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Weight Gain and Withdrawal Symptoms After Smoking Cessation: A Preventive Intervention Using d-Fenfluramine

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Directly measured food intake in 31 overweight female smokers to test whether (a) calorie and carbohydrate intakes increase after smoking cessation and (b) double-blind d-fenfluramine (30 mg), a serotonin-releasing drug, suppresses weight gain, overeating, and dysphoric mood associated with stopping smoking. Placebo-treated patients grew dysphoric after smoking withdrawal and ate 300 kcal/day more from 2 to 28 days after, showing a 3.5-lb weight gain. Fat and protein intakes did not change, but carbohydrate intake increased (30% to 40%). D-fenfluramine prevented postcessation dysphoria. Although drug-treated patients ate more carbohydrate snacks just after quitting, they returned to baseline by 4 weeks, showing a 1.8-lb weight loss. Agents that enhance brain serotonin-mediated neurotransmission may help prevent weight gain, overeating, and dysphoric mood after smoking withdrawal.

Key words: cigarette smoking, smoking cessation, weight, carbohydrates, food intake

Quitting smoking often results in weight gain averaging 6 to 10 lb (cf. Gross, Stitzer, & Maldonado, 1989; Hall, McGee, Tunstall, Duffy, & Benowitz, 1989; R. C. Klesges, Meyers, L. M. Klesges, & La Vasque, 1989; U.S. Public Health Service, 1988; Wack & Rodin, 1982). Increased calorie intake has been reported to explain 69% of postcessation weight gain (Stamford, Matter, Fell, & Papanek, 1986). Yet, although subjects often describe increased calorie intake after quitting smoking (Clavel, Benhamou, & Flamant, 1987; Dallosso & James, 1984; Gross et al., 1989; Hall et al., 1989; Hughes, Hatsukami, Pickens, & Svikis, 1984), contradictory findings also exist. In one prospective investigation, Rodin (1987) failed to find significantly increased calorie intake, even in ex-smokers who gained weight. In another, Hall et al. (1989) found a transient rise in calorie intake, which predicted long-term weight gain for females. Males, in contrast, gained weight despite reporting intakes of 1,000 kcal/day less several months postcessation compared to that prior to quitting. Similarly, Lincoln (1969) found an 8-lb weight gain even though ex-smokers reported a 200 kcal/day reduction in food intake.

The limited validity of self-report measures of dietary intake (Myers, R. C. Klesges, Eck, Hanson, & Klem, 1988; A. Smith, 1988; Stuff, Garza, E. O. Smith, Nichols, & Montandon, 1983; Todd, Hudes, & Calloway, 1983; Trulson & McCann, 1959) is one possible explanation for discrepancies between reported calorie intake and changes in weight. Similar inconsistencies characterize findings on self-reported nutrient intake after smoking cessation. In one prospective study (Rodin, 1987), ex-smokers who gained weight reported increased intake of carbohydrates (albeit insufficient to elevate total caloric intake significantly) and somewhat decreased intake of protein, but no change in intake of fat. In contrast, ex-smokers in another study (Hall et al., 1989) reported increased intake of fat and sucrose but no changes in intake of protein and nonsugar carbohydrates.

Direct quantification of food intake is needed to corroborate findings from self-reports, yet only three published studies of people have weighed intake from a diet of predesignated constituents, and none has reported nutrient intake during verified smoking abstinence. In one study, smokers who were self-reportedly abstinent for 12 hr snacked as much as nonsmokers and smokers who smoked (Grunberg, 1982). In contrast, after longer deprivation (up to 4 days), ex-smokers increased their calorie intake (Hatsukami, Hughes, Pickens, & Svikis, 1984), especially from snacks (Gilbert & Pope, 1982). Consumption of different nutrients was not reported in these studies of people, but carbohydrate intake did increase in rats that were chronically exposed to and then withdrawn from nicotine (Grunberg, 1982; Grunberg, Bowen, Maycock, & Nespor, 1985).

We directly measured food intake to test the hypotheses that (a) consumption of calories increases immediately after withdrawal from smoking and persists for 1 month, (b) weight gain correlates with increased calorie intake, and (c) consumption of carbohydrates (sugars and starches) increases more than consumption of protein.

Additionally, we administered double-blind d-fenfluramine, a drug that, by releasing serotonin and blocking its re-uptake, enhances brain serotoninergic neurotransmission. Postmortem brain samples from smokers showed increased nicotine binding sites in several brain regions including the median raphe nuclei, the neurons of which release serotonin (Benwell, Balfour, & Anderson, 1988). This suggests that, in the absence of nicotine, serotonin neurons fire less frequently and release less serotonin. Hypothetically, these effects may

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give rise to dysphoria and, consequently, to carbohydrate snacking in a compensatory effort to elevate brain serotonin (Fernstrom & Wurtman, 1971) and to improve mood (Spring, Chiodo, & Bowen, 1987). If so, then postcessation dysphoric mood, excess carbohydrate intake, and weight gain should be ameliorated by drugs that enhance serotonin-mediated neurotransmission, as occurs in other syndromes characterized by the same symptom triad (Brzezinski et al., in press; O'Rourke et al., 1987).

Obese female smokers were chosen to comprise the sample so that the potential clinical benefit of preventing additional weight gain would balance risks accompanying the use of medication.

METHOD

Subjects

Community announcements solicited overweight female smokers to participate in a free 5-week stop-smoking research program. Participants were required to be 25 to 65 years old and 20% or more above ideal body weight and to have smoked 15 or more cigarettes daily for the past year. Exclusion criteria included pregnancy, hypoglycemia, diabetes, anorexia, bulimia, hypretension, medically or self-imposed food restrictions, and chronic use of medications. After an explanation of the procedures, 31 subjects gave informed consent, received a physical exam and blood tests, and were randomly assigned to receive d-fenfluramine (n = 16) or placebo (n = 15).

Schedule

Groups of 5 to 6, including some placebo-treated and some d-fenfluramine-treated subjects, participated in therapy and assessment sessions. Baseline assessments and the first treatment session were conducted 1 week before subjects quit smoking. Drug treatment began the next morning. On-drug baseline assessments (for some measures) and the second treatment session occurred after 1 week of drug treatment. Subjects quit smoking at the second therapy session. Treatment sessions were conducted 2 to 7 days after smoking cessation; behavioral status was reassessed during this first postcessation week. The final treatment session and assessments occurred 4 weeks after the quit date.

Drug Treatment

Subjects received double-blind d-fenfluramine[1] (two 15 mg doses—one taken upon arising, the second 12 hr later) or placebo (administered on the same schedule), orally. Medication began 6 to 7 days before cessation so that drug levels would stabilize prior to quitting smoking.

[1]D-fenfluramine was administered under IND 20,205, a dossier, filed with the Food and Drug Administration, that permits its use.

Behavioral Treatment

Smoking-cessation treatment groups were led by an experienced American Lung Association facilitator. Precessation treatment components included motivational assessment, a stop-smoking contract, and self-management strategies. Postcessation sessions offered support and relapse prevention.

Assessments

Descriptive data. Before enrollment, subjects complete the Beck (1972) Depression Inventory (BDI) and questionnaires about demographic characteristics, health history, and smoking habits. Usual exercise level was rated such that 0 = *little or no activity,* 1 = *1-4 hours/week of moderate exercise* (e.g., walking, housework, gardening), and 2 = *>4 hours/week of exercise.*

Smoking abstinence. Participants reported any smoking since the last visit and provided breath samples that were immediately analyzed for exhalation carbon monoxide by means of Ecolyzer Model 200/CoHb (Becton, Dickenson, & Co., Hawthorne, NY). Ecolyzer assessment effectively validates short-term changes in smoking behavior (Benowitz, 1983). Subjects were judged nonabstinent if, in the 4 weeks after the quit date, they reported one puff or more, had an ecolyzer value of 8 or more parts per million carbon monoxide, or had missing data.

Weight. Subjects were weighed at the premedication baseline, the on-medication baseline, and 4 weeks after discontinuing smoking.

Food intake. Calorie and nutrient intakes from meals and snacks were measured over three 48-hr periods: a baseline just prior to the start of drug treatment and two treatment periods (2 to 3 and 28 to 29 days after the quit day). Foods were provided in weighed, portion-controlled containers that were reweighed after eating to quantify food intake. Breakfasts and dinners were eaten in the laboratory; lunches and snacks, to be consumed outside, were given in insulated bags with frozen coolant. All foods eaten outside the laboratory were returned and weighed at the end of each measurement day. Participants were told to consume their usual amounts of coffee, tea, and nonsugar carbonated beverages. One serving of orange juice and two servings of low-fat milk and fresh vegetables and fruit were provided daily. No other foods were allowed during the measurement period. At the end of each measurement day, subjects reported any additional foods eaten. These foods (usually beverages) were included in the food-intake computations.

Test foods (see Table 1) were isocaloric (containing equivalent calories) and classified according to their protein-to-carbohydrate ratios. Foods in the high-carbohydrate category contained insufficient protein (1 to 4 g) to block the carbohydrate-induced insulin effect that elevates brain tryptophan uptake and, subsequently, brain serotonin synthesis and release (Fernstrom & Wurtman, 1971, 1972). Foods in the high-protein category contained a mixture of protein and carbohydrates such that no increase in brain tryptophan

TABLE 1
Calorie and Nutrient Contents of Test Foods

Food[a]	kcal	Nutrient: Protein (g)	Nutrient: Carbohydrates (g)	Nutrient: Fat (g)
Breakfast				
Plain yogurt (P)	160	9	13	8
Crescent roll with jam (C)	160	2	25	6
Lunch				
Cottage cheese with wheat germ (P)	150	16	7	6
Tuna salad (P)	150	25	0	6
Oyster crackers (C)	140	2	22	4
Pasta salad (C)	140	4	25	4
Supper				
Mock-crabmeat salad (P)	142	22	0	5
Chicken with barbecue sauce (P)	150	26	2	4
Potato salad (C)	153	4	26	4
Cinnamon-raisin roll (C)	147	3	18	7
Snacks				
Chocolate-flavored high-protein bar (P)	108	10	16	1
String cheese (P)	80	7	1	5
Maple-sugar candy (C)	104	0	26	0
Mixed, sweetened breakfast cereal (C)	110	1	25	1

Note. P = high protein, C = high carbohydrate.

uptake or serotonin carbohydrate category included both sweet and starchy carbohydrates (e.g., sweetened breakfast cereal, pasta, rolls, potatoes) because other studies correlating mood change with carbohydrate intake found no difference between preferences for sweet and starchy carbohydrates (Brzezinski et al., in press; O'Rourke et al., 1987). High-fat ingredients such as butter, cream, and mayonnaise were added to foods like tuna or pasta to make them isocaloric with foods that naturally contain fat (cheese, chicken, yogurt) or with foods commercially prepared with fat (cinnomon raisin roll, crescent roll).

Mood. To assess mood during smoking withdrawal, we asked subjects to complete the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971) just prior to the evening meal. Sampling periods were unmedicated baseline (7 to 8 days before quitting), medicated baseline (0 to 3 days before quitting), and 1 to 3, 4 to 7, 12 to 14, 19 to 21, and 27 to 29 days after quitting. Scores were averaged across days of a sampling period to enhance reliability.

Withdrawal symptoms. A modified version of the Smoker Complaint Scale (SCS; Schneider & Jarvik, 1984) assessed withdrawal symptoms on scales (endpoints = 1 and 7) following the same schedule used with the POMS. We added 19 additional symptoms (e.g., craving for sweets, constipation), to the original 20 items, yielding a 39-item self-report questionnaire.

Performance. Slowed reaction time (RT) detects the acute emergence of concentration problems during smoking withdrawal (Benowitz, 1988; Wesnes & Warburton, 1983). To measure concentration, we collected 125 trials of log-transformed simple auditory RT at predrug baseline, on-drug baseline, and 2 and 29 days after smoking cessation.

Data Analysis

T tests compared demographic and smoking differences between the two treatments and between fully abstinent subjects versus subjects who returned to some smoking. Weight, food intake, mood, withdrawal, and performance data for all subjects randomized to treatment were analyzed by mixed-model analyses of variance, with Drug Treatment as the between-subjects factor and Time as the repeated-measures factor. Support for the study hypotheses was given by significant Drug Treatment × Time interactions. Interactions were interpreted by post hoc Newman-Keuls tests examining changes over time within each treatment group or differences between the two treatments at each time point. In the absence of interactions, significant main effects of time were interpreted by Newman-Keuls combined. Abstinence differences between the two treatments were compared by the Fisher exact test. The correlations among weight gain, increased calorie intake, and mood were examined by Pearson *r*.

RESULTS

Sample Characteristics

As Table 2 indicates, subjects were middle-aged chronic smokers who varied considerably in their histories of weight gain after smoking cessation (range = 0 to 80 lb). The treatment groups showed no significant differences on demographic or smoking variables.

TABLE 2
Demographic and Smoking-History Characteristics of the Treatment Groups

Characteristic	Treatment Group: d-Fenfluramine M	d-Fenfluramine SD	Placebo M	Placebo SD
Age (years)	46.4	10.0	40.0	11.3
Education (years)	14.6	2.8	14.4	1.6
BDI	7.9	5.4	5.3	5.1
Weight (lb)	195.4	28.9	188.2	38.6
Exercise level[a]	.7	.6	.8	.7
Packs/day	1.5	.6	1.4	.3
Years as a smoker	24.9	10.9	21.8	11.2
Number of prior quit attempts	2.4	1.1	4.1	4.6
Years since last quit attempt	2.8	2.9	1.9	2.4
Weight gained in last quit attempt	16.3	21.1	9.0	12.9

[a] 0 = little or no activity, 1 = 1–4 hours/week of moderate exercise, 2 = >4 hours/week of exercise.

Abstinence

Eight of 16 d-fenfluramine-treated subjects (50%) and 5 of 15 placebo-treated subjects (33.3%) met criteria for smoking abstinence—a nonsignificant difference. All subjects substantially reduced their smoking. At 4-week follow-up, 5 nonabstinent placebo-treated patients smoked 1 cigarette or less per day, 2 smoked 3 cigarettes or fewer per day, 2 had missing ecolyzer values (1 was suspected absinent and did not smoke at 1 week, and 1 smoked .3 cigarette per day at 1 week), and 1 smoked 17.3 cigarettes per day (57% of her baseline). At 4-week follow-up, 1 nonabstinent d-fenfluramine-treated patient smoked less than 1 cigarette per day, 3 smoked 5 cigarettes or fewer per day, 3 had missing ecolyzer values (2 were suspected abstinent and did not smoke at 1 week, and 1 smoked 5 cigarettes per day at 1 week), and 1 smoked 30 cigarettes per day (50% of her baseline).

Weight

The placebo group gained more weight than the d-fenfluramine group, $F(2, 51) = 9.07, p < .001$, averaging 3.5 lb ($SD$ = 3.2 lb)—a significant increase—in the month after quitting smoking. The d-fenfluramine group actually lost 1.8 lb (SD = 5.0 lb), a nonsignificant change. Considering only abstinent subjects, the placebo group still gained more than the d-fenfluramine group ($t = -2.45, p < .05$). Within each treatment, the weight change of fully abstinent subjects failed to differ from that of subjects who returned to some smoking, probably because all subjects radically reduced their smoking.

Weight gain was greater for subjects who showed greater increases in calorie intake ($r = .41, p < .05$) and was uncorrelated with study-entry weight ($r = .10$) or initial calorie intake ($r = .04$). Increases in calorie intake were negatively related to baseline dietary intake: Intake increased more in those whose intake was lower initially ($r = -.45, p < .05$).

Food Intake

Calorie intake from meals increased more for placebo-treated patients than for d-fenfluramine-treated patients after smoking withdrawal, $F(2, 51) = 9.44, p < .001$, and calorie intake from snacks tended to do the same, $F(2, 51) = 2.79, p = .07$. As Table 3 indicates, mealtime calorie intake rose significantly for the placebo group 2 days after the quit-smoking day and remained elevated 4 weeks later. Calorie intake from snacks followed the same pattern, although nonsignificantly. Combining meals and snacks, placebo-treated subjects consumed about 300 cal more per day from 2 days after the quit date through the final food-intake measurement 4 weeks after smoking withdrawal, paralleling their weight gain. Carbohydrate-rich foods from meals, $F(2, 51) = 8.53, p < .001$, and snacks, $F(2, 51) = 3.41, p < .05$, contributed most to the rise in calorie intake. Carbohydrate intake increased by about 30% at meals and 40% at snacks. Neither meal nor snack protein intake changed significantly. Mealtime fat intake increased more for placebo patients than for d-fenfluramine patients, $F(2, 51) = 6.66, p < .01$, but the increase was not significant on post hoc testing. Because fat was a fixed constituent of all foods, the increased intake by the placebo-treated patients presumably reflected their proportionally increased consumption of the carbohydrate-rich meal foods.

TABLE 3
Daily-Meal and Snack Calorie and Nutrient Intakes in Withdrawn Smokers Treated With d-Fenfluramine and Placebo

	Baseline		*Withdrawal*			
			Day 2		*Day 28*	
	M	*SD*	*M*	*SD*	*M*	*SD*
Daily Meal						
kcal						
d-Fenfluramine	1264.5	294.2	1168.5	303.8	1115.0	234.4
Placebo	1068.3	310.2	1237.1	297.6	1262.6	195.9
Carbohydrates (g)						
d-Fenfluramine	124.9	35.0	122.6	39.9	118.0	30.0
Placebo	106.4	33.0	137.9	33.0	137.7	28.4
Fat(g)						
d-Fenfluramine	42.2	10.9	37.8	11.0	36.4	8.7
Placebo	36.2	12.7	40.9	10.0	41.3	8.5
Protein (g)						
d-Fenfluramine	92.4	19.8	79.6	18.7	74.5	16.5
Placebo	76.7	28.0	74.7	31.0	80.4	30.5
Snack						
kcal						
d-Fenfluramine	439.6	163.6	533.1	297.9	443.6	170.7
Placebo	410.0	202.9	535.5	275.8	511.3	252.9
Carbohydrates (g)						
d-Fenfluramine	76.3	36.4	98.7	58.5	82.8	35.8
Placebo	76.6	44.7	108.4	67.7	106.0	63.2
Fat (g)						
d-Fenfluramine	8.3	3.0	8.4	5.6	6.7	3.7
Placebo	6.7	4.7	7.3	3.6	6.3	3.2
Protein (g)						
d-Fenfluramine	17.2	7.9	18.7	13.7	15.7	9.7
Placebo	13.1	7.5	12.3	7.0	10.8	6.4

Increases in calorie and carbohydrate intakes observed among placebo-treated subjects were not seen in d-fenfluramine-treated subjects (see Table 3). Calorie intake from meals decreased slightly and nonsignificantly, and meal carbohydrate intake was similar to baseline levels. Snack calorie intake increased nonsignificantly, and snack carbohydrate intake increased significantly 2 days after smoking cessation, but both increases were transient and returned to baseline levels 4 weeks after smoking withdrawal. Mealtime protein intake decreased slightly, $F(2, 51) = 5.28, p < .01$, although significantly. Mealtime fat intake also decreased slightly, but the change was nonsignificant.

There were no significant differences between the calorie- or nutrient-intake changes of those who remained abstinent compared to those who resumed some smoking. Carbohydrate intake increased more among patients who showed a greater concurrent rise in POMS Anxiety (rs = .44 to .58, ps < .05 to .001). Changes in other mood states were uncorrelated with changes in food intake.

Mood

D-fenfluramine prevented a rise in anxiety, $F(6, 159) = 2.61$, $p < .05$, and anger, $F(6, 159) = 2.14, p = .05$, and tended to

suppress a rise in depression, $F(6, 159) = 2.09$, $p = .057$, during the first week after smoking cessation. Placebo-treated subjects reported more anxiety than d-fenfluramine-treated subjects 1 to 3 days after quitting smoking and more anger 4 to 7 days after quitting smoking (see Figures 1 and 2). Considering only abstinent patients, the placebo group still showed a greater increase in anxiety ($t = -2.86$, $p < .05$) and anger ($t = -2.35$, $p < .05$) than the d-fenfluramine group. After the initial week of smoking withdrawal, the groups no longer differed significantly, and their scores did not differ from baseline. Both groups reported most vigor at the initial baseline, $F(6, 159) = 4.55$, $p < .001$, and most confusion 1 to 3 days after quitting smoking, $F(6, 159) = 2.12$, $p = .05$, as shown in Table 4. Means were in the same direction for abstinent subjects, but the differences among days were not significant.

Withdrawal Symptoms

To limit Type I error, a significance level of $p < .01$ was set for analyses of the SCS items. D-fenfluramine failed to prevent diminished alertness accompanying quitting smoking (see Table 4). Immediately after smoking cessation, both groups reported increased disorientation, $F(6, 159) = 5.95$, $p < .001$, and concentration difficulties, $F(6, 159) = 3.94$, $p < .001$, that later subsided. "Spacy" feelings worsened just prior to cessation and persisted for several days after quitting, $F(6, 159) = 5.93$, $p < .001$. Starting treatment with d-fenfluramine may have diminished alertness: Subjective slowing, $F(6, 159) = 3.02$, $p < .01$, light-headedness, $F(6, 159) = 3.36$, $p < .01$, and lethargy, $F(6, 159) = 3.37$, $p = .01$, worsened after the onset of d-fenfluramine treatment and persisted until several days postcessation. For placebo-treated subjects, these symptoms did not worsen until after smoking cessation.

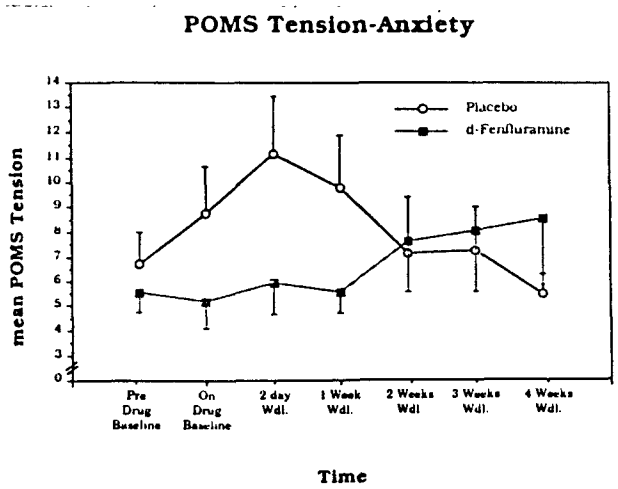

FIGURE 1 Mean (and standard error) POMS Tension-Anxiety before and after withdrawal from cigarette smoking for subjects treated with double-blind d-fenfluramine (30 mg) or placebo. Predrug baseline is prior to both medication and smoking cessation. On-drug baseline is prior to quitting smoking and after 1 week on medication. Postwithdrawal (wdl) assessments are 2 days, 1 week, 2 weeks, 3 weeks, and 4 weeks after the quit-smoking date.

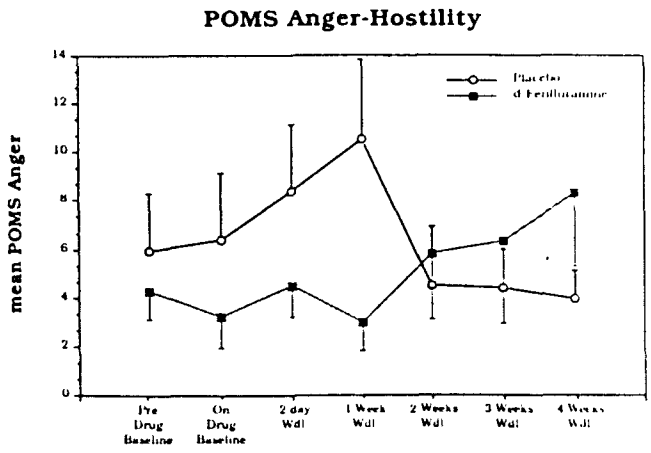

FIGURE 2 Mean (and standard error) POMS Anger-Hostility before and after withdrawal from cigarette smoking for subjects treated with double-blind d-fenfluramine (30 mg) or placebo. Predrug baseline is prior to both medication and smoking cessation. On-drug baseline is prior to quitting smoking and after 1 week on medication. Postwithdrawal (wdl) assessments are 2 days, 1 week, 2 weeks, 3 weeks, and 4 weeks after the quit-smoking date.

Performance

Because RT failed to stabilize until the predrug baseline, only data from the on-drug baseline and 2 and 28 days after smoking cessation were analyzed. Regardless of drug treatment, RT slowed during the acute phase of smoking withdrawal, $F(2, 51) = 4.39$, $p < .05$, corroborating other signs of lowered alertness (see Table 4). There was no significant difference in the degree of slowing shown by abstinent patients versus those who still smoked some. D-fenfluramine neither prevented nor worsened performance impairment.

DISCUSSION

Direct measures of food intake corroborated self-report findings that food consumption increases during smoking discontinuation. Calorie intake increased within the first 48 hr of smoking withdrawal and persisted at a relatively constant level for 4 weeks. Unmedicated individuals consumed about 300 kcal/day more. This may be a conservative estimate because it includes only foods for which consumption was verified by virtue of being eaten in or returned to the laboratory and for which calories were minimized by restricting fat content. This degree of calorie increase would be expected to augment weight gain somewhat more than the 100 kcal/day estimated to be added by metabolic slowing after nicotine withdrawal (Perkins, Epstein, Marks, Stiller, & Jacob, 1989). That weight gain correlated with increased

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TABLE 4
Subjective and Objective Mental Alertness as a Function of Drug Treatment and Time

	Baseline				*Cessation*									
	Predrug		*On Drug*		*Days 1 to 3*		*Days 4 to 7*		*Days 12 to 14*		*Days 19 to 21*		*Days 27 to 29*	
Index	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
POMS														
Vigor														
d-Fenfluramine	13.63	5.66	8.54	6.10	8.21	5.91	9.21	6.15	9.91	6.59	11.53	6.74	10.39	5.89
Placebo	14.73	6.44	10.84	5.40	9.56	6.46	10.53	5.79	10.08	6.46	10.02	5.94	10.95	8.41
Confusion														
d-Fenfluramine	4.97	2.32	6.58	5.09	6.58	4.07	5.13	3.50	4.42	3.42	5.49	4.87	5.55	4.93
Placebo	4.53	2.38	6.69	6.65	7.83	6.46	6.95	6.57	5.94	5.75	5.15	3.83	3.98	1.81
SCS														
Disorientation														
d-Fenfluramine	.84	.87	1.98	1.50	2.13	1.37	1.45	1.13	1.03	.79	1.00	.88	.91	.93
Placebo	1.23	.94	1.22	1.15	2.18	1.45	1.46	1.32	1.55	1.39	1.12	1.03	1.01	.90
Concentration Difficulties														
d-Fenfluramine	1.22	1.05	2.31	1.53	2.47	1.38	1.83	1.27	1.46	1.10	1.18	1.12	1.27	1.53
Placebo	1.70	1.07	1.40	1.22	2.41	1.77	1.98	1.40	1.70	1.60	1.76	1.49	1.25	.87
"Spacy"														
d-Fenfluramine	.56	.77	2.38	1.88	2.03	1.35	1.35	1.29	.87	.98	.81	.93	.85	.89
Placebo	1.13	1.22	1.33	1.57	1.84	1.60	1.33	1.55	.96	1.30	.81	.98	.70	.83
Slowed Down														
d-Fenfluramine	2.88	1.96	3.73	1.74	3.31	1.72	2.82	1.60	2.12	1.45	1.72	1.29	1.79	1.52
Placebo	2.63	1.62	1.91	1.59	2.73	1.68	2.37	1.44	2.33	1.96	2.33	1.46	1.50	1.39
Light-Headed														
d-Fenfluramine	.78	.58	2.52	1.76	2.31	1.38	1.48	1.17	1.15	.91	.97	.81	1.15	1.55
Placebo	1.17	1.05	.98	1.32	1.78	1.60	1.33	1.44	1.24	1.56	.93	1.08	.69	.72
Lethargic														
d-Fenfluramine	1.63	1.49	3.17	1.95	2.88	1.87	2.14	1.67	1.33	1.31	1.47	1.54	1.64	1.74
Placebo	1.33	1.13	1.58	1.57	1.83	1.38	1.48	1.22	2.04	2.08	1.71	1.55	1.26	1.23
Antilog RT														
d-Fenfluramine	213.40	45.81	200.86	54.03	239.57	95.00							210.83	36.80
Placebo	182.46	31.97	166.98	30.79	181.27	31.64							177.73	34.40

calorie intake is consistent with the assumption that overeating contributes to weight gain after smoking cessation.

Smoking withdrawal caused a disproportionate increase in carbohydrate intake rather than a generalized increase across nutrients. Although protein and carbohydrates were equally available, the placebo group's protein intake did not change. Although a change in taste preferences cannot be ruled out, it seems unlikely that heightened carbohydrate intake after smoking cessation was due primarily to increased preference for sweet foods. Within the constraints of product availability, an effort was made not to confound high carbohydrate content with sweet taste. For example, nonsweet foods were served for both lunch-time high-carbohydrate selections (pasta salad, oyster crackers) and one supper-time selection (potato salad). Conversely, one dinner-time high-protein selection (chicken) had a sweet barbecue sauce, and the snack protein bar tasted sweet.

As predicted, the serotonin-releasing agent, d-fenfluramine, suppressed certain symptoms associated with smoking withdrawal. Specifically, d-fenfluramine prevented an increase in calorie and carbohydrate intakes from meals throughout the month after smoking withdrawal. Although the d-fenfluramine group increased their carbohydrates intake from snacks immediately after smoking cessation, their calorie and nutrient intakes returned to baseline after 4 weeks of treatment. The weight of the subjects at 4 weeks reflected differences in calorie intake: Weight increased significantly for the placebo group and decreased slightly for the d-fenfluramine group. Carbohydrate intake increased most in patients who became most anxious after smoking cessation, and d-fenfluramine prevented this increase in anxiety. Additionally, d-fenfluramine prevented an increase in hostility and tended to suppress depression during the first week of smoking withdrawal.

D-fenfluramine alleviated certain symptoms associated with smoking withdrawal but had no effect on other symptoms. Although the drug prevented an initial rise in dysphoric mood, it failed to prevent and may have speeded the onset of a simultaneous deterioration in mental alertness. Subjective and objective signs of impaired concentration were prominent several days after smoking cessation and were not prevented by d-fenfluramine.

Despite the positive features of this investigation, the results should be interpreted with caution. First, it is unclear whether these results will generalize to nonobese women or to men. Postcessation weight gain might be expected to be greater in obese than in lean individuals, but some findings have indicated that thin persons, particularly those who restrict calories, gain the most weight (Bosse, Garvey, & Costa, 1980). Accordingly, our subjects who ate less initially showed greater

postwithdrawal increases in calorie intake, although there was neither a negative nor a positive correlation between initial weight and weight gain. Some evidence suggests that cessation of nicotine intake affects the body weight and appetitive behavior of females more strongly than males (Grunberg, Winders, & Popp, 1987; Hall et al., 1989), but both sexes risk weight gain after smoking cessation (Hall et al., 1989; Lincoln, 1969).

A second limitation of the present research was the absence of plasma assays to verify drug treatment or smoking status. Hence, it remains possible that departures from compliance with either the drug regimen or smoking abstinence went undetected. It may be noted, though, that violations of the drug regimen would be expected to minimize differences between the two treatment groups, such that the current results may represent a conservative test of the drug effect. The impact of unreported departures from full smoking abstinence cannot be estimated with certainty, but several observations are relevant. First, some biochemical verification of smoking status was available from the ecolyzer, and self-reports of smoking behavior were actually more stringent: More abstinence violations were detected from self-report than from ecolyzer assessment. Second, conservative criteria for abstinence were employed: Smoking one puff during the 4-week follow-up constituted a failure of abstinence. Third, departures from smoking abstinence would be expected to influence the results in a direction opposite to study hypotheses, yielding a conservative test. By virtue of their somewhat higher relapse rate and, therefore, greater exposure to nicotine, the placebo group would be expected to exhibit greater mood regulation and appetite suppression than the d-fenfluramine group.

A third limitation is that d-fenfluramine, although available in several European countries, is available in the United States only under an investigational new drug license. D-fenfluramine is the dextro-isomer of dl-fenfluramine, a drug available in the United States. However, because the d and l isomers and their respective metabolites have different biochemical and functional effects, it cannot be assumed that the effects engendered by d-fenfluramine will be reproduced by dl-fenfluramine. Dl-fenfluramine acts on catecholamine-containing neurons mainly due to the l isomer. D-fenfluramine, in contrast, lacks catecholaminergic effects and chiefly inhibits neuronal uptake of serotonin and enhances serotonin release.

A final limitation concerns the lack of long-term follow-up data on food intake, weight changes, and abstinence from smoking. The current findings suggest that heightened calorie and carbohydrate intakes characterize the initial month after smoking withdrawal. Moreover, these changes can apparently be prevented by an agent that enhances serotoninergic neurotransmission. The reliability and persistence of both phenomena warrant additional investigation.

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