

Weight Suppression and Weight Rebound in Ex-Smokers Treated With Fluoxetine

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Fluoxetine's effect (30 mg, 60 mg, and placebo) on postcessation weight gain was studied among participants from a randomized, double-blind 10-week smoking cessation trial who met strict criteria for abstinence and drug levels. It was hypothesized that (a) fluoxetine would dose-dependently suppress postcessation weight gain and (b) drug discontinuation would produce dose-dependent weight rebound. During the on-drug phase, placebo participants gained weight linearly ($M = 2.61$ kg), exceeding both fluoxetine groups (30-mg group $M = 1.33$ kg, 60-mg group $M = 1.25$ kg). Weight suppression was initially greater for 60 mg than 30 mg, but both were followed by weight gain. Six months off drug produced greater dose-dependent weight rebound for 60 mg than 30 mg or placebo. Considering both on- and off-drug phases, weight gain for 60 mg of fluoxetine ($M = 6.5$ kg) was comparable with that for placebo ($M = 4.7$ kg) but greater than that for 30 mg ($M = 3.6$ kg). Fluoxetine appears to forestall postcessation weight gain, allowing time for the weight-conscious smoker to focus on quitting smoking rather than on preventing weight gain.

Despite the risks of smoking and the benefits of quitting, almost a quarter of adults continue to smoke (Centers for Disease Control

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and Prevention, 1994). Although there are many reasons for continuing to smoke, fear of weight gain after quitting may be a significant barrier to both initial quitting efforts (Klesges, Meyers, Klesges, & LaVasque, 1989; Pirie et al., 1992; Streater, Sargent, & Ward, 1989) and the maintenance of abstinence (Borrelli & Mermelstein, 1998; Hall, Ginsburg, & Jones, 1986). Quitters gain an average of 6 to 8 lb (2.7 to 3.6 kg), with some gaining considerably more than this (Klesges et al., 1989, 1997; Williamson et al., 1991). The mechanisms posited to underlie postcessation weight gain include changes in metabolic rate due to the withdrawal of nicotine (e.g., Klesges, Klesges, & Meyers, 1991; Perkins, Epstein, Marks, Stiller, & Jacob, 1989; Stamford, Matter, Fell, & Papanek, 1986) and changes in dietary consumption (e.g., Grunberg, 1985; Hall, McGee, Tunstall, Duffy, & Benowitz, 1989; Spring, Wurtman, Gleason, Wurtman, & Kessler, 1991). However, the relationship between weight and cessation remains controversial. Some evidence suggests that large weight gains actually predict continued abstinence rather than relapse (Hall et al., 1986; Killen et al., 1996). On the other hand, a high degree of weight concern has usually been associated with cessation failure (e.g., Meyers et al., 1997).

Nonpharmacological interventions to prevent postcessation weight gain have offered a combination of self-management strategies, including physical activity and dietary counseling (Hall, Tunstall, Vila, & Duffy, 1992; Pirie et al., 1992). However, the majority have been unsuccessful in preventing weight gain or have tended to be detrimental to smoking cessation (Hall et al., 1992). In contrast, pharmacological interventions have shown more promise in both reducing postcessation weight gain and promoting smoking abstinence. The nicotine patch appears to have little or no effect on postcessation weight gain (Fiore, Jorenby, Baker, & Kenford, 1992; Tonnesen, Norregaard, Simonsen, & Sawe, 1991),

whereas findings with nicotine gum (NG) and nicotine nasal spray (NNS) are more encouraging (Gross, Johnson, Sigler, & Stitzer, 1995; Leischow, Sachs, Bostrom, & Hansen, 1992; Nides et al., 1994; Sutherland et al., 1992), possibly because of the faster nicotine delivery of NG and NNS (Perkins, 1993). However, both NG and NNS postpone, rather than prevent, postcessation weight gain (Gross et al., 1995; Nides et al., 1994; Sutherland et al., 1992).

Appetite suppressants, such as phenylpropanolamine, promote weight loss among obese individuals (Weintraub, Ginsberg, Stein, Sundaresan, & Schuster, 1986) and have been shown to reduce weight gain and calorie intake among recent ex-smokers (Klesges et al., 1995), although longer term outcome studies are needed. Serotonergic agents, such as fenfluramine, dexfenfluramine, and fluoxetine, decrease food intake and body weight among obese patients (Goldstein et al., 1994; Silverstone, 1992; J. Wurtman et al., 1993) and ex-smokers (Spring, Pingitore, & Kessler, 1992; Spring et al., 1991, 1995). These agents inhibit serotonin re-uptake and in some instances enhance serotonin release (Silverstone, 1992), which may attenuate carbohydrate snacking and dysphoria after quitting smoking (Pijl et al., 1993; Rodin, 1987; Spring et al., 1991, 1992). Some evidence also indicates that serotonergic agents increase resting energy expenditure (Bross & Hoffer, 1995; Stinson, Murphy, Andrews, & Tomkin, 1992). Thus, drugs that enhance serotonergic function may decrease postcessation weight gain through effects on both energy intake and expenditure.

To our knowledge, only one double-blind controlled trial (Spring et al., 1995) has examined the effect of fluoxetine on postcessation weight gain. Spring et al. compared the efficacies of dexfenfluramine (30 mg) and fluoxetine (40 mg) in preventing postcessation weight gain among abstainers. As compared with placebo, both drugs reduced weight gain in the 1st month after quitting, but the weight-suppressing effect of dexfenfluramine was maintained over the subsequent 2 months, whereas the weight-suppressing effect of fluoxetine dissipated. The superior efficacy of dexfenfluramine versus fluoxetine may be a function of the former's action as a releaser as well as an uptake inhibitor of serotonin. However, as Spring et al. acknowledged, the disparity may also have resulted from the use of dosages that were unmatched in terms of their effects on weight control. Whereas dexfenfluramine was administered at the dose recommended for weight loss, fluoxetine was administered at two thirds the dose effective for weight loss (Goldstein et al., 1995; Levine et al., 1989). Clinical trials have shown a clear dose-response effect of fluoxetine on weight loss, with 60 mg having an effect superior to 40 mg (Levine et al., 1989). Thus, it is possible that a dose of 60 mg may also be needed to suppress weight gain after quitting smoking. Also, plasma drug levels were not analyzed in the Spring et al. study, precluding biological verification of adherence to medication. To clarify these issues, the present study biochemically verified medication adherence and examined the dose-dependent effect of fluoxetine (placebo vs. 30 mg vs. 60 mg) on postcessation weight gain among ex-smokers.

Weight rebound (weight gain after discontinuing a weight-suppressing agent) has been addressed by only a minority of smoking-cessation investigations (Gross et al., 1995; Spring et al., 1995), some of which were not placebo controlled (e.g., Nides et al., 1994). Weight rebound may be especially disconcerting for smokers who seek out medications specifically to suppress postcessation weight gain. Some studies (e.g., Gross et al., 1995) have

evaluated weight rebound by comparing weight after drug discontinuation with weight before the beginning of drug treatment. This comparison fails to capture and may even mask the full temporal pattern of the medication effect on postcessation weight changes. Prior findings suggest that postcessation weight change while receiving an anorectic agent can be divided into two phases. The first, a weight-suppression phase, involves an initial weight loss, followed by medication tolerance and slow regain while patients remain on drug. This phase is often followed by a period of very rapid weight gain (the weight rebound phase) that ensues when medication is discontinued. Most studies of postcessation weight gain have confounded these two processes. To our knowledge, this is the first study to compare the effect of administering and withdrawing two different doses of a selective serotonin reuptake inhibitor on weight suppression and weight rebound after smoking cessation.

The present study examined the dose-dependent effect of fluoxetine (30 mg vs. 60 mg vs. placebo) on postcessation weight gain in a subgroup of participants from a randomized double-blind trial that tested the effect of fluoxetine on smoking cessation. The subgroup was composed of participants who maintained biologically verified abstinence and medication compliance (in order to eliminate confounding effects of variable nicotine and drug exposure on weight change). We hypothesized that (a) fluoxetine would suppress postcessation weight gain among continuous abstainers in a dose-dependent manner and (b) weight rebound would occur in a dose-dependent manner after discontinuation of the drug. We expected that fluoxetine would reduce postcessation weight gain during the period that ex-smokers remained on medication. However, we did not expect that participants would benefit from this weight-suppression effect over the long-term because of the occurrence of weight rebound triggered by stopping the medication.

Method

Participants

Participants were from a double-blind, placebo-controlled multicenter trial that investigated the effect of fluoxetine on smoking cessation (Eli Lilly and Company, 1991). Sixteen sites screened 1,137 participants, of whom 989 met eligibility criteria and were randomized. Entry criteria required that participants be 18–65 years old, have smoked daily for at least 1 year, exhibit a baseline expired carbon monoxide level of greater than 8 ppm, and agree to declare a quit date within 2 weeks after the second study visit. Exclusion criteria were a Hamilton Depression Rating Scale (Endicott, Cohen, Nee, Fleiss, & Sarantakos, 1981; Hamilton, 1960) score greater than 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 past 6 months, use of smokeless tobacco, pipes or cigars, recent experience of a major life event (e.g., divorce or major job change), suicidal ideation, and history of bipolar disorder. The present study examined weight changes in a subset of participants from the randomized trial who met strict criteria for abstinence and therapeutic drug levels over the course of the study (see the *Procedure* section below).

Measures

Smoking status. Smoking status was assessed at each visit. To be considered abstinent, participants were required to meet all three of the following criteria: self-report of no smoking, expired air carbon monoxide

level of less than 8 ppm, and salivary cotinine less than 20 ng/ml. Saliva cotinine samples were analyzed by SciCor Laboratory (Indianapolis, Indiana).

Weight change. We measured participants' weight in kilograms with shoes off at each visit using a balance beam scale. We measured weight-suppressing effects of medication by subtracting baseline weight (before the start of medication) from the weights at each visit during the on-drug phase. We measured weight rebound after drug discontinuation by subtracting weight at Visit 9, the last week on medication, from postmedication weights at Visits 10, 11, and 12.

Plasma fluoxetine levels. To be included in this study's sample, participants in the two active treatment conditions were required to meet criteria for therapeutic drug levels of fluoxetine at both Visits 5 and 9, as assessed by biological assay. Plasma fluoxetine and norfluoxetine were assayed by SciCor Laboratory using gas chromatography with electron capture detection. We summed the blood levels of fluoxetine and its major active metabolite, norfluoxetine, to yield a total blood level of fluoxetine metabolites (Bergstrom, Beasley, Levy, Blumenfeld, & Lemberger, 1993). Participants in the 30-mg condition were required to have levels greater than or equal to 150 ng/ml, and participants in the 60-mg condition were required to have levels greater than or equal to 300 ng/ml (Bergstrom et al., 1993).

Procedure

The study began with a screening phase, including a physical examination, chest X-ray, blood tests (complete blood cell count and differential) and medical history. Patients fulfilling eligibility criteria were randomly assigned to placebo, 30-, 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. Weight management was not a focus of study recruitment or behavioral treatment. At Visit 2, participants were required to set a quit date within the subsequent 2 weeks. They also paid a \$25 deposit, which was refunded at their last visit (noncontingent on study completion or smoking status). During a treatment phase that began at Visit 2 and continued through Visit 9, participants were given either study medication or placebo and instructed to take one capsule every morning. This double-blind medication phase lasted for 10 weeks. Following this was a no-drug follow-up phase of the study, which included only those participants who had been abstinent for 1 month before Visit 9. One month elapsed between Visits 9 and 10 and between visits 10 and 11. Two months elapsed between Visits 11 and 12. Thus, the full study duration was 6.5 months, including 2.5 months on drug or placebo and 4 months after treatment.

Analytic Plan

The very large size of the parent sample enabled this substudy to examine weight suppression in ex-smokers who were biologically verified to be continuously nicotine free as well as adequately medicated. Although very difficult to attain, such conditions represent the only valid way to rule out confounding influences on weight gain that might result from partial exposure to nicotine or incomplete treatment adherence. To ensure treatment integrity and eliminate effects of continuing nicotine exposure, we analyzed data from only those participants who both met therapeutic-drug-level criteria and were continuously abstinent. We used Visit 12 (6 months after quit day) as an end point.

We performed analyses using the Statistical Package for the Social Sciences (1988) and BMDP (1992). A repeated measures multivariate analysis of variance (MANOVA) was used to test the effects of treatment condition, gender, and time on weight change in kilograms. We conducted the first, overall analysis that tested the predicted Treatment \times Time interaction using only the subset of participants ($n = 78$) who continuously

met therapeutic-drug-level criteria based on the blood samples (collected at Visits 5 and 9) and who also met strict criteria for continuous abstinence over the entire postquit phase of the study (from Visits 6 through 12).

When specifically characterizing weight suppression, we analyzed data from the slightly larger sample of 119 participants who were abstinent from Visits 6 through 9 and whose plasma metabolites indicated medication compliance. The number of participants who met these conditions was as follows: placebo ($n = 46$), 30 mg ($n = 37$), and 60 mg ($n = 36$). We used the larger sample to quantify linear and quadratic trends more reliably so that the time trends of each treatment could be compared more accurately. Characterization of weight rebound was, necessarily, based on the smaller pool of participants who showed evidence of medication compliance and who also met abstinence criteria for the full interval between Visits 6 and 12 ($n = 78$). For both the weight suppression ($n = 119$) and weight rebound analyses ($n = 78$), we calculated the linear and quadratic trends in weight change over time within each medication condition to isolate the source of the significant Treatment \times Time interaction. We compared these trends across treatment groups by performing orthogonal polynomial contrasts that tested for the difference between drug and placebo and between 30 versus 60 mg of fluoxetine. There were no significant differences between the sample of $n = 119$ and the sample of $n = 78$ on any baseline demographic variable.

Results

Participant Characteristics

Table 1 shows demographic characteristics for the sample of 78 participants who were continuously abstinent from Visits 6 through 12. The average participant was a middle-aged, normal-weight adult. At study entry, the modal participant was a moderately nicotine-dependent heavy smoker, with a long history of tobacco use. As shown in Table 1, participants in the 30-mg group reported a higher daily smoking rate than participants in the

Table 1
Demographic Characteristics

Characteristic	Treatment		
	Placebo ($n = 29$)	30 mg ($n = 24$)	60 mg ($n = 25$)
% female	59	54	60
Age (years)			
<i>M</i>	40.4	43.5	41.9
<i>SD</i>	7.3	9.3	8.0
Smoking rate (cigarettes/day)			
<i>M</i>	23.4 _a	29.7 _b	28.0
<i>SD</i>	10.5	12.2	9.6
Body Mass Index			
<i>M</i>	25.6	26.9	26.1
<i>SD</i>	4.2	4.8	4.9
Years smoking			
<i>M</i>	22.3	26.7	24.4
<i>SD</i>	8.2	9.0	8.4
Fagerstrom score			
<i>M</i>	5.5 _a	6.3	6.6 _b
<i>SD</i>	1.9	1.7	1.8
Baseline saliva cotinine (ng/ml)			
<i>M</i>	271.3	271.9	252.6
<i>SD</i>	153.8	163.4	168.8

Note. Participants were appropriately medicated and continuously abstinent from Visit 6 through Visit 12. Different subscript letters denote significant differences at $p \leq .05$.

placebo group, and the participants in the 60-mg group demonstrated higher scores on the Fagerstrom scale (Fagerstrom, 1978) than participants in the placebo group. There were no significant differences between the treatment conditions on any of the other demographic and smoking-history variables.

Fluoxetine Metabolites

The mean combined fluoxetine–norfluoxetine level at Visit 5 was 247.4 ng/ml ($SD = 53.4$) for the 30-mg group and 489.8 ng/ml ($SD = 123.4$) for the 60-mg group, $t(47) = -8.86, p < .0001$. At Visit 9, the mean combined fluoxetine–norfluoxetine level was 329.4 ($SD = 86.4$) for the 30-mg group and 661.6 ($SD = 181.0$) for the 60-mg group, $t(47) = -8.14, p < .0001$.

Overall Postcessation Weight Change Across On- and Off-Drug Intervals

The predicted Treatment \times Time interaction was first tested through a repeated measures MANOVA that examined only those 78 participants who were adequately medicated during the on-drug phase, completed the full 6-month follow-up up to Visit 12, and were continuously abstinent from Visits 6 through 12. Treatment condition and gender were between-subjects variables, time was the within-subject variable, and weight change since baseline (in kilograms) was the dependent variable, producing a $3 \times 2 \times 11$ model. Both age and body mass index (BMI) at Visit 1 were included as covariates. There were no significant effects of the covariates nor were there main effects or interactions involving gender. Therefore, these variables were dropped from the analysis. The results showed a significant Treatment \times Time interaction, Wilks's lambda $F(2, 75) = 3.74, p < .001$, indicating that the treatment groups exhibited different patterns of weight gain over time. Figure 1 shows the time course of weight change for continuously abstinent and appropriately medicated participants across the entire course of the study, including both on- and off-drug phases.

At the end of the full study period, including both on- and

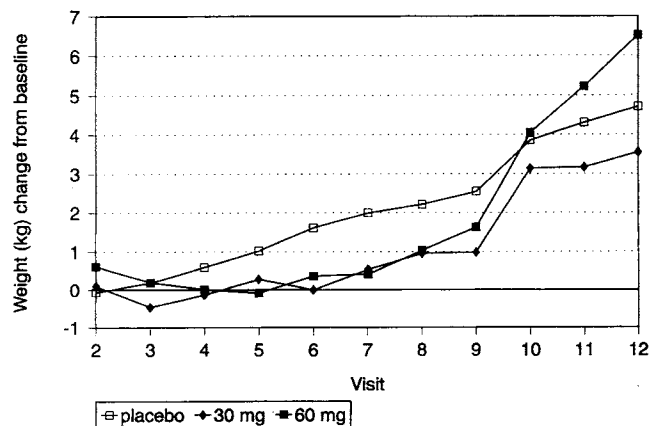


Figure 1. Overall mean weight change in kilograms by condition for participants ($n = 78$) who completed all follow-up visits and were adequately medicated and continuously abstinent from Visit 6 through Visit 12 (on- and off-drug intervals).

off-drug phases, participants randomized to 60 mg of fluoxetine had gained 6.5 kg ($SD = 3.1$) compared with their study weight at baseline (see Table 2). Their overall weight gain significantly exceeded that of participants randomized to 30 mg of fluoxetine (mean gain = 3.6 kg, $SD = 3.5$), $t(47) = -3.13, p < .003$, but did not differ from that of patients randomized to placebo, (mean gain = 4.70 kg), $t(52) = -1.91, p = .06$.

Weight Suppression by Fluoxetine

To more reliably quantify medication effects during the on-drug period only, we examined the larger sample of 119 participants who were appropriately medicated and continuously abstinent up through Visit 9, the end of the medication phase. Table 3 displays the means and standard deviations for weight (in kilograms) before the medication phase and at the end of the medication phase. A repeated measures MANOVA showed a significant interaction between treatment and time, Wilks's lambda $F(2, 116) = 3.84, p < .0001$, without significant covariate effects or differences as a function of gender (see Figure 2). Supplementary analyses showed that both linear, $F(2, 116) = 6.16, p = .003$, and quadratic, $F(2, 116) = 8.40, p = .004$, Treatment \times Time interaction effects were significant, indicating differences in the trajectory of weight change among the three treatment groups. The linear trend for the placebo group differed from that of both the 30-mg, $F(1, 81) = 4.28, p = .04$, and the 60-mg, $F(1, 80) = 13.58, p = .004$, groups. In contrast, the 30- and 60-mg groups only differed from each other on the quadratic trend, $F(1, 71) = 7.40, p = .008$. As Figure 2 shows, the significant linear trend for the placebo group indicates a steady weight gain over the course of treatment for unmedicated participants. In contrast, the significant quadratic trend in the two drug groups indicates an initial weight suppression, followed by an increasing rate of weight gain toward the end of the treatment, despite the continuation of medication. Thus, the temporal pattern of postcessation weight change varied as a function of treatment. Whereas the placebo group gained weight at a gradual and steady pace, the fluoxetine-treated groups remained weight stable or even lost weight initially but later showed an increasing rate of weight gain. The significant difference in quadratic trends between the 30- and 60-mg groups indicates the presence of a dose-response effect, such that 60 mg of fluoxetine produced greater weight suppression than 30 mg. Although these differences are also significant and evident in Figure 1, which shows the smaller sample of participants who remained continuously abstinent during both the on- and off-drug phases, the difference is more robust and clear in Figure 2, which shows the larger sample of individuals who remained abstinent during the medication phase.

Weight Rebound After Fluoxetine Withdrawal

We calculated weight change after fluoxetine discontinuation by subtracting weight at Visit 9 (the end of drug treatment) from weight at each of the subsequent drug-free visits (i.e., Visits 10, 11, and 12). We examined weight rebound through a repeated measures MANOVA with treatment group and gender as between-subjects variables and time as the within-subject variable, producing a 2 (gender) \times 3 (treatment) \times 3 (time) model. Both age and BMI at Visit 1 were included as covariates. There were no signif-

Table 2
Mean Weight (in Kilograms) and Standard Deviations of
Participants Across On- and Off-Drug Intervals

Variable	Treatment					
	Placebo (n = 32)		30 mg (n = 24)		60 mg (n = 25)	
	M	SD	M	SD	M	SD
Weight at baseline	73.8	16.0	77.8	13.8	77.9	15.2
Weight at Visit 12	78.5	17.0	81.4	13.0	84.5	16.6

icant effects of the covariates nor were there significant main effects or interactions involving gender, so these variables were dropped from the analyses.

The analyses yielded a significant interaction between treatment and time, Wilks's lambda, $F(2, 77) = 2.79, p = .03$, indicating that the degree of weight gain after discontinuing drug or placebo varied significantly as a function of treatment. Orthogonal polynomial contrasts showed that the linear trend for the 60-mg group significantly exceeded that for both the placebo, $F(1, 54) = 6.77, p < .01$, and the 30-mg group, $F(1, 47) = 8.93, p < .004$. The 30-mg and placebo groups did not differ, however. The analyses suggest that discontinuing fluoxetine treatment triggered a weight rebound that occurred in a dose-dependent fashion, such that the 60-mg group gained weight at a significantly more rapid rate than either the placebo or the 30-mg group. After drug discontinuation, weight increased linearly for both previously medicated groups in contrast to the curvilinear weight change that both groups exhibited while continuing drug treatment.

Discussion

The present study stringently tested the effect of fluoxetine on postcessation weight gain and weight rebound. Three groups were created such that participants on two different doses of fluoxetine were required to have specific blood levels of the drug, and participants in all three groups were required to meet strict biochemically verified criteria for abstinence from smoking. To our knowledge, no other study has used such stringent, objective criteria for examining postcessation weight gain.

We began by examining weight change over the entire study, including both on- and off-drug phases, and found that weight gain was least for participants on 30 mg of fluoxetine and greater for

Table 3
Mean Weight (in Kilograms) and Standard Deviations of
Participants Abstinent During the Medication Phase

Variable	Treatment					
	Placebo (n = 46)		30 mg (n = 37)		60 mg (n = 36)	
	M	SD	M	SD	M	SD
Weight at baseline	74.6	16.2	74.4	14.4	76.3	13.8
Weight at Visit 9	77.2	16.9	75.8	13.9	77.5	14.3

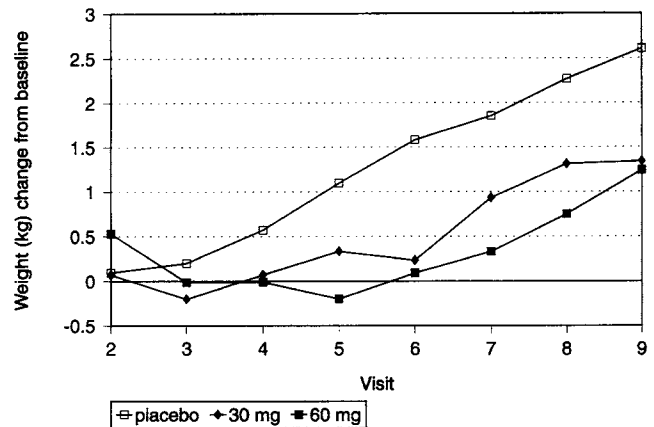


Figure 2. Weight suppression (in kilograms) over time as a function of medication treatment for participants ($n = 119$) who were adequately medicated and continuously abstinent from Visit 6 through Visit 9 (medication phase).

those on placebo or 60 mg of fluoxetine. To determine whether those differential weight gains emerged while participants were on medication or after medication was withdrawn, we compared the groups' patterns of weight change during the two intervals. We confirmed the hypothesis that, during the course of drug treatment, fluoxetine suppresses postcessation weight gain in a dose-dependent manner, with the placebo group gaining more weight after quitting than those in either the 30- or 60-mg fluoxetine groups. Although weight suppression was initially greater in the 60-mg group than in the 30-mg group, by the end of the drug period, both groups began to gain weight.

We also confirmed the hypothesis that weight rebound would occur in a dose-dependent manner after drug discontinuation. After fluoxetine was withdrawn, the 60-mg group increased weight at the greatest rate, exceeding the gains shown by those in either the 30-mg or placebo group. Thus, in the long term, ex-smokers in the 60-mg group who were medicated and then withdrawn from drug experienced no reduction in postcessation weight gain versus those who received the placebo. In contrast, in the long term, 30 mg of fluoxetine did suppress postcessation weight gain in comparison with both the placebo and 60 mg of fluoxetine. Although the 30-mg dose engendered less initial suppression of weight gain while participants were on the drug, its withdrawal produced less rebound weight gain. On balance, then, the long-term picture for weight-gain suppression was more favorable for 30 mg of fluoxetine than 60 mg.

The present results are consistent with others that have shown that fluoxetine is a potent weight-control agent for obese patients (Goldstein et al., 1994) and ex-smokers (Spring et al., 1995), independent of gender. Although higher doses of fluoxetine produce greater weight suppression than lower doses among obese patients (Levine et al., 1989), such dose-response effects had not been systematically investigated among smokers who are trying to quit. The weight-suppressing effect of fluoxetine may be a function of its effects on energy intake, which include accelerating the onset of satiety (Blundell, 1986) and reducing carbohydrate intake (Bross & Hoffer, 1995; R. J. Wurtman & Wurtman, 1995; Spring et al., 1991; Pomerleau, Pomerleau, Morrell, & Lowenbergh,

1991; cf. Stinson et al., 1992). Those with depression or mood problems secondary to a deficiency of serotonin may especially be at risk for increased carbohydrate intake and, thus, postcessation weight gain.

Nicotine and serotonergic agents affect energy expenditure as well as intake. Findings suggest that smokers who quit gain an average of approximately 150–200 kcal/day as a result of decreases in resting energy expenditure (REE; Stamford et al., 1986). If nicotine withdrawal decreases REE, administering fluoxetine to ex-smokers might compensate by increasing REE. That possibility is suggested by one study that found that fluoxetine increased REE by approximately 100 kcal/day, even after holding energy intake constant (Bross & Hoffer, 1995). In sum, fluoxetine's effects on postcessation weight gain might be mediated by influences on energy intake, energy expenditure, or both.

It is noteworthy that both 30- and 60-mg-treated participants began to gain weight toward the end of the treatment phase, even though they remained on medication. These results are consistent with those found by Spring et al. (1995), who found that a 40-mg dose of fluoxetine initially suppressed postcessation weight gain but that tolerance to this effect ensued over treatment. Tolerance to fluoxetine's weight-suppressing effect has also been found by Darga, Carroll-Michals, Botsford, and Lucas (1991) in obesity treatment. Nonetheless, in the present study, some overall benefit was maintained because, by the end of the study, participants in the 30-mg group gained less weight than those in the placebo group. The mechanisms that underlie tolerance to fluoxetine's weight-suppressing effect remain unclear.

The prospect of rebound weight gain after an anorectic agent is withdrawn is one of the most significant deterrents to using pharmacotherapy to promote weight loss. The present results show that this problem is also substantial when using pharmacotherapy to prevent postcessation weight gain. In the present study, weight rebound occurred dose-dependently and linearly over time, and the amount gained was not trivial. The 60-mg group gained an average of 4.9 kg after fluoxetine was withdrawn, whereas the 30-mg group gained 2.5 kg. Placebo recipients gained 2.17 kg. The design of prior studies may have masked weight rebound by failing to separate the two phases of weight change. Temporal comparisons against baseline weight captures the way in which an antiobesity agent gradually promotes weight loss and maintenance over time. Temporal comparisons against end-of-study weights characterize the steep slope of the rebound weight gain that can occur after medication is withdrawn. Both phases must be evaluated to attain a comprehensive understanding of an agent's long-range effects on body weight.

Weight rebound might be especially problematic for those smokers who are sufficiently weight conscious to seek out medication to suppress postcessation weight gain. The weight-conscious person who initially succeeds at quitting smoking and maintaining body weight might be particularly alarmed to experience rapid weight gain after discontinuing an anorectic agent. Weight rebound could then trigger the resumption of smoking, although that prospect remains to be examined. The causes of weight rebound remain to be systematically investigated, as the relative contributions of energy intake and expenditure are unclear. Nevertheless, changes in eating and physical activity are possible ways to offset weight-promoting changes in the energy balance equation (Marcus, King, Bock, Borrelli, & Clark, 1998).

Several factors limit the generalizability of the present results. We used a highly select sample that cannot be assumed to be representative of the majority of those who dropped out or failed to adhere to treatment or to quit smoking. Our aim, however, was to provide an initial test of the effect of fluoxetine on postcessation weight gain in a pure sample in which it was possible to remove the confounding influences of continued exposure to nicotine and insufficient exposure to treatment. It remains unclear whether the present findings can be generalized beyond those who were fully adherent with treatment and able to complete the trial without smoking. Examination of a subset from a larger randomized trial limits generalizability to what might be expected from a quasi-experimental design. Also, although we obtained serum blood levels of fluoxetine as a check for compliance, we cannot be certain that the placebo group was compliant with its protocol. Therefore, unlike those assigned to fluoxetine, those not compliant with taking the placebo could not be detected and eliminated, possibly resulting in a larger and more heterogeneous group.

Because smoking cessation, not weight control, was the overall aim of the larger study, it might be argued that no valid inferences can be drawn about treatment effects on postcessation weight gain. Some would maintain that such inferences can only be derived from a randomized trial directly devoted to preventing postcessation weight gain. Such a trial presents marked disadvantages for generalizability, however, in that highly weight-conscious smokers are disproportionately attracted to enroll. From that perspective, generalizability of the present findings to the average smoker is enhanced by the fact that the present trial never presented weight change as an issue of particular interest to us.

The relationship between postcessation weight gain and maintenance of abstinence is not completely understood. Many ex-smokers tolerate weight gain without relapse to smoking. Indeed, some studies have found that weight gain either fails to predict relapse or predicts a greater likelihood of maintaining abstinence (e.g., Hall et al., 1986, 1992; Killen et al., 1996). However, it may be premature to suggest that postcessation weight gain has a protective effect on abstinence. Most research data to support that conclusion derive from correlating weight gain and cessation outcome in the subset of study participants who are continuously abstinent. Missing from that subsample are participants who were unable to sustain abstinence and who relapse early in treatment for reasons that included weight gain. Most relapse occurs in the first 3 months of abstinence (Mermelstein, Karnatz, & Reichmann, 1992), and some data suggest that weight gain may be associated with early relapse (Borrelli & Mermelstein, 1998). Moreover, because research procedures for validating continued abstinence are variable and all incorporate some error of measurement, there is variation in the degree of nicotine exposure (from slips back to smoking) even among participants included in a smoke-free sample. To the extent that nicotine exposure suppresses body weight, completely abstinent individuals should exhibit greater weight gains than those who experienced nicotine exposure. The apparent relationship between greater weight gain and abstinence may, therefore, be an epiphenomenon of the fact that those who can initially sustain absolute abstinence without slipping (and therefore experienced no weight-suppressive effect of nicotine) are likely to remain smoke free in the future. One might also expect weight gain to be predictive of relapse for those highly weight-conscious smokers to whom it matters most. It remains to be determined

whether prior findings concerning weight gain and relapse are distorted by an absence of weight-conscious smokers who would not attempt cessation unless offered a means of preventing weight gain and who may drop out of treatment on perceiving (or even imagining) weight gain.

Future studies should examine the degree to which treatment effects on postcessation weight gain are mediated by changes in diet, physical activity, and metabolism. To date, only extreme behavioral interventions have shown success in simultaneously promoting weight maintenance and abstinence from smoking (Talcott et al., 1995). A more realistic treatment approach may be to combine cognitive-behavioral and pharmacological treatments either simultaneously or sequentially to promote greater or more long-lasting lifestyle change. One possible strategy would be to introduce adjunctive behavioral techniques (e.g., exercise) at the time when recent ex-smokers become tolerant either to the hypophagic effect of fluoxetine or to its effect on metabolic enhancement. Such behavioral techniques might also be added to prevent rebound weight gain when fluoxetine is discontinued. Cognitive interventions, such as restructuring beliefs about postcessation weight gain, may be promising (Perkins et al., 1998).

An important application of postponing postcessation weight gain through pharmacological agents may be to "buy time" during which the very weight-conscious smoker can focus on quitting smoking without being distracted by worries about weight gain. Even after cessation is attained, drug treatment can allow the recent ex-smoker time to adjust to the lifestyle change of being a nonsmoker without having to implement additional behavior changes to prevent weight gain. To date, there is no evidence to suggest that treatment with fluoxetine undermines smoking cessation. Thus, medication offers another tool that provides a window of opportunity for the smoker to explore cognitive and behavioral strategies to promote healthy lifestyle change.

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