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Treatment of Seasonal Depression With *d*-Fenfluramine

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Eighteen patients with seasonal affective disorder (SAD) participated in a double-blind, placebo-controlled crossover study in 1986-1987. Each received, in random order, *d*-fenfluramine (15 mg p.o. twice daily)—a serotonin-releasing drug previously shown to suppress carbohydrate craving—or a placebo; these were given for 4 weeks separated by a 2-week washout period. Symptoms were assessed by means of clinical interviews and the Hamilton Rating Scale for Depression (HAM-D) with a special SAD addendum (AAD). Patients were also weighed. Depression scores (mean±SE) were identical before treatment with drug (20.9±1.3, HAM-D; 13.3±0.8, AAD) or placebo (21.4±1.2, HAM-D; 13.2±0.6, AAD). During placebo treatment, mean HAM-D scores declined by 22% ($p < .02$) and AAD scores by 9% ($p > .2$). During *d*-fenfluramine treatment, HAM-D scores fell by 71% ($p < .001$) and AAD scores by 73% ($p < .001$). Thirteen (72%) of the patients demonstrated complete reversal of their abnormal test scores while taking *d*-fenfluramine. The group as a whole lost weight (mean=1.2 kg) while receiving *d*-fenfluramine ($p < .033$) but not when taking placebo. A second study, conducted in 1987-1988 with nine subjects who had previously responded to *d*-fenfluramine, showed that the drug remains effective for the full 3-month annual period of symptoms. These results indicate that *d*-fenfluramine may be useful in treating SAD and suggest that serotonin is involved in both SAD's affective and appetitive symptoms.

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Of the approximately 8 million Americans who suffer a major depressive episode each year,[1] 4% to 10%[2] are believed to be afflicted with seasonal affective disorder (SAD), a syndrome that recurs each fall and winter and disappears during the subsequent spring or early summer.[2,3] Its symptoms include many common manifestations of typical depressions (e.g., mood disturbance, diminished interest in previously enjoyed activities, lowered energy, increased fatigue, reduced productivity, psychomotor retardation, difficulty concentrating, social withdrawal), as well as some symptoms associated with the atypical depressions (e.g., hypersomnia, hyperphagia, carbohydrate craving, weight gain).[4]

As the days grow longer and spring follows winter, all of these symptoms disappear.[5] Patients describe increased energy levels, the resumption of creative thinking, reduced sleep requirements, increased productivity, decreased appetite—especially for carbohydrate-rich foods, and increased social activity. Some patients actually exhibit signs of mania during this time.[1,2] Seasonal light deprivation has been proposed as the trigger for the annual onset of clinical symptoms,[6,7] because the prevalence of SAD and the amplitude of the annual rhythm in day length both increase with the distance from the equator. Moreover, exposing SAD patients to supplemental light in fall or winter often relieves their symptoms.[5,7]

The association of affective and appetitive symptoms that occurs in SAD has also been observed in patients with the late luteal phase dysphoric disorder (premenstrual syndrome)[8] and normal-weight bulimia.[9] Moreover, we noted in unpublished studies that a majority of obese patients who intermittently exhibited severe carbohydrate craving[10] also had psychiatric histories or current symptoms that satisfied established criteria[1] for major depression. Previous studies[10] from our laboratory had shown that *d*-fenfluramine, a drug that selectively enhances serotonin-mediated neurotransmission, could alleviate the carbohydrate craving of this latter group and diminish their characteristic daily consumption of 800 calories or more of carbohydrate-rich, protein-poor snack foods. These patients reported an improvement in mood following carbohydrate consumption[11]; this improvement is possibly related to accelerated brain serotonin synthesis, which can follow ingestion of carbohydrate-rich, protein-poor foods.[12] *d*-Fenfluramine may have reduced their snack intake by producing serotonin-mediated mood changes similar to those experienced after carbohydrate consumption.

The present report describes two studies of the effect of *d*-fenfluramine on mood, appetite, and weight among individuals suffering from SAD. In an earlier, preliminary, double-blind study[13] involving seven patients, *d*-fenfluramine treatment was associated with complete remission of the affective and appetitive symptoms in four patients; the other three patients exhibited partial improvement when taking *d*-fenfluramine or they had responses to both the drug and its placebo. In the first

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controlled study reported here, a larger group of patients was tested, and a more complete assessment was made of *d*-fenfluramine's effects on symptoms characteristic of SAD. In a follow-up uncontrolled study a subgroup of responders received active treatment during the subsequent fall and winter to assess ongoing effectiveness of the drug.

METHOD

During the fall of 1986, potential subjects—outpatients at the Massachusetts Institute of Technology Clinical Research Center—were screened by completing questionnaires about their psychiatric and weight histories and through interviews by a psychiatrist and a clinical nutritionist. Twenty-six patients satisfied the diagnostic criteria for SAD. Of these, 23 (19 women and 4 men) participated in the study; 3 others chose not to do so.

All subjects were free of other medical or psychiatric disorders, took no medications, and were 10% to 40% above their ideal body weight, as determined by Metropolitan Life Insurance Company's height and weight tables for men and women (1983). A physician conducted physical examinations, blood samples for clinical measurements (CBC, thyroid indices, Blood Chemistry 20 Profile, serum pregnancy test) were obtained, and a urinalysis and ECG were performed. Each subject received a comprehensive psychiatric evaluation by a psychiatrist to rule out other psychopathology, including Axis II diagnoses. Psychometric testing, consisting of the Hamilton Rating Scale for Depression (HAM-D)[14] and its SAD addendum (AAD),[15] was used to quantify depressive symptoms before and after each of the two treatment periods, and again during the month of June following the completion of the study. Only patients with HAM-D scores of 15 or more or a combined HAM-D + AAD score of 21 or more were included in the studies. At each of these times, subjects were also weighed and interviewed by a psychiatrist and a clinical nutritionist. Participating subjects were contacted weekly by telephone to ensure early detection of possible treatment side effects or deterioration of clinical condition. Every subject signed an informed consent form, which included specific commitments not to travel to a southern latitude, nor to change eating or life-style patterns, nor to become pregnant while participating in the study.

In a double-blind crossover study, subjects received *d*-fenfluramine (15 mg p.o. twice daily) and its active placebo in random order for 4-week periods, separated by a 2-week washout period. (In humans, the half-life of *d*-fenfluramine is 18.3 ± 1.1 hours, with peak plasma levels occurring 3 to 4 hours after a single dose. Steady-state concentrations occur in 4 to 5 days. While the drug's long half-life would permit administration of a single daily dose, dividing the dose decreases peak plasma levels and improves clinical responses, without reducing efficacy.) Only the nurse who controlled administration of the drug knew the code; patients and researchers were blind to it. *d*-Fenfluramine and placebo were obtained from the Servier Company, Neuilly-sur-Seine, France. The drug's use in this study was based on an Investigational New Drug application previously approved by the United States Food and Drug Administration.

Side effects were determined by means of a checklist, which was self-administered by the subjects, and then returned to an outpatient nurse (who was not a member of the research team). The nurse would have informed the study physician about significant side effects had they occurred, but that was not necessary for any of the subjects who completed the study. Patients did not report that side effects provided them with an indication of when they were receiving the drug.

Five female subjects failed to complete the study. Two violated the study protocol by taking a vacation in Southern California during the treatment phase (which resulted in their being exposed to summer levels of illumination); one became pregnant; one developed dysuria while receiving *d*-fenfluramine and was discharged from the study; and the fifth had to leave Massachusetts for personal reasons. Statistical analyses included data from the 18 subjects (14 women, 4 men) who completed the study. The null hypothesis of no change was tested for significance using analysis of variance with repeated measures followed by Tukey's test for pairwise comparisons. The relationship between weight change and depression score was evaluated using Pearson's product-moment correlation.[16,17]

A second study—this one uncontrolled—was conducted in 1987-1988 on nine of the subjects who had responded to *d*-fenfluramine during the previous fall-winter; this second study's purpose was to determine whether the drug can be effective for more than a single treatment period, and whether it remains active in responders for the full duration of each year's period of symptoms. As in the first study, patients were seen by a psychiatrist and underwent psychometric testing by the HAM-D and AAD on November 20 and again on December 4, when treatment (*d*-fenfluramine 15 mg p.o. twice daily) was started. Treatment continued for 12 weeks; patients were evaluated at intervals during treatment and again on March 18, 3 weeks after the treatment's discontinuance.

RESULTS

Demographic data describing the 14 women and 4 men who completed the first year's study, and including the 6 women and 1 man (Patients 1, 2, 3, 4, 7, 8, 9, 11, 13) who completed the second study, are summarized in Table 1. In the first study, the ages ranged from 29 through 55 years (mean $\pm$ SE = 40.4 ± 1.9 years). Mean $\pm$ SE depression scores were identical before drug (21 ± 1.3, HAM-D; 13 ± 0.8, AAD) and before placebo (21 ± 1.2, HAM-D; 13 ± 0.6, AAD) treatments (Table 2). Placebo treatment resulted in a small (22%) but significant mean decline in HAM-D scores (by 4.5 ± 1.6, $p < .02$), but no significant mean decline in AAD scores (by 1.2 ± 1.1, $p > .2$). Treatment with *d*-fenfluramine significantly reduced both the mean HAM-D score (by 71%, i.e., 14.8 ± 1.2) and the AAD score (by 73%, i.e., 9.7 ± 1.3; $p < .001$). *d*-Fenfluramine also caused significant improvements in various AAD subscales (Table 3), including decreased en-

Table 1. Effect of *d*-Fenfluramine on Body Weight in SAD Patients

Patient	Sex	Age (y)	Body Weight (kg)					
			Predrug	Postdrug	Difference	Preplacebo	Postplacebo	Difference
1[a]	F	35	68.3	66.9	−1.4	68.7	68.0	−0.7
2[a]	F	44	83.1	80.8	−2.3	78.9	81.4	2.5
3[a]	F	36	68.0	67.3	−0.7	63.3	65.8	2.5
4[a]	M	30	79.0	76.8	−2.2	79.4	78.0	−1.4
5	F	35	118.1	117.8	−0.3	117.1	106.3	−10.8
6	M	45	84.1	81.7	−2.4	84.4	83.0	−1.4
7[a]	F	43	140.0	135.3	−4.7	135.6	137.9	2.3
8[a]	F	52	69.0	66.6	−2.4	69.3	70.1	0.8
9[a]	F	32	132.9	129.7	−3.2	130.2	131.5	1.3
10	F	41	71.1	71.5	0.4	71.7	72.1	0.4
11[a]	F	54	59.0	56.6	−2.4	57.0	56.4	−0.6
12	F	41	75.3	75.4	0.1	75.5	76.7	1.2
13[a]	F	55	63.5	62.0	−1.5	64.8	65.1	0.3
14	M	48	76.9	80.2	3.3	81.4	81.7	0.3
15	M	42	90.2	85.5	−4.7	87.5	89.4	1.9
16	F	31	65.3	63.9	−1.4	65.7	66.7	1.0
17	F	29	96.7	98.7	2.0	104.2	105.3	1.1
18	F	35	81.8	84.4	2.6	83.9	88.6	4.7
Mean		40.4	84.6	83.3	−1.2[b]	84.3	84.6	0.3[c]
SE		1.9	5.5	5.3	0.5	5.3	5.3	0.7

[a]Patients who participated in uncontrolled follow-up study.
[b]Differs from predrug group, $p < .033$.
[c]Differs from preplacebo group, $p < .69$.

Table 2. Effect of *d*-Fenfluramine on Depression Scores in SAD Patients

Patient	Fall[a]								Spring[b]	
	Predrug		Postdrug		Preplacebo		Postplacebo			
	HAM-D	AAD	HAM-D	AAD	HAM-D	AAD	HAM-D	AAD	HAM-D	AAD
1	31	14	10	4	19	14	20	16	0	0
2	23	16	4	4	25	11	21	15	0	0
3	18	14	1	0	24	14	12	13	0	0
4	18	10	0	0	19	10	17	7	0	0
5	18	16	3	2	18	14	16	14	0	2
6	26	13	3	1	24	12	26	10	0	0
7	22	17	5	1	22	15	22	17	0	0
8	10	11	5	0	15	8	13	11	1	1
9	22	16	1	0	19	17	18	15	0	0
10	21	15	6	2	29	15	28	16	3	0
11	16	13	1	3	15	12	19	19	0	0
12	22	17	6	1	34	15	32	16	0	0
13	15	4	0	0	24	14	14	11	0	0
14	15	12	0	4	15	9	1	2	5	0
15	19	11	6	4	21	14	4	7	0	1
16	22	10	15	12	20	15	2	2	0	0
17	27	13	20	14	18	14	17	14	0	1
18	32	18	25	14	24	15	22	12	5	0
Mean	21	13	6.0[c]	3.6[c]	21	13	17	12	0.8[c]	0.2[c]
SE	1.3	0.8	1.7	1.1	1.2	0.6	1.9	1.1	0.4	0.13

[a]Fall tests were conducted in November.
[b]Spring tests were conducted in June.
[c]Differs from predrug Fall scores, $p < .001$.
Abbreviations: AAD = Addendum for Atypical Depression to the Hamilton Rating Scale for Depression; HAM-D = Hamilton Rating Scale for Depression.

ergy ($p < .001$), fatigue ($p < .001$), social withdrawal ($p < .001$), increased appetite ($p < .001$), carbohydrate craving ($p < .001$), and hypersomnia ($p < .05$). The placebo diminished subjective fatigue by 25% ($p < .05$), compared with the 74% reduction seen with *d*-fenfluramine, and failed to affect any of the other subscales significantly.

Subjects who received *d*-fenfluramine before receiving placebo (N = 11) exhibited significantly greater responses ($p < .05$; unpaired t test) in mood scores than those initially receiving placebo (N = 7); however, the effects of the drug on HAM-D and AAD scores were highly significant ($p < .0001$) in both subgroups.

Thirteen (72%) of the 18 subjects demonstrated complete reversal of their SAD symptoms when taking *d*-fenfluramine. Of the remaining subjects, 2 responded to both drug and placebo; 1 responded only to placebo; and 2 failed to respond to either treatment.

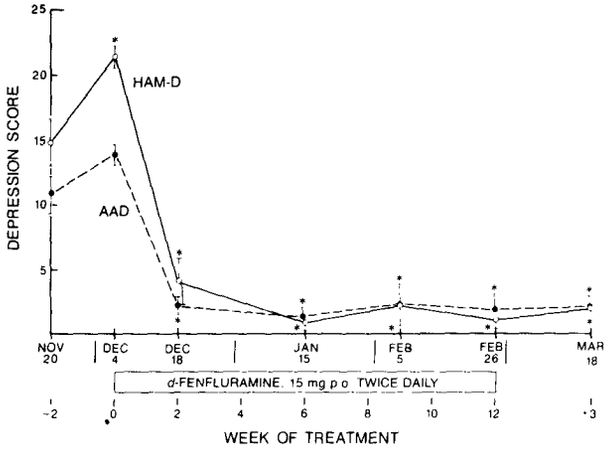
Thirteen of the 18 subjects lost weight while taking *d*-fenfluramine (mean ± SE = 1.2 ± 0.5 kg; $p = .033$), but only 5 of these 13 also lost weight while taking the placebo (mean ± SE = 0.3 ± 0.7 kg; $p = .69$, Table 1). More-

Table 3. Effect of *d*-Fenfluramine on Scores for Individual Symptoms in the Hamilton SAD Addendum Scale

	Predrug		Postdrug		Difference		Preplacebo		Postplacebo		Difference	
Subscales	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Decreased energy	2.1	0.07	0.4	0.18	1.8	0.2[a]	2.0	0.08	1.6	0.19	0.3	0.2
Fatigue	2.7	0.13	0.7	0.26	2.0	0.3[a]	2.8	0.14	2.1	0.27	0.7	0.2[b]
Social withdrawal	2.5	0.25	0.7	0.28	1.8	0.3[a]	2.4	0.24	2.2	0.31	0.2	0.3
Increased appetite	1.7	0.10	0.3	0.14	1.4	0.2[a]	1.5	0.12	1.4	0.14	0.1	0.1
Carbohydrate craving	2.7	0.13	0.5	0.21	2.2	0.3[a]	2.7	0.15	2.4	0.20	0.3	0.3
Hypersomnia	2.4	0.25	0.9	0.20	1.4	0.3[b]	1.9	0.24	1.9	0.29	−0.1	0.2

[a] $p < .001$ (Pre/post) score versus 0.
[b] $p < .05$ (Pre/post) score versus 0.

Figure 1. Effect of *d*-Fenfluramine Treatment on Depression Scores in Patients With Seasonal Affective Disorder (SAD)[a]



[a]Nine patients who had previously exhibited a short-term (1 month) therapeutic response to *d*-fenfluramine received the drug for 12 weeks, starting on December 4, 1987. Depressive symptoms were quantified by the Hamilton Rating Scale for Depression (HAM-D) and its SAD addendum (AAD) at intervals before, during, and after drug treatment. *Differs from initial (November 20) score, $p < .05$.

over, only 1 subject lost more weight while taking placebo than while taking *d*-fenfluramine; no one lost weight only while taking the placebo, but 2 gained less when taking placebo than when taking *d*-fenfluramine. Eleven of these 13 subjects also experienced a significant decrease in affective symptoms while taking the drug; however, no significant correlations were observed between weight loss or gain and mood score in either the placebo- or the drug-treated group.

None of the 18 patients showed evidence of depression, either by clinical observation or by psychometric testing, when evaluated in June, 3 months after completion of the study (Table 2). On questioning, a majority of subjects reported frequent but not severe cases of dry mouth, as well as infrequent episodes of mild headache and diarrhea. The latter conditions were experienced by only a small number of patients. None of the subjects showed symptoms of depression or reduced energy on cessation of the drug.

Among the nine patients retested in 1987-1988, HAM-D and AAD scores were abnormally elevated by November 20, and the HAM-D scores exhibited a further substantial rise by December 4, when treatment was started (Figure 1). Within 2 weeks, mean scores of both tests had fallen to their normal ranges (from 21.4 ± 0.9 to 4.1 ± 1.8, HAM-D, and from 13.8 ± 0.8 to 2.2 ± 0.7, AAD); scores remained normal during the subsequent 10 weeks of treatment and were also normal on March 18, 3 weeks after treatment had been discontinued. Moreover, each of the subscales described in Table 3 reflected similar responses.

DISCUSSION

These data show that *d*-fenfluramine, a drug that selectively enhances serotonin-mediated neurotransmission without causing psychostimulant effects or enhancing catecholamine-mediated neurotransmission,[11] was effective in relieving both the depressive and appetitive symptoms of SAD, whereas placebo had only minor effects on the depressive symptoms and none on the appetitive symptoms. Moreover, patients apparently retained their ability to respond to *d*-fenfluramine from year to year, and the drug remained effective throughout the annual 3-month period when symptoms usually are worst. Atypical depressive symptoms were also completely resolved by *d*-fenfluramine but unaffected by placebo. This finding is particularly encouraging since these symptoms, also often encountered in depressed patients without SAD, can be refractory to, and even aggravated by, currently available antidepressants. In practice, some tricyclic antidepressants and monoamine oxidase inhibitors commonly cause weight gain associated with hyperphagia and carbohydrate craving.[18-20] The rapidity of symptom relief in SAD patients treated with *d*-fenfluramine, when compared with rapidity of relief following treatment with tricyclic antidepressants or monoamine oxidase inhibitors in major depression, may be related to the different neurochemical mechanisms of action of these drugs; in addition to blocking the reuptake of serotonin, *d*-fenfluramine gives rise to its secretion from the presynaptic neuron. Perhaps this latter quality causes its ability to elicit a response.

A significant ($p < .05$) order effect was observed: patients who received *d*-fenfluramine prior to placebo exhibited a greater drug response (i.e., in mood scores) than those initially receiving placebo. However, in both subsets, the effect of the drug on HAM-D and AAD was very highly significant ($p < .001$). The order effect may reflect the fact that patients given placebo first probably had more severe symptoms by the time they received *d*-fenfluramine later in the winter.

d-Fenfluramine was highly effective in ameliorating hyperphagia and carbohydrate craving within the patient population as a whole, whereas placebo affected neither of these symptoms. All of our subjects had described a history of annual weight gain during the "winter depression

months," and, indeed, 13 of them gained weight while receiving placebo. Our data also suggest that the drug may remain effective in SAD patients when administered for the 3 months per year when their symptoms are usually worst.

The observed responses of SAD patients to *d*-fenfluramine, a drug known to enhance serotonin-mediated neurotransmission selectively,[21] are consistent with the known roles of serotonergic neurons in the control of appetite and mood.[22] 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.[13] These changes facilitate the uptake of circulating tryptophan into the brain, and thus increase the substrate-saturation of tryptophan hydroxylase and the production and release of serotonin. Conversely, the administration to normal rats of *d,l*-fenfluramine or of such other selectively serotonergic drugs as fluoxetine or MK-212 can (as discussed in reference 10) decrease their consumption of carbohydrates, while not affecting their consumption of protein-rich foods[10]; nonserotonergic anorectic agents like *d*-amphetamine lack these nutrient-specific effects.

Among obese subjects who professed to be carbohydrate cravers, and in whom this behavior was quantified in a clinical research center,[10] administration of *d*-fenfluramine also selectively diminished carbohydrate intake without significantly diminishing intake of protein. Carbohydrate intake was shown, in these patients, to have a positive effect on mood[11]; this improvement was not exhibited among obese individuals who did not snack on carbohydrate-rich foods (noncarbohydrate cravers). The present data on patients with SAD raise the possibility that serotonergic drugs might also be useful in patients with other depressive disorders associated with hyperphagia and carbohydrate craving, such as normal weight bulimia[9] and the late luteal phase dysphoric disorder.[8]

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