Efficacies of dexfenfluramine and fluoxetine in preventing weight gain after smoking cessation[1-4]

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ABSTRACT We tested whether 14 wk of dexfenfluramine (30 mg) or fluoxetine (40 mg) treatment would prevent weight gain after subjects quit smoking. Normal-weight women ($n = 144$) were randomly assigned to drug or placebo on a double-blind basis for 2 wk before quitting smoking and 12 wk thereafter. The fluoxetine group had more dropouts (28/49, 57.1%) than the dexfenfluramine group (17/47, 36.2%), with an intermediate number of dropouts from the placebo group (21/48, 43.8%). All groups gained weight during treatment, but their amount and pattern of weight gain differed. In the first month after quitting smoking, the placebo group gained more weight than either the dexfenfluramine or fluoxetine group ($P < 0.05$). By 2 mo postcessation, dexfenfluramine still suppressed weight gain in comparison with placebo ($P < 0.05$); weight gain with fluoxetine was not differentiable from either dexfenfluramine or placebo. By 3 mo postcessation, the dexfenfluramine group had gained 1.0 ± 0.7 kg, significantly less than either the placebo (3.5 ± 0.7 kg) or fluoxetine (2.7 ± 0.5 kg) groups. Three months after drug discontinuation, formerly medicated, but not placebo patients, showed additional weight gain, eliminating differences between groups. Results indicate that weight gain, an adverse accompaniment of smoking cessation, can be minimized to some degree by serotoninergic drugs, although only for the duration of drug treatment. *Am J Clin Nutr* 1995;62:1181–7.

KEY WORDS Obesity, weight maintenance, cigarette smoking, serotonin, fluoxetine, dexfenfluramine

INTRODUCTION

Weight gain usually follows the cessation of smoking (1, 2) and increasingly, fear of weight gain discourages many smokers from attempting to quit (3). More females are initiating smoking, so that if current trends continue, there will soon be more female than male smokers (4). A majority of women say that the prospect of weight gain increases their reluctance to stop smoking (3). Yet, weight gain after quitting smoking has proved so refractory to preventive efforts as to suggest that weight maintenance might even be incompatible with successful smoking cessation (5, 6). Innovative treatments that can prevent or minimize weight gain are badly needed to encourage women to quit smoking.

The mechanisms that cause postcessation weight gain are partially understood and probably involve more than one contributing factor. Quitting smoking has not been found to produce any consistent change in physical activity (1), but alterations in metabolism and energy intake both appear to change energy balance. Some findings suggest that quitting smoking reduces metabolic expenditure by ≈418 kJ (100 kcal)/d (7), which explains 39% of the variance in postcessation weight gain (8), although other investigations failed to show that cessation reduces resting metabolic rate (9). Heightened energy intake probably makes a larger contribution to weight gain, because energy intake increases by ≈627–1463 kJ (150–350 kcal)/d after smoking cessation (1, 10–12). Energy intake increases immediately after smoking cessation (11, 13) and has been estimated to account for 69% of the variance in postcessation weight gain (8).

Quitting smoking usually alters eating behavior by selectively increasing the intake of sweets and other carbohydrate-rich snack foods that commonly contain large amounts of fat; protein intake changes minimally (14–16). The exsmoker's heightened intake of sweet treats resembles the kind of carbohydrate preference that has been observed in other syndromes in which patients claim that they self-administer carbohydrates to improve mood. Overconsumption of sweets is presumably reinforced by their efficacy in dispelling the agitation and dysphoria that result from a functional deficiency in brain serotonin (17), even though the eating pattern is also punished by weight gain. In a variety of syndromes that exhibit carbohydrate preference [eg, carbohydrate-craving obesity (18), seasonal affective disorder (19), and premenstrual dysphoric disorder (20)], serotoninergic agents have been found to reduce

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[2] MIT holds patents governing the use of both dexfenfluramine and fluoxetine for various weight control applications with JW and RW as copatent assignees. BS is copatent assignee for the application to prevent postcessation weight gain.

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energy intake by decreasing consumption of carbohydrate-rich, protein-poor foods. Because nicotine administration is known to increase serotonin release (21), it is possible that the carbohydrate craving associated with smoking withdrawal reflects diminished serotoninergic neurotransmission that can also be corrected pharmacologically.

To test whether serotoninergic agents minimize weight gain after quitting smoking, Bowen et al (22) administered 50 mg L-tryptophan·kg^{-1}·d^{-1} or placebo to adults who were in the process of quitting smoking. Tryptophan was very successful at preventing dysphoric mood after nicotine withdrawal, but did not suppress weight gain. To test a more potent serotoninergic agent, Spring et al (11) subsequently conducted a double-blind, placebo-controlled trial of the serotonin reuptake inhibitor and releasing agent dexfenfluramine among overweight women who were quitting smoking. Like L-tryptophan, dexfenfluramine prevented a worsening of mood, but, in addition, it prevented an increase in energy and carbohydrate intakes and caused a slight weight loss during the first month after subjects discontinued smoking (11). Although widely used internationally as an antiobesity agent, dexfenfluramine is unavailable in the United States. Consequently, a goal of this study was to test whether fluoxetine, an accessible serotonin reuptake-inhibiting drug that has anorectic properties (23) would also prevent postcessation weight gain. We aimed to compare the efficacies of dexfenfluramine and fluoxetine in preventing weight gain among nonobese women during a longer postcessation period than previously studied (3 mo) and after drug discontinuation.

SUBJECTS AND METHODS

Subjects

We used newspaper advertisements to recruit normal-weight women who feared gaining weight after quitting smoking. Study candidates were screened via telephone and asked to mail back questionnaires about their smoking and health habits and histories. Entry criteria required that subjects had smoked at least one pack of cigarettes daily for the past year and that they were within the range of recommended weight for height according to the 1983 height and weight tables of the Metropolitan Life Insurance Co for midpoint frames (24). Participants were also required to be committed to stopping smoking and in good general health. To verify health status, a physician performed an evaluation that included a medical history and physical examination, urine analysis, electrocardiogram, thyroid profile, human chorionic gonadotropin test, complete blood count, and blood profile (glucose, blood urea nitrogen, creatinine, total protein, albumin, calcium, phosphorous, total bilirubin, uric acid, cholesterol, triacylglycerol, sodium, potassium, chloride, total carbon dioxide, alkaline phosphate, lactic dehydrogenase, serum glutamic acid, oxaloacetic transaminase, and serum glutamic-pyruvic transaminase).

At the time of their medical evaluation subjects signed a consent form. The consent form and all procedures were approved by the MIT Committee on the Use of Humans as Experimental Subjects and the Advisory Committee of the MIT CRC.

Methods

Subjects who met the entry criteria were randomly assigned to receive daily placebo, 30 mg dexfenfluramine, or 40 mg fluoxetine. The study was conducted in a double-blind fashion. All subjects received identical packets of three pills with instructions to take one pill in the morning, one at noon, and one in the early evening. (The noon pill for all groups was a placebo). To ensure that plasma drug concentrations had stabilized before smoking cessation, medication was started 2 wk before the quit date, when behavioral stop-smoking treatment also began. Study medication was dispensed every 2 wk, at which time subjects reported any side effects occurring during the previous 2 wk. Except for an additional session held 48 h after the quit day, group behavioral treatment sessions occurred weekly for the initial 4 wk after the quit day and biweekly thereafter until a last treatment session 12 wk after the quit date. The last day of medication coincided with the last treatment visit and was preceded by 3 d of decreasing doses. Subjects who relapsed to smoking were encouraged to continue treatment and regular assessments, and to try to quit again.

To evaluate weight status after drug treatment ended, subjects were offered a small gift if they returned for a follow-up visit 6 mo after the quit day (ie, 3 mo after drug discontinuation). Of those who completed the study, 80% returned for follow-up.

Measurements

Nicotine dependence

The eight-item, self-report Fagerstrom Tolerance Questionnaire (25) was used to assess attributes suggesting physiologic dependence on nicotine. Scores ≥ 7 suggest nicotine dependence.

Smoking status

Self-reports of smoking status were validated against two biological measures. First, at every visit, exhaled carbon monoxide was assessed via an ecolyzer. Second, plasma cotinine, nicotine's major metabolite, was quantified from blood samples taken at baseline and 4, 8, and 12 wk after the quit day. Blood samples were analyzed by the American Health Laboratory (Valhalla, NY) using modified gas-liquid chromatography (26). To be considered abstinent from smoking, all of the following were required: self-report of no smoking, expired carbon monoxide < 8 ppm, and plasma cotinine < 10 μg/L. Subjects were categorized as "chipping" if they self-reported between one puff and five cigarettes per day smoked at any time during the past week, had expired carbon monoxide concentrations between 8 and 15 ppm and had plasma cotinine concentrations between 11 and 125 μg/L, based on the estimate that each of five cigarettes would contribute 25 μg/L (Neil Benowitz, personal communication, 1993). They were designated as "relapsed to smoking" if they exceeded any one of the three criteria for chipping. At the follow-up visit 3 mo after drug withdrawal, cotinine was not measured, and self-reported abstinence status was biochemically verified by carbon monoxide alone.

Body weight

Body weight of subjects without shoes was always measured by using the same balance-beam scale. Baseline weight was assessed 1 d before the start of drug treatment. Subjects were reweighed 1, 2, and 3 mo after the quit day, and 3 mo after study medications were discontinued.

Snack intake

To quantify snack intake, the Massachusetts Institute of Technology (MIT) Clinical Research Center (CRC) provided subjects with all of their food to be eaten during a 48-h period at three intervals during the study. Food intake measurements occurred at baseline before drug treatment began, on the second and third days after the quit day, and 10 wk after the quit day. Only those subjects who remained smoke-free participated in the last two assessments. Subjects were told to follow a fixed meal plan consisting of foods provided by the CRC diet kitchen. They were told to consume meal foods in their entirety to minimize the use of snacks as substitutes for missed or incomplete meals. The subjects were also given an assortment of preweighed snacks in excess of what they anticipated consuming each day. Snacks were either carbohydrate-rich and low in protein, or protein-rich, as shown in **Table 1**. The snack packages had colored labels that subjects removed and attached to a log book to record which snacks they ate. They returned the book and snack packages to the CRC diet kitchen at the end of each measurement period.

Statistics

Between-subjects analyses of variance (ANOVAs) were used to compare the characteristics of subjects assigned to the three treatment groups. Mixed-model ANOVAs contrasted the treatment groups on changes in the outcome variables over time. The Huynh-Feldt (27) correction was used to compensate for violations of the compound symmetry assumption. Significant results were interpreted by supplementary comparisons of pairs of groups by using the Newman-Keuls test and by simple-effects F tests of change over time. Survival analyses of attrition and smoking status followed an intent-to-treat approach, with all subjects who were randomly assigned to treatment included in the analyses. These analyses were based on the conservative assumption that dropouts had relapsed to smoking.

The primary analyses of weight gain and food intake included only those subjects who continued to take the medication and completed the 14-wk trial without relapsing to smoking. Because subjects who relapse to smoking self-administer nicotine, a weight-suppressing agent, the inclusion of smokers in the analyses of weight change could potentially have biased the outcome in favor of the drug treatment that produced the worst smoking cessation outcome. Limiting these analyses to nonsmokers enabled us to compare the drugs' abilities to minimize postcessation weight gain and overeating when the confounding influence of self-administration of nicotine was removed. Chippers who smoked five or fewer cigarettes per day at some time during the study but did not exceed this amount (as verified by biological markers) were considered to have slipped but not to have relapsed to smoking. They were included in the analyses of nonrelapsed subjects because there were no differences between chippers and continuously abstinent subjects on any outcome measure.

TABLE 1
Energy and macronutrient composition of snack food choices[1]

Snack item	Portion size	Energy	Protein	Fat	Carbohydrate
	g	*kJ(kcal)*	*g*	*g*	*g*
Caramel corn (C)[2]	36.9	627 (150)	2.5	3.8	28.0
Rice cakes (C)	37.0	648 (155)	2.6	2.3	30.0
Rice puffs (C)	38.0	665 (159)	2.9	4.5	29.0
Fruit chews (C)[3,4]	7.0	627 (150)	0	3.0	30.0
Graham cookies (C)[5]	22.7	376 (90)	1.5	3.0	16.5
Chocolate chews (C)[6]	45.0	702 (168)	0.5	3.8	36.0
String cheese (P)	23.0	293 (70)	7.0	4.0	0.7
Lean turkey (P)	70.9	523 (125)	12.5	7.5	2.5
Yellow cheese (P)	28.3	368 (88)	7.0	6.0	1.0
Fruit yogurt (P)	125.0	543 (130)	10.0	3.0	15.0

[1] C, carbohydrate-rich, protein-poor snack choice; P, protein-rich snack choice.
[2] Cracker Jacks, Borden, El Paso, TX.
[3] Starburst, M&M/Mars, El Paso, TX.
[4] Portion size is number of pieces, rather than grams.
[5] Teddy Grahams, Nabisco, Easton, MD.
[6] Tootsie Roll, Tootsie Roll Inc, Chicago.

RESULTS

Demographic characteristics

The 144 female smokers who enrolled in the study were randomly assigned to treatment as follows: 48 placebo, 47 dexfenfluramine, and 49 fluoxetine. At study entry, the three groups were comparable in age, body mass, and smoking characteristics, as shown in **Table 2**.

Attrition

Survival analysis showed that the three treatment groups differed significantly in their rates of attrition [log-rank chi-square (df = 2) = 7.9, $P < 0.05$]. **Figure 1** displays the number of weeks until dropout for subjects in each group. Significantly more dexfenfluramine (30/47, 63.8%) than fluoxetine (21/49, 42.9%) subjects completed the trial, and the number of placebo subjects who completed the study (27/48, 56.3%) was intermediate.

Each dropout's main reason for attrition was coded as side effects, personal reasons, disappointment about failure to quit smoking, intercurrent illness, or noncompliance (failure to take medications or attend groups). The major causes of attrition for each treatment group are shown in **Table 3**. Some dropouts were attributed to drug side effects in all three groups. Reported side effects that caused dropouts for the placebo group were mood disturbance ($n = 2$), confusion ($n = 2$), and hair loss. In the dexfenfluramine group, dropouts because of side

TABLE 2
Demographic characteristics of subjects at study entry[1]

Characteristic	Treatment		
	Placebo ($n = 48$)	Dexfenfluramine ($n = 47$)	Fluoxetine ($n = 49$)
Age	41.1 ± 1.4	40.5 ± 1.4	41.0 ± 1.3
Height (cm)	163.4 ± 0.8	164.8 ± 1.1	164.0 ± 1.1
Weight (kg)	64.6 ± 1.3	62.9 ± 1.1	62.4 ± 1.1
BMI (kg/m^2)	24.2 ± 0.5	23.2 ± 0.4	23.2 ± 0.4
Cigarettes/d	27.3 ± 1.6	27.5 ± 1.6	28.0 ± 1.5
Fagerstrom score[2]	6.7 ± 0.3	6.5 ± 0.3	6.1 ± 0.3
Plasma cotinine (μg/L)	289.7 ± 16.4	262.2 ± 17.4	268.1 ± 15.0

[1] $\bar{x}$ ± SEM.
[2] Reference 25.

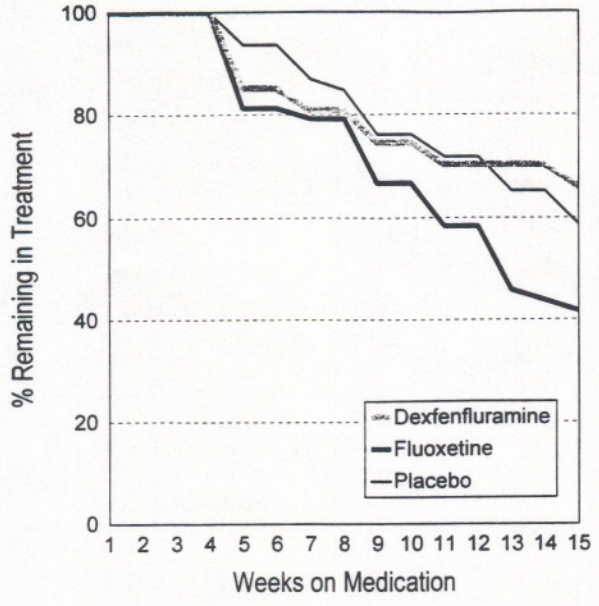

FIGURE 1. Attrition expressed as the percentage of each group remaining in double-blind treatment at each protocol week.

effects were for nausea ($n = 2$), diarrhea ($n = 2$), and nervousness. In the fluoxetine group, dropouts occurred because of urticaria ($n = 2$), nausea ($n = 2$), weakness ($n = 2$), agitation, and hypertension.

Smoking cessation

Table 4 shows the number of subjects in each group who completed the trial and remained continuously abstinent from smoking throughout treatment, those who chipped occasionally, and those who at some time during treatment met criteria for a relapse to smoking. Survival analysis of the relapse curves showed that the drugs did not differentially influence success at remaining smoke-free, although end of treatment cessation rates were somewhat better for dexfenfluramine (53.2%) than placebo (48.3%) or fluoxetine (33.3%).

Weight gain

A preliminary analysis compared body weights measured at baseline, and at 1, 2, and 3 mo after the quit-smoking date by means of a mixed-model ANOVA that included time as the repeated-measures factor, as well as drug treatment group and end-of-study smoking status (abstinent, chipping, or relapsed) as between-subjects factors. The analysis included only subjects who completed the trial and remained continuously and

TABLE 3
Number of women citing each primary reason for dropping out

Reason	Treatment		
	Placebo ($n = 48$)	Dexfenfluramine ($n = 47$)	Fluoxetine ($n = 49$)
Side effects	5	5	8
Personal reasons	3	6	5
Noncompliance	3	4	7
Treatment failure	8	1	4
Intercurrent illness	2	1	4

TABLE 4
Status of women from random assignment through end of treatment

Status	Treatment		
	Placebo	Dexfenfluramine	Fluoxetine
Random assignment to treatment	48	47	49
Dropped out	21	16	28
Completed treatment	27	31	21
Continuously smoke-free[1]	15	18	10
Chipping[2]	6	7	6
Smoking[3]	6	6	5

[1] Completed the trial, and between the quit date and end of treatment reported continuous no-puff abstinence, and never exhibited expired carbon monoxide >8 ppm nor plasma cotinine >10 μg/L.

[2] Completed the trial, and at some time between the quit date and end of treatment self-reported smoking between 1 puff and 5 cigarettes/d or showed expired carbon monoxide between 8 and 15 ppm or plasma cotinine between 11 and 125 μg/L.

[3] Completed the trial, and at some time between the quit date and end of treatment exceeded at least one of the criteria for chipping.

appropriately medicated throughout treatment. The ANOVA yielded a significant main effect of time ($F_{[3,192]} = 22.6$, $P < 0.001$), which was embedded within significant drug × time ($F_{[6,192]} = 7.4$, $P < 0.001$), and smoking status × time ($F_{[6,192]} = 4.5$, $P < 0.01$) interactions. To interpret the status × time interaction, we performed Newman-Keuls tests comparing weight gain at 1, 2, and 3 mo after the quit date as a function of smoking status. The results indicated that 3 mo after the quit date, subjects who relapsed to smoking had gained significantly less weight than those who had chipped or remained abstinent ($P < 0.05$). No differences in weight gain as a function of smoking status were evident earlier. Because relapse to smoking demonstrably suppressed weight gain by the end of the trial, smokers were excluded from all subsequent analyses. No differences between abstinent subjects and chippers were evident at any time point, so that these subgroups were combined in subsequent analyses.

The mixed-model ANOVA excluding smokers and comparing the three drug groups' weight gain during the treatment period yielded a significant drug × time interaction ($F_{[6,180]} = 5.6$, $P < 0.001$). Simple-effects analyses showed that all groups gained weight, but the extent and time course of their weight gains differed, as shown in **Figure 2**. The placebo group showed significant weight gain from baseline to the first month postcessation ($P < 0.001$), after which further weight gains were nonsignificant. The dexfenfluramine group showed a significant weight gain between the first and second months postcessation ($P < 0.05$), but not between baseline and 1 mo or between 2 and 3 mo postcessation. The fluoxetine group showed significant weight gains across all time intervals: baseline to 1 mo postcessation ($P < 0.05$), 1 to 2 mo, and 2 to 3 mo postcessation (both $P < 0.01$). One month after quitting smoking, the placebo group's weight gain exceeded that of both the dexfenfluramine and fluoxetine groups ($P < 0.05$). Thus, both drugs reduced weight gain for the first month after quitting smoking. Dexfenfluramine continued to suppress weight gain, compared with placebo, in the second month postcessation ($P < 0.05$), whereas fluoxetine's effect became intermediate: ie, not differentiable from either dexfenfluramine or placebo. Three months after the quit date, dexfenfluramine reduced

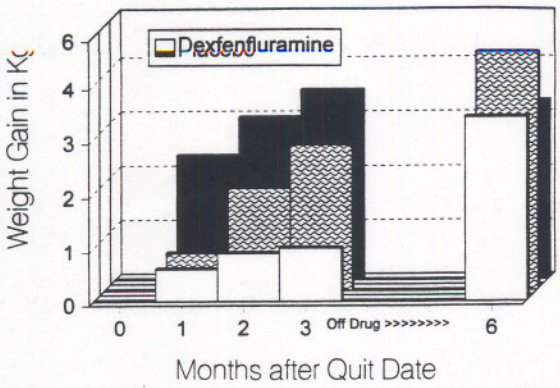

FIGURE 2. Weight gain 1, 2, 3, and 6 mo after stopping smoking for patients treated with placebo, 30 mg dexfenfluramine, or 40 mg fluoxetine/d. The 6-mo assessment period occurred 3 mo after the double-blind drug treatment ended.

weight gain to a greater degree than either placebo or fluoxetine ($P < 0.05$), suggesting that subjects had developed tolerance to fluoxetine's weight-suppressing action.

After medications were discontinued, the groups showed different amounts of weight gain. A mixed-model ANOVA comparing each group's weight at the end of treatment and 3 mo after drug withdrawal yielded a significant drug × time interaction ($F_{[2,54]} = 5.6$, $P < 0.01$). After treatment was stopped, the average placebo group member did not gain any additional weight. In contrast, subjects formerly treated with either dexfenfluramine ($P < 0.001$) or fluoxetine ($P < 0.05$) did show significant weight gains of slightly > 2 kg, as shown in Figure 2. The weight rebound after drug discontinuation was such that, by the time of the 6-mo follow-up, the treatment groups no longer differed in weight gain.

Snack intake

Two mixed-model ANOVAs examined changes in the carbohydrate and protein snack intakes of the nonsmoking subjects. Those data appear in **Table 5**. Both analyses yielded significant effects of time in the absence of time × drug interactions, showing that most subjects, regardless of treatment, increased their carbohydrate ($F_{[2,92]} = 29.6$, $P < 0.001$) and protein ($F_{[2,58]} = 6.3$, $P < 0.01$) snack intakes after stopping smoking. The analysis of carbohydrate snacking also signed to receive dexfenfluramine had lower carbohydrate snack intakes than those randomly assigned to receive other medications. To compensate for between-group differences in intakes, we computed two change scores that reflected each subject's carbohydrate snack intakes 2 and 70 d after the quit date, subtracting out her baseline, premedication intake. Between-group comparison ($P < 0.05$) showed that 2 d after smoking withdrawal, carbohydrate snacking had increased significantly more in the placebo group (1659 ± 259 kJ, or 397 ± 62 kcal) than in the dexfenfluramine group (723 ± 259 kJ, or 173 ± 62 kcal), whereas the fluoxetine group's (1517 ± 418 kJ, or 363 ± 100 kcal) increase in carbohydrate snacking was intermediate. Ten weeks later, there were no between-group differences in carbohydrate snacking.

TABLE 5
Energy intakes from carbohydrate-rich and protein-rich snacks[1]

	Treatment		
Snacks and days	Placebo (n = 48)	Dexfenfluramine (n = 47)	Fluoxetine (n = 49)
		kJ	
Carbohydrate-rich			
Baseline	1337.6 ± 179.7	1153.7 ± 133.8	1316.7 ± 255.0
Day 2	3063.9 ± 326.0	1885.2 ± 250.8	2834.0 ± 418.0
Day 70	3268.8 ± 443.1	2077.5 ± 267.5	3043.0 ± 522.5
Protein-rich			
Baseline	334.4 ± 54.3	242.4 ± 58.5	292.6 ± 75.2
Day 2	501.6 ± 108.7	505.8 ± 87.8	597.7 ± 163.0
Day 70	497.4 ± 129.6	627.0 ± 125.4	894.5 ± 296.8

[1] $\bar{x}$ ± SEM.

DISCUSSION

The results of this study are relevant to the growing number of women whose fears of weight gain make them reluctant to quit smoking. Behavioral techniques have thus far proved ineffective at minimizing postcessation weight gain (5, 6). Among the possible pharmacologic interventions, only phenylpropanolamine (28) and the serotoninergic agents (5, 11, 29, 30) have shown promise in short-term trials. The present findings suggest that two serotoninergic drugs, dexfenfluramine and fluoxetine, can both be of some value in minimizing weight gain after quitting smoking as long as subjects continue to take the medication. These findings are important in that they provide evidence against the premise that smoking cessation and weight maintenance are fundamentally incompatible. The results demonstrate that weight gain can be minimized without jeopardizing abstinence from smoking, at least when an alternative anorectic agent substitutes for nicotine.

It merits comment that neither dexfenfluramine nor fluoxetine significantly enhanced success at quitting smoking, despite their weight-control properties. These findings for dexfenfluramine are directionally consistent with prior results showing that serotoninergic agents increase the probability of successful smoking cessation by 13–17% (11, 22, 30). The finding that fluoxetine lowered cessation rates slightly in comparison with placebo was unexpected and is inconsistent with other findings (29, 30).

Even though most subjects did gain weight after quitting smoking, dexfenfluramine and fluoxetine were both helpful in reducing weight gain. Their efficacies were comparable for the first month postcessation, when both curtailed weight gain in comparison with placebo. Food intake data suggested that the drugs worked at least partly by preventing an increase in carbohydrate snacking. In the second month after quitting, dexfenfluramine was relatively more potent, because it retained a significant weight-suppressing action relative to placebo, whereas fluoxetine's effect was no longer significant. After 3 mo, tolerance had developed to fluoxetine's weight-suppressing action, as others have also observed (31). Thus, 3 mo after quitting smoking, dexfenfluramine's ability to limit weight gain surpassed that of both fluoxetine and placebo.

Dexfenfluramine's somewhat superior performance in comparison with fluoxetine may reflect its greater range of actions as a releaser as well as a reuptake inhibitor of serotonin. Alternatively, it can be argued that the doses of dexfenfluramine and fluoxetine were unmatched in their efficacies for weight control. We administered 30 mg dexfenfluramine, the dose recommended for weight loss, but only 40 mg fluoxetine, whereas 60 mg is recommended for weight loss. It is possible that treatment with 60 mg fluoxetine would have yielded weight suppression comparable with that achieved by 30 mg dexfenfluramine. The prospect of implementing fluoxetine treatment at an increased dose, however, needs to be considered in light of the high dropout rate shown by participants medicated with fluoxetine. Only ≈43% of fluoxetine-treated subjects completed the 3-mo trial, an attrition rate significantly higher than that for dexfenfluramine. The differential attrition permits several possible explanations. Possibly, the agitation that can be a side effect of fluoxetine proved unusually difficult to tolerate when it augmented agitation associated with nicotine withdrawal. An alternative explanation is that the MIT study physicians may have been less tolerant of fluoxetine's side-effect profile because they had fewer years of experience with administering fluoxetine than dexfenfluramine. Arguing against these explanations, however, is the fact that similar side effects were reported for both serotoninergic drugs. In view of these uncertainties, further research is needed to test whether a dose of fluoxetine sufficient to prevent weight gain can be well-tolerated during smoking cessation.

The current findings suggest that the weight-control benefits of serotoninergic agents during smoking cessation, although evident, persist only as long as subjects continue to take the medication. We had hoped that the first 3 mo after nicotine withdrawal might constitute a phase of reequilibration after which the risk of weight gain diminished. Apparently, however, the interval from 3 to 6 mo postcessation was not a safe period for weight maintenance, at least for subjects initially medicated with dexfenfluramine or fluoxetine. In contrast, note that by 3 mo postcessation, the unmedicated subjects in this trial did reach an asymptotic weight, after which they accrued no additional weight gain for the remainder of the study.

Unlike placebo-treated subjects, those medicated and then removed from serotoninergic treatment showed significant weight gain when treatment was discontinued. By 6 mo postcessation, their weight gain equalled that of never-medicated subjects. These results show that a 3-mo serotoninergic intervention during smoking withdrawal only served to delay weight gain. The possible use of more extended treatments or combined or sequential pharmacologic and behavioral approaches warrants further investigation.

A question can be raised about whether the usual magnitude of weight gain after quitting smoking (4.4 kg; 2) should be considered sufficient to warrant prolonged drug therapy. We suggest that medication may be warranted in two contexts: *1*) when the patient's history indicates that she is among the 13–14% of women who gain > 15.6 kg after quitting (2), and *2*) when the smoker is so highly weight conscious that she is unwilling to try to quit without a means of preventing weight gain. In the latter instance, the risks associated with receiving serotoninergic treatment are smaller than the morbidity and mortality associated with nicotine intake.

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