analysis was reduced slightly from the total sample of nonpregnant participants ( $n = 170$ ) because of missing data on predictor variables. The cut-point criteria for the test of the overall model is based on the likelihood ratio test, whereas that reported for the stressor reappraisal interaction is based on the Wald statistic. OR = odds ratio; 95% CI = confidence interval; FHQ = Fearful Avoidance Questionnaire; MBQ = Multidimensional Brief Symptom Inventory; Drug Treatment = 1 = 12-Week Treatment; 0 = 12-Week Waitlist.

Table 2. Results of Hierarchical Logistic Regression Analysis Predicting Abstinence 1 Month After the Quit Date

**Table 2. Results of Hierarchical Logistic Regression Analysis Predicting Abstinence 1 Month After the Quit Date**

Step	Variable	Beta	SE	$\chi^2$	OR	95% CI
1	FHQ	-0.30	0.11	7.61	0.74	0.55-1.00
2	MBQ	-0.32	0.10	10.00	0.72	0.55-0.95
3	Stressor Reappraisal	-0.10	0.18	0.33	0.91	0.53-1.54
4	MBQ	0.00	0.09	0.01	1.00	0.80-1.24
5	Drug Treatment	0.34	0.16	4.69	1.41	1.02-1.97
6	MBQ $\times$ Drug Treatment	0.30	0.13	5.00	1.35	1.02-1.80

Note. Model  $\chi^2(6, N = 145) = 18.1, p < .01$ . The sample size for this analysis was reduced slightly from the total sample of nonpregnant participants ( $n = 170$ ) because of missing data on predictor variables. The cut-point criteria for the test of the overall model is based on the likelihood ratio test, whereas that reported for the interaction of the predictors is based on the Wald statistic. OR = odds ratio; 95% CI = confidence interval; FHQ = Fearful Avoidance Questionnaire; MBQ = Multidimensional Brief Symptom Inventory; Drug Treatment = 1 = 12-Week Treatment; 0 = 12-Week Waitlist.

Table 3. Results of Hierarchical Logistic Regression Analysis Predicting Abstinence at the Conclusion of Drug Treatment

**Table 3. Results of Hierarchical Logistic Regression Analysis Predicting Abstinence at the Conclusion of Drug Treatment**

Step	Variable	Beta	SE	$\chi^2$	OR	95% CI
1	FHQ	-0.16	0.11	2.00	0.85	0.60-1.21
2	MBQ	-0.14	0.10	2.00	0.87	0.62-1.22
3	Stressor Reappraisal	0.30	0.17	3.00	1.35	0.97-1.88
4	MBQ	-0.07	0.10	1.00	0.93	0.75-1.15
5	Drug Treatment	0.18	0.16	0.75	1.19	0.80-1.79
6	MBQ $\times$ Drug Treatment	0.12	0.10	1.40	1.13	0.92-1.39
7	FHQ $\times$ Drug Treatment	-0.22	0.12	3.70	0.81	0.61-1.08

Note. Model  $\chi^2(7, N = 145) = 18.1, p < .01$ . The sample size for this analysis was reduced slightly from the total sample of nonpregnant participants ( $n = 170$ ) because of missing data on predictor variables. The cut-point criteria for the test of the overall model is based on the likelihood ratio test, whereas that reported for the interaction of the predictors is based on the Wald statistic. OR = odds ratio; 95% CI = confidence interval; FHQ = Fearful Avoidance Questionnaire; MBQ = Multidimensional Brief Symptom Inventory; Drug Treatment = 1 = 12-Week Treatment; 0 = 12-Week Waitlist.

Figure 1. Likelihood of abstinence 1 and 3 months after the quit date as a function of baseline Hamilton Rating Scale for Depression scores.

