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d-Fenfluramine Suppresses the Increased Calorie and Carbohydrate Intakes and Improves the Mood of Women With Premenstrual Depression

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The ability of d-fenfluramine, a drug that releases brain serotonin and blocks its reuptake, to relieve premenstrual depression and excessive calorie and carbohydrate intakes was examined in 17 women with premenstrual syndrome. Subjects received d-fenfluramine (15 mg twice daily) or placebo, in random order, during the luteal phases of six menstrual cycles; ie, for three control and three treatment cycles each. Behavior was assessed with the Hamilton Rating Scale for Depression and its Addendum, and intakes of calories and nutrients were measured by allowing subjects unlimited access to isocaloric meal and snack foods rich in carbohydrates or protein. Pre-treatment follicular scores using the Hamilton Rating Scale for Depression and its Addendum were 2.0 ± 0.5 and 0.5 ± 0.5 (mean ± SEM), respectively; corresponding luteal scores were 21.2 ± 0.8 and 10.2 ± 0.6 ($P < .0001$). Luteal phase intakes of kilocalories, carbohydrates, and fats were also increased above follicular levels ($P < .01$). d-Fenfluramine decreased premenstrual Hamilton Rating Scale for Depression and Addendum scores by 62% ($P < .001$) and 60% ($P < .001$), respectively; placebo reduced them by only 28% ($P < .02$) and 30% ($P < .02$). d-Fenfluramine also fully suppressed the premenstrual rise in kilocalorie, carbohydrate, and fat intakes ($P < .01$). *(Obstet Gynecol 76:296, 1990)*

Premenstrual syndrome (PMS), or the "late luteal phase dysphoric disorder,"[1] is characterized by a cluster of affective, appetitive, and somatic complaints that recur each month during the late luteal phase of the menstrual cycle. In a previous study, direct measurements of food intake and mood state made during the follicular and late luteal phases of the cycle revealed a significant premenstrual increase in caloric intake from carbohydrate-rich foods associated with abnormal depression scores, decreased work efficiency, social withdrawal, and fatigue.[2]

A similar association of affective and appetitive symptoms has been observed in patients with "seasonal affective disorder"[3] and in many carbohydrate-craving obese people.[4] In both conditions, as in PMS, patients typically complain of mood disturbances, diminished interest in previously enjoyed activities, decreased energy and increased fatigue, reduced productivity, social withdrawal, and an increased appetite for carbohydrate-rich foods leading to weight gain.[3] Like PMS, these disorders also recur cyclically; patients experience seasonal affective disorder each fall as the days grow shorter, and the syndrome disappears spontaneously each spring as the days grow longer. Excessive craving for carbohydrate-rich foods and their consumption among obese individuals usually occurs only in the late afternoon or during the evening.[4] Individuals suffering from seasonal affective disorder or carbohydrate-craving obesity are also similar to those with PMS in reporting improvement in their mood after carbohydrate consumption.[5,6] Because eating carbohydrate-rich, protein-poor foods can enhance brain serotonin synthesis,[7] this effect suggests an involvement of brain serotonin in the symptoms of these conditions.

The possible involvement of serotonin in the disturbed food intake and mood of patients with seasonal affective disorder and carbohydrate-craving obesity has also been supported by studies using d-fenflu-

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Supported in part by a grant from the Center for Brain Sciences and Metabolism Charitable Trust.

ramine, a drug that selectively enhances serotonin-mediated neurotransmission by releasing the neurotransmitter and blocking its reuptake.[8] This drug effectively relieved both the depressive and appetitive symptoms of patients suffering from seasonal affective disorder during the annual 3-month period of severest symptoms[3]; it also diminished kilocalorie intake and body weight among carbohydrate-craving obese subjects.[4]

We examined the possibility that d-fenfluramine might also relieve the affective and appetitive symptoms of PMS, particularly depression and excessive carbohydrate intake.

Materials and Methods

Subjects were recruited through newspaper, radio, and television advertisements directed toward women who suffered from severe PMS. Potential subjects were asked to complete and return a health history questionnaire and a PMS symptomatology report,[9] which asked them to assess changes in their mood, appetite, sleep, and somatic symptoms during the follicular and luteal stages of their menstrual cycle. To qualify as eligible subjects, these women had to indicate significant changes in mood and appetite between the follicular and late luteal phases and also to state that these symptoms had occurred monthly during the preceding year. Eligible subjects were then screened as outpatients at the Clinical Research Center during the late luteal phase of their menstrual cycle. At that time, they were interviewed about their premenstrual symptomatology and underwent a physical examination by a nurse and gynecologist. Because we were interested in selecting subjects whose major complaints were depression and increased appetite for carbohydrate-rich foods, we used tests for screening (and subsequently during the treatment) that specifically assessed these behaviors. The Hamilton Rating Scale for Depression,[10] which is administered by trained interviewers, was used to quantify the depressive symptoms of PMS. According to this test, scores above 15 are considered diagnostic of clinical depression.[10] To assess changes in appetite, carbohydrate craving, fatigue, and sociability, a four-item Addendum was used. This test, which is also administered by an interviewer, was developed by Rosenthal et al[5] to measure the symptoms of atypical depression. Both tests ask how the individual has been feeling for the past week; answers are rated on a three- or four-point scale. Urine and blood samples were obtained for clinical measurements (eg, complete blood count, thyroid indices, blood chemistry 20 profile, pregnancy test), and an electrocardiogram was performed on subjects 40 years old or older. Subjects were also weighed and interviewed by a clinical nutritionist to exclude those with eating disorders. Subjects were admitted to the study if their Hamilton Rating Scale for Depression was 20 or higher and their combined Hamilton Rating Scale for Depression and Addendum score was 30 or higher during the late luteal phase of the cycle. All subjects exhibited regular menstrual cycles ranging in periodicity from 26 to 35 days. An informed consent form approved by the Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects and by the Clinical Research Center (CRC) Advisory Committee was signed before participation in any aspect of the studies.

Before initiation of treatment, the subjects underwent a baseline evaluation of menstrual-cycle-associated changes in mood and food intake while inpatients at the CRC inpatient facility. During two 48-hour admissions (one between days 4–7 of their cycle and the other 3–5 days before the expected onset of menses), their moods were evaluated by psychometric testing using the Hamilton Rating Scale for Depression and its Addendum. Food intake was measured concurrently. Subjects were restricted to the meals and snacks provided by the CRC. Each meal provided unlimited quantities of three high-carbohydrate (13–15 g carbohydrate) and three high-protein (13–15 g protein) foods. The high-carbohydrate foods contained 1–2 g of protein, an amount known to be insufficient to block the ability of the carbohydrate to elevate brain tryptophan and serotonin levels.[11,12] The six food items were isocaloric and iso-fat. When necessary, high-fat ingredients such as butter, cream, or mayonnaise were added to increase their caloric value and fat content. Each food item contained about 120–130 kcal. The foods were weighed before being served, and any remaining food was reweighed after the meal was completed.

At all other times, the subjects had continuous access to eight snacks stored in a refrigerated vending machine. Four of the snacks were high-protein (11–12 g) and four were high-carbohydrate (12–13 g). The carbohydrate snacks contained less than 1% protein. All the snacks contained 105–110 kcal and 5–7 g of fat and represented foods that are available commercially (cookies, candy) or are often eaten as snacks at home (cheese, cold cuts). The vending machine was interfaced to a microcomputer programmed to allow the subject to obtain any of the eight snacks after typing a personal access code on an attached keyboard. The foods presented at meals and snacks remained constant throughout the baseline and treatment components of the study.

Blood samples were obtained between days 4–7 of

their cycle and 3–5 days before the expected onset of menses to determine progesterone levels for verification of ovulation.

Subjects were admitted to the clinical trial after completion of the baseline evaluation. Administration of the drug or placebo over six menstrual cycles followed a double-blind, multiple-crossover design. Each subject received d-fenfluramine (15 mg orally twice daily) or its placebo during the entire luteal phase for three cycles. Approximately half the subjects were treated with placebo during the first test cycle. Treatment was started on the 14th day of each month and discontinued 2 days after the onset of menses. Thus, each subject underwent a 12–14-day washout period before starting the subsequent treatment. In man, the half-life of d-fenfluramine is 18.3 ± 1.1 hours (mean ± SEM), with peak plasma levels occurring 3–5 hours after a single dose.[8] Plasma levels of d-fenfluramine reach a steady-state in 4–5 days and thus would be able to exert a constant therapeutic effect by day 19–20 of the menstrual cycle in our study design.

Monthly assessments of depressive and appetitive symptoms were made by having subjects return to the CRC outpatient clinic 2–3 days before the expected onset of menses. At that time, an interviewer blinded to the treatment program administered the Hamilton Rating Scale for Depression and its Addendum. By having the subjects evaluated at the CRC, we were able to assess mood and appetite changes under identical and controlled clinical conditions each month. The subjects underwent a final outpatient evaluation of mood and appetite during the follicular stage of the cycle after conclusion of the clinical trial.

Inpatient assessments of food intake and mood were done twice during the study. Subjects were readmitted to the CRC for a 48-hour period at the end of one drug and one placebo treatment period. (A non-blinded collaborator ensured that one placebo and one treatment period would be represented.)

Two subjects were dropped from the study: one because of pregnancy occurring during a placebo trial and the other for failure to comply with the study protocol. One subject was evaluated for only two drug and two placebo months because back problems prevented her from participating in the full study.

An analysis of variance with repeated measures was performed to compare the consistency of the results within each treatment period and the results of the drug and placebo treatment periods with each other.

Results

Sixteen subjects completed the full clinical trial and one subject completed 4 months of the trial. Their average age was 33 ± 1.7 years, and all subjects were within 105% of ideal body weight (Table 1). Baseline measurements of plasma progesterone carried out 3–5 days before menstruation indicated that most of the subjects had ovulatory cycles; however, two women had luteal progesterone levels of 2 ng/mL or lower, suggesting anovulation. All subjects exhibited regular menstrual cycles, ranging in periodicity from 26 to 35 days.

Table 1. Profile of Subjects

N	17
Age (yr)	33 ± 1.7
Height (cm)	164 ± 2.1
Weight (kg)	65 ± 2.4
% of ideal body weight	105 ± 4.5
Progesterone (ng/mL)	
Follicular	0.4 ± 0.06
Luteal	7.2 ± 1.75

All subjects exhibited significantly elevated depression scores during the late luteal baseline measurement period using both the Hamilton Rating Scale for Depression and its Addendum as test instruments (Table 2). The late luteal Hamilton Rating Scale for Depression and Addendum scores (mean ± SEM) were 21.2 ± 0.8 and 10.2 ± 0.6, respectively; follicular phase Hamilton Rating Scale for Depression and Addendum scores were 2.0 ± 0.5 and 0.5 ± 0.5, respectively. Scores on the Hamilton Rating Scale for Depression and Addendum subscales that assess symptoms characteristic of PMS were also changed significantly during the late luteal test period; work efficiency decreased ($P < .0001$) while anxiety, fatigue, social withdrawal, general appetite, and carbohydrate craving all increased ($P < .0001$) (Table 2).

Kilocalorie, carbohydrate, and fat intakes increased significantly during the late luteal phase (Table 3). Late luteal phase kilocalorie intake from meals increased from follicular levels by about 300 kcal ($P < .01$), and intakes from snacks increased from follicular levels by

Table 2. Premenstrual Symptom Profile

	Follicular	Luteal
Hamilton Rating Scale for Depression	2.0 ± 0.5	21.2 ± 0.8*
Addendum	0.5 ± 0.5	10.2 ± 0.6*
Subscales		
Work efficiency	0.0 ± 0.0	2.9 ± 0.1*
Fatigue	0.0 ± 0.0	2.6 ± 0.2*
Social withdrawal	0.0 ± 0.0	2.5 ± 0.2*
Anxiety	0.12 ± 0.1	2.0 ± 0.4*
Appetite	0.0 ± 0.0	1.7 ± 0.2*
Carbohydrate craving	0.1 ± 0.1	2.5 ± 0.2*

Data are presented as mean ± SEM.
* Differs from follicular values, $P < .0001$.

Table 3. Effect of d-Fenfluramine and Placebo on Calorie and Nutrient Intakes

	Baseline		Treatment	
	Follicular	Luteal	Placebo	Drug
Meals				
Kcal	1443 ± 112	1740 ± 129*	1512 ± 116	1362 ± 127*
Protein (g)	76 ± 5	74 ± 5	63 ± 5	71 ± 9
Carbohydrate (g)	110 ± 13	151 ± 16*	131 ± 12	103 ± 12*
Fat (g)	78 ± 6	93 ± 7*	82 ± 6	74 ± 7*
Snacks				
Kcal	430 ± 80	606 ± 71‡	778 ± 156	415 ± 72*
Protein (g)	19 ± 5	23 ± 3	28 ± 6	16 ± 3
Carbohydrate (g)	32 ± 7	53 ± 8‡	68 ± 15	34 ± 7*
Fat (g)	25 ± 4	34 ± 4§	43 ± 9	24 ± 4*

* Differs from follicular values, $P < .01$.
† Differs from luteal and placebo values, $P < .01$.
‡ Differs from follicular values, $P < .003$.
§ Differs from follicular values, $P < .05$.

Table 4. Effect of d-Fenfluramine and Placebo on Premenstrual Mood Scores

	Drug	Placebo
Hamilton Rating Scale for Depression	8 ± 1*	16 ± 1
Addendum	4 ± 1†	6 ± 1
Subscales		
Depression	0.5 ± 0.1‡	1 ± 0.2
Work efficiency	1 ± 0.2‡	2 ± 0.2
Anxiety	0.7 ± 0.1‡	2 ± 0.1
Fatigue	1 ± 0.2	1 ± 0.2
Social withdrawal	1 ± 0.2	1 ± 0.2
Appetite	0.6 ± 0.1*	1 ± 0.1
Carbohydrate craving	0.8 ± 0.1*	2 ± 0.1

* Differs from placebo values, $P < .001$.
† Differs from placebo values, $P < .05$.
‡ Differs from placebo values, $P < .01$.

about 180 kcal ($P < .003$). Carbohydrate intake from meals increased by 37% ($P < .01$) and from snacks by 65% ($P < .003$). Of necessity, fat intake increased in proportion to calorie intake, inasmuch as the fat contents of all of the foods were similar. No change associated with the menstrual cycle was noted in the consumption of protein-rich foods (Table 3).

d-Fenfluramine suppressed the late luteal phase increases in kilocalorie, carbohydrate, and fat intakes ($P < .01$) in all of the subjects. Kilocalorie and nutrient intakes did not differ from the subjects' follicular levels. Placebo treatment had no effect; kilocalorie and nutrient intakes on placebo were similar to those observed during the baseline luteal phase (Table 3).

d-Fenfluramine treatment significantly reduced both the mean Hamilton Rating Scale for Depression and its Addendum scores compared with those observed during the baseline cycle or with placebo treatment. The mean Hamilton Rating Scale for Depression score with d-fenfluramine was 8 ± 1 and with placebo, 16 ± 1 ($P < .001$) (Table 4). Subscales on the Hamilton Rating Scale for Depression that measured depressed mood, anxiety, and work impairment were significantly improved ($P < .01$) (Table 4). The Addendum scores were also significantly lower with drug treatment than with placebo ($P < .05$). This was due primarily to significant decreases in the appetite and carbohydrate craving subscales. No significant changes were found in the fatigue and social withdrawal subscales (Table 4).

Individual subjects varied in the consistency of their responses to placebo and drug treatment (Table 5). Nine subjects demonstrated significant improvement or a total reversal of their PMS symptoms during each of the three drug treatment months; of these, eight never responded to placebo and one subject improved only during her first placebo trial. One subject in this group reported considerable fatigue during the drug treatment months; her elevated Addendum score may have been due to this side effect of d-fenfluramine. (This subject participated in only two placebo and two drug trials because back problems prevented her from coming to the CRC for evaluation.) Three subjects demonstrated positive mood responses during both the drug and placebo trials. Five subjects had inconsistent responses to both the placebo and the drug and

Table 5. Effect of Treatments on Hamilton Rating Scale for Depression Scores and Addendum Scores of Individual Subjects

	Placebo		d-Fenfluramine	
	Ham-D	Add	Ham-D	Add
Responders				
779	20.6 ± 1.45	8.3 ± 2.7	2.6 ± 0.89	1 ± 1.0
856	13 ± 2.5	6.3 ± 2.3	6 ± 2.5	3 ± 1.3
887	12 ± 0.9	5.3 ± 1.2	0.7 ± 0.7	1.7 ± 0.9
891	17 ± 8.0	6.6 ± 3.5	6.3 ± 1.8	1.3 ± 0.9
913	26 ± 1.2	9.3 ± 1.2	11.3 ± 2.6	6.6 ± 0.6
983	19 ± 1.7	11.3 ± 0.9	1 ± 1.0	3 ± 1.0
999	15.3 ± 6.0	8 ± 3.0	5.6 ± 5.2	2.6 ± 2.6
091	20 ± 2.6	11 ± 0.7	4.3 ± 0.89	2.3 ± 0.89
012	26 ± 4.0	7 ± 1.2	13 ± 2.0	10 ± 5.0
Non-responders				
780	9.6 ± 4.0	7.3 ± 2.3	14.3 ± 7.5	4.3 ± 1.2
089	17 ± 4.5	6.3 ± 2.0	15.3 ± 6.2	5.6 ± 1.4
824	9 ± 3.5	5.3 ± 1.6	13.3 ± 1.4	6.3 ± 1.1
829	10 ± 4.0	6 ± 0.7	17 ± 2.4	6 ± 1.1
838	15 ± 2.0	5 ± 1.8	18 ± 2.6	9.3 ± 2.0
Responders on both treatments				
803	6.3 ± 4.4	1.3 ± 0.9	6.7 ± 3.2	2.6 ± 1.6
036	4.6 ± 3.7	2.0 ± 1.0	9 ± 5.3	4.3 ± 3.3
076	9.0 ± 5.0	5.3 ± 2.7	6.6 ± 6.6	4 ± 2.6

Ham-D = Hamilton Rating Scale for Depression; Add = Addendum.
Data are presented as mean ± SEM of 3-month treatments each on placebo and drug.

were not shown to be helped by drug treatment. However, even these subjects significantly decreased their subjective reports of increased appetite and carbohydrate craving while on drug treatment, and they all consumed significantly fewer calories and carbohydrates while on the drug than they did while on the placebo.

With the exception of the subject who experienced fatigue, none of the subjects reported any consistent side effects other than dry mouth. (d-Fenfluramine appears to induce fewer side effects than the racemic compound dl-fenfluramine because the levoisomer has a direct antidopaminergic action not found with the dextroisomer. Thus, although drowsiness has been reported for d-fenfluramine, sedation and depression have not.[13,14]) Measurements of mood during the first follicular stage after completion of the overall study were not significantly different from pre-treatment follicular levels.

Discussion

We found that d-fenfluramine, a drug that selectively enhances serotonin-mediated neurotransmission,[6] can be effective in relieving the excessive food intake and cravings for carbohydrate-rich foods that characterize PMS[1,2]; moreover, in the majority of subjects, the drug also relieved the premenstrual symptoms of depression, anxiety, and inability to work. The subjects reported no side effects other than dry mouth, and there were no differences in the incidence of drowsiness between the placebo- and drug-treated groups.

The uniform effectiveness of the drug in reducing subjective feelings of increased appetite and carbohydrate craving and in preventing the luteal increase in carbohydrate consumption is of particular interest. These responses to d-fenfluramine are consistent with the known roles of serotoninergic neurons in the control of appetite.[4,15] Transmitter release from these neurons is affected by food consumption and, in turn, may influence subsequent food choice. Consumption of carbohydrate-rich, protein-poor foods can enhance serotonin synthesis via insulin-mediated changes in the plasma amino acid pattern which facilitates the uptake of circulating tryptophan, serotonin's precursor, into the brain.[7,11] Subsequently, the substrate saturation of tryptophan hydroxylase facilitates the production and release of serotonin. Drugs such as d-fenfluramine or norfenfluramine that selectively release brain serotonin or block its reuptake also diminish elective carbohydrate intake in normal rats.[15]

The selective effect of d-fenfluramine in reducing the excessive intake of carbohydrate-rich, protein-poor foods by premenstrual patients is similar to its previously described effect among obese individuals who claim to be carbohydrate-cravers.[4] In a series of inpatient studies in which the overeating of carbohydrate-rich foods by obese subjects was quantified using methods for measuring food intake similar to those described herein, d-fenfluramine selectively diminished carbohydrate intake without significantly decreasing protein consumption.[4] Similarly, administration of d-fenfluramine to subjects suffering from seasonal affective disorder also decreased their excessive carbohydrate craving and prevented the weight gain that they otherwise would have experienced.[3] The drug's ability to correct abnormalities in food intake among the premenstrual women in the present study suggests its utility in helping such women maintain body weight. That the drug restored food and nutrient intake to follicular levels rather than depressing intakes below what the subjects would normally have consumed may make it particularly valuable in sustaining adequate nutrient intake, especially of protein-rich foods.

Our observation that d-fenfluramine, which selectively enhances serotoninergic neurotransmission, alleviates premenstrual depression in the majority of subjects supports the hypothesis that serotonin-releasing raphe neurons are involved in producing the affective and appetitive symptoms characteristic of this disorder. An involvement of peripheral serotonin has previously been proposed, based on the observations that platelet serotonin uptake[16] and blood serotonin levels[17] were depressed in subjects with PMS during the luteal phase of the cycle. However, circulating serotonin is not thought to cross the blood-brain barrier and there is no reason to believe a priori that the mechanisms controlling the synthesis of peripheral serotonin within enterochromaffin cells, or its storage within platelets, are at all related to those regulating its production in and release from brain neurons.

We reported previously that subjects with severe premenstrual depression demonstrated significant improvements in mood after consuming a carbohydrate-rich, protein-poor test meal.[2] These changes were observed only during the late luteal stage of the cycle and were not found among symptom-free controls. Because dietary carbohydrate can accelerate brain serotonin synthesis,[7,11] these observations also support the possible involvement of serotonin in the premenstrual mood disorder.

The range of responsiveness of our subjects was considerable. Nine demonstrated a total reversal of their symptoms or considerable improvement while on drug treatment, with no or almost no responses to placebo (Table 4). In contrast, five showed no pattern of consistent responsiveness to placebo or to drug treatment, and three responded to both. We examined the influence of treatment order and found that only

one subject responded positively to the placebo when it was the first treatment given; hence, expectations that the initial treatment would be effective were not a factor. We also looked at the influence of time of year because subjects were entered individually into the study, and thus the 6-month treatment phase followed different seasonal patterns for each subject. There was no effect of time of year on responsiveness to either drug or placebo. What we did note was an unpredictable variety of non-study-related problems among the non-responders: One experienced an unrelenting series of social, financial, and housing crises; two others experienced family or financial crises (including a bankruptcy); and one encountered unexpected job stress. Of anecdotal interest was the benign acceptance by a patient on drug treatment of a household of children infected with chicken pox during a family celebration.

This study used standardized observer-rated tests of mood and appetite. These tests asked the subject to evaluate her mood, work activity, fatigue, appetite, and sociability over the immediate past 7-day period. Such tests may prevent the reporting of symptoms occurring only infrequently during the past week. It is possible that only those symptoms with the greatest severity were remembered and described and that the use of daily ratings may have revealed less severe or infrequent changes in mood, fatigue, or appetite. However, the observer-rated assessments permitted the investigators to see the subject in the research facility at the end of each treatment, allowing an evaluation of her premenstrual symptomatology under identical clinical conditions each month. Moreover, by having a trained observer rate the symptoms, we avoided the possibility that the mood of the subject might itself have an effect on the care and accuracy of a self-assessment report.

Our data suggest that d-fenfluramine and other drugs that increase serotoninergic transmission may be useful in treating premenstrual disorders of appetite and mood. Drugs such as d-fenfluramine, which produce their clinical effects within a few days of initial administration and which can be withdrawn abruptly without risk during the nonsymptomatic stages of the cycle, have obvious advantages in the long-term treatment of this cyclic disorder. Their use may be particularly valuable to patients who are engaged in long-term weight loss programs and whose ability to maintain control over calorie intake is impaired because of premenstrual depression.

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Received December 7, 1989.
Received in revised form March 16, 1990.
Accepted March 22, 1990.